EUPO 2018

European University Professors
of Ophthalmology

October 3-4 in NICE, France

Retina, Intraocular Inflammation & Uveitis

Course Directors:

Prof. Catherine Creuzot-Garcher, University of Dijon, France
Prof. Bahram Bodaghi, University of Pierre and Marie Curie, France

In conjunction with EVER 2018
Acropolis Convention Center in Nice, France

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The sequence of the EUPO courses

2019	Nice (SOE)	Glaucoma, Cataract & Refractive Surgery
2018	Nice (EVER)	Retina, Intraocular Inflammation & Uveitis
2017	Barcelona (SOE)	Cornea, Conjunctiva and Refractive Surgery
2016	Nice (EVER)	Neuro-ophthalmology and Strabismus
2015	Vienna (SOE)	Uveitis and Glaucoma
2014	Nice (EVER)	Retina
2013	Copenhagen (SOE)	Cornea, Conjunctiva and Refractive Surgery
2012	Leuven	Neuro-ophthalmology and strabismus
2011	Geneva (SOE)	Uveitis & Glaucoma
2010	Athens	Retina
2009	Amsterdam (SOE)	Cornea, Conjunctiva and Refractive surgery
2008	Geneva	Neuro-ophthalmology and strabismus
2007	Vienna (SOE)	Glaucoma and uveitis
2006	Ghent	Retina
2005	Berlin (SOE)	Cornea
2004	Nijmegen	Neuro-ophthalmology and strabismus
2003	Madrid (SOE)	Glaucoma and uveitis
2002	Erlangen	Retina
2001	Istanbul (SOE)	Cornea
2000	Leuven	Neuro-ophthalmology and strabismus
1999	Stockholm (SOE)	Glaucoma and uveitis
1998	Amsterdam (ICO)	Chorioretina
1997	Budapest (SOE)	Cornea, conjunctiva, lids, orbit
1996	Athens	Neuro-ophthalmology and strabismus
1995	Milano (SOE)	Uveitis, lens, glaucoma
1994	Montpellier	Retina
1993	Santiago de Compostella	The external eye
1992	Brussels (SOE)	Neuro-ophthalmology and strabismus
1991	Torino	Uveitis, lens, glaucoma
1990	Bonn	Chorioretina
1989	Leuven	The external eye and orbit
1988	Nijmegen	First EUPO course

Word from the EUPO President

Bienvenue au Nice!

Whether you are a resident looking forward to eventually passing your final examination or a specalist looking toward an update on retina and uveitis, we – your EUPO Course Faculty, representing the European University Professors of Ophthalmology – are most delighted to have you here with us. This course is for you.

The EUPO course is a tradition established three decades ago, in 1988. It provides annual structured subspecialty instruction in four fields of ophthalmology, rotating on a yearly basis. Key points of the ophthalmology curriculum are covered so as to provide a full and broad update on most relevant and latest knowledge for delegates who partake in all four courses.

The course is an excellent concept, yet every endeavour benefits from continuous feedback and assessment. Upon returning home, please, make use of the opportunity to provide comments and suggestions to the Faculty and contribute to the future of the EUPO Course. We will much appreciate your opinion!

We have redesigned the EUPO Course Cycle for years 2018 to 2021 by alligning it more precisely with the four viva voces of the European Board of Ophthalmology (EBO) Diploma Examination in which about 650 residents and specialists sit annually. The topic this year is thus "Retina, Intraocular Inflammation & Uveitis" and next year, also in Nice in conjunction with the Societas Ophthalmologica Europaea (SOE) Congress, "Glaucoma, Cataract & Refractive Surgery". We definitely hope to see you here again.

The structure of the Course likewise has been thoroughly revised by our Course Co-Directors Prof. Catherine Creuzot-Garcher and Prof. Bahram Bodaghi. Short lectures are amended with case-based round tables that resemble the EBO viva voces and, hopefully, further help residents prepare for that part of the Diploma Examination. Moreover, the course even more than before focuses on what is new since the previous EUPO course on the same topic.

We have kept the EUPO Course Book with its key point summaries of most talks that you are presently reading. At the end of each summary, you will find a brief list of recommended reading that directs you to recent literature on each topic; papers that often include imporant new information not yet incorporated in your textbooks. We recommend that you familiarise yourself with these references when you prepare for your final examination.

The Faculty is at your disposal for the next two days. Make use of this opportunity and bombard it with questions and comments!

Thank you to the EVER Board for its collaboration in organising the EUPO Course.

Tero Kivelä, MD, FEBO
President, EUPO

available on www.eupo.eu

EUPO 2018
Retina, Intraocular Inflammation & Uveitis

EUPO 2017
Cornea, Conjunctiva and Refractive Surgery

EUPO 2016
Neuro-ophthalmology and Strabismus

EUPO 2015
Uveitis & Glaucoma

EUPO 2014
Retina

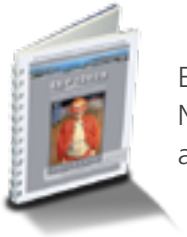
EUPO 2013
Cornea, Conjunctiva and Refractive Surgery

EUPO 2012
Neuro-ophthalmology and Strabismus

EUPO 2011
Uveitis and Glaucoma

EUPO 2010
Retina

EUPO 2009
Cornea, Conjunctiva and Refractive surgery



EUPO 2008
Neuro-Ophthalmology and Strabismus

EUPO 2007
Uveitis

EUPO 2006
Retina

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Programme EUPO 2018
Wednesday, 3 October, Morning Sessions

Course directors: Catherine CREUZOT, Bahram BODAGHI

• Introduction to the EUPO Course — 08:00 - 08:30

Introduction EUPO by President Tero KIVELÄ

Introduction EUPO 2018 course by Bahram BODAGHI

• Anatomy and imaging techniques — 08:30 - 09:45

Moderator: Andrew DICK

		Course	Page
• 08:30	Blood-retinal barrier *BEHAR COHEN F*	01	11
• 08:45	Fluorescein angiography and ICG *PILOTTO E*	02	16
• 09:00	OCT: from anatomy to imaging *MIERE A*	03	23
• 09:15	OCT angiography *STAURENGHI G*	04	28
• 09:30	Immune tolerance and its alteration *DICK A*	05	29

• Break — 09:45 - 10:15

Programme EUPO 2018
Wednesday, 3 October, Noon Sessions

Course directors: Catherine CREUZOT, Bahram BODAGHI

• What to do when I see... **10:15 - 12:00**

Moderator: Tero KIVELÄ

• 10:15	Serous retinal detachment *MIDENA E*	06	34
• 10:30	Atrophy of the retina *CREUZOT C*	07	40
• 10:45	Detachment of pigment epithelium *DELYFER MN*	08	51
• 11:00	Black & white dots *NERI P*	09	54
• 11:15	Vasculitis *KHAIRALLAH M*	10	58
• 11:30	Inflammatory macular oedema *JONES N*	11	63
• 11:45	Pigmented tumour *KIVELÄ T*	12	66

• Round table 1: How do you diagnose these cases? **12:00 - 13:15**

Moderators: Stephanie BAILLIF, Talin BARISANI

Panel: Stephanie Baillif; Alexandra Miere; Piergiorgio Neri;
Marie-Noelle Delyfer; Tero Kivelä; Moncef Khairallah

• Lunch break **13:15 - 14:15**

Programme EUPO 2018
Wednesday, 3 October, Afternoon Sessions

Course directors: Catherine CREUZOT, Bahram BODAGHI

• How does it work? **14:15 - 15:45**

Moderator: Andrzej GRZYBOWSKI

• 14:15	Anti-VEGF *GRZYBOWSKI A*	13	80
• 14:30	Steroids *WILLERMAIN F*	14	85
• 14:45	Laser *LARSEN M (presenter CREUZOT C)*	15	88
• 15:00	PDT *BATTAGLIA PARODI M*	16	93
• 15:15	Radiotherapy *PARROZZANI R*	17	99
• 15:30	Immunosuppression and biologics *BODAGHI B*	18	106

• Break **15:45 - 16:15**

• Round table 2: How do you treat these cases? **16:15 - 17:45**

Moderator: Piergiogio NERI

Panel: Piergiorgio Neri ; Maurizio Battaglia Parodi; Bahram Bodaghi; Nicholas Jones; François Willermain; Catherine Creuzot

Programme EUPO 2018
Thursday, 4 October, Morning Sessions

Course directors: Catherine CREUZOT, Bahram BODAGHI

• EVER-ACTA lecture **08:45 - 09:15**

• My children cannot see! **09:15 - 10:30**

			Course	Page
	Moderator: Isabelle AUDO			
•	09:15	Inherited disease: from diagnosis to treatment *AUDO I*	19	124
•	09:30	Macular oedema *AUDO I*	20	127
•	09:45	Toxoplasmosis *KODJIKIAN L*	21	130
•	10:00	Exudative diseases *DE SMET M*	22	141
•	10:15	ROP *BREMOND GIGNAC D*	23	148

• Break **10:30 - 11:00**

• EVER Lecture **11:00 - 11:30**

Programme EUPO 2018
Thursday, 4 October, Noon Sessions

Course directors: Catherine CREUZOT, Bahram BODAGHI

• Surgical diseases and miscellaneous 11:30 - 12:15

Moderator: Jan VAN MEURS

• 11:30	Vitreomacular interface: new disease or new classification *VAN MEURS J*	24	153
• 11:39	Retinal detachment in myopic patient *MEIER P*	25	155
• 11:48	Central serous chorioretinopathy and ERD *BOUSQUET E*	26	158
• 11:57	Pars planitis *MISEROCCHI E*	27	162
• 12:06	Lymphoma *TOUITOU V*	28	166

• Round table 3: My job is difficult! 12:15 - 12:45

Moderator: Constantin POURNARAS

Panel: Leonidas Zografos; Moncef Khairallah; Alain Bron; Constantin Pournaras; Frédéric Mouriaux

• Closure and Farewell 12:45 - 12:50

Catherine CREUZOT

Evaluation form and Certificate of Attendance

The certificate of attendance and CME certificate for EUPO 2018 can be downloaded on www.ever.be after the EUPO Course. It is mandatory to complete the survey before downloading the certificates.

01

Blood-retinal barrier

BEHAR COHEN F - France

MCQ's

1. Choroidal vessels

a. Do not have tight junctions
b. Are highly permeable to proteins
c. Do not have pericytes
d. VEGF induces permeability

2. Retinal vessels

a. Are formed by endothelial cells linked with tight junctions
b. Pericytes coverage is the highest in the body
c. Pericytes are derived from neuroblasts
d. Retinal Müller glial cells are part of the inner bloold-retinal barrier
e. Maturation of the blood-retinal barrier after birth is due to formation of tight junctions

THE RETINA IS VASCULARISED by two independent systems. Transport between the retina and the circulation is controlled through the inner blood-retinal barrier at the level of retinal vessels, and through the outer blood-retinal barrier at the level of the retinal pigment epithelium and choroidal vessels.

1. The inner blood-retinal barrier

The inner blood-retinal barrier is formed by the tight junctions between the endothelial cells of retinal vessels, dynamically regulated by a neuro-glio-vascular cross-talk involving astrocytes and retinal Müller glial (RMG) cells.

Endothelial cells of retinal capillaries are connected by molecular complexes, consisting of tight junctions (zonula occludens), adherens junctions (zonula adherens), and gap junctions. Besides their role in cell-to-cell adhesion, these complexes regulate contact inhibition for endothelial cell division, cell survival, polarity, and paracellular permeability. The exact transcellular resistance of the retinal vascular endothelium is not known but is thought to be similar to the one measured in the cerebral vascular endothelium, reaching 1000-1500 ohm·cm^2, much higher than the outer retinal barrier resistance. Endothelial cells of the retina and the brain have the highest number of tight junction strands. Under normal conditions, water and ions move passively through paracellular routes according to osmotic gradients. Albumin does not cross the tight junction complex, preventing osmotic leakage.

Transport across the endothelium is highly regulated by active membrane transporters and by vesicular transport. Caveolae-mediated transcytosis is defined as migration of plasma membrane vesicles from one side of the cell to the other, the formation of a pore resulting from vesicular fusion, or both. Caveolin-1, the major protein component of caveolae is expressed in the developing and mature retinal vessels and in the choroidal vasculature. Transcytosis that allows plasma macromolecules such as albumin, transferrin, insulin, lipoproteins and, possibly, immunoglobulins to penetrate from the circulation into tissues, is less active in the retina as compared to other organs. In contrast, this mechanism seems important in driving macromolecules out of the retina and into the circulation. In the developing retina, the inner blood-retinal barrier properties are progressively acquired concomitantly ith the reduction of endothelial transcytosis

Pericytes are specialised mural cells that are located at the abluminal surface of retinal veins and capillaries. They share their basement membrane with endothelial cells, and are covered by an external basal membrane. Pericytes contribute to the regulation of the inner blood-retinal barrier, to microvascular blood flow through their contractile properties, and to angiogenesis. There is recent evidence that brain, retinal and choroidal pericytes derive, at least in part, from the neural crest. In the retina, pericyte density with respect to endothelial cells reaches a 1:1 ratio, and pericyte coverage of human retinal capillaries is as high as 94%, as compared to 11% in the choriocapillaris

Glial cells of the retina include macroglia, composed of RMG cells and astrocytes, and microglia. Their processes wrap around retinal capillaries to form a glia limitans. Retinal arterioles, venules, and capillaries are closely ensheathed by macroglia. The superficial retinal vasculature is ensheathed by both astrocytes and RMG cells whilst the deep vascular plexus is ensheathed solely by RMG cells. Macroglial cells are key players in the dynamic neuro-glio-vascular unit and they regulate a wide range of endothelial cell functions. Astrocytes and RMG cells both have the ability to induce the formation of competent barriers by vascular endothelial cells. They also stabilize the tight junctions between endothelial vascular cells, and play fundamental roles in local immune responses and immune surveillance. Microglia also contribute to the formation and maintenance of the inner blood-retinal barrier, mostly through production of soluble factors but also through vesicular communication and gap junctions.

2. The outer blood-retinal barrier

The outer blood-retinal barrier is classically defined as the intercellular junction complex of the RPE, separating the neuroretina from the choroidal circulation. The outer limiting membrane (OLM) also contributes to the outer blood-retinal barrier function.

The junctional complex of the RPE is formed, just like in other highly polarized epithelia, by tight, adherens, and gap junctions. The transepithelial resistance is much lower than the resistance of the interendothelial junctions at the inner blood-retinal barrier. However, the estimated transepithelial resistance of human adult RPE (around 80 ohm·cm^2) efficiently prevents water and protein entry from the choroid to the subretinal space, and allows water exit towards the choroid following an osmotic gradient. The RPE junction complex also participates to the regulation of RPE cell shape, polarity, and proliferation control through the interaction with specific cytoskeletal, adapter and effector proteins.

The polarized organisation of RPE cells creates differential compartments. RPE apical microvilli are in contact with the immune privileged subretinal milieu, whereas RPE basal and lateral cell membranes are in contact with a protein enriched fluid, emanating from the choroid, that provides compounds critical for retinal metabolism, including retinol-binding protein needed for retinol uptake that is essential for the visual pigment cycle.

The OLM is formed by heterotypic tight-like and adherens junctions, located at the interface between RMG cells and photoreceptor inner segments. The exact role of the OLM in the regulation of fluid movements across the macula is not fully understood. Earlier studies have demonstrated that the OLM is a barrier to protein diffusion. Biotinylated protein probes of known Stokes radius were used to determine the pore size of the OLM on *ex vivo* rabbit retina. The Stokes radius is the effective theoretical radius of a given molecule in a hydrated state that influences its movement in solution. This experiment estimated the pore radius of the OLM junction to be between 30 and 36 Å, much smaller than albumin and globulins. The OLM thus serves as an important barrier to free protein diffusion across the retina from the inner retinal layers to the subretinal space, and vice versa. This observation should be considered when therapeutic proteins are injected into the vitreous to target sub-RPE pathological processes.

RECOMMENDED READING

Recent

1. Hosoya K, Tachikawa M. The inner blood-retinal barrier: molecular structure and transport biology. Adv Exp Med Biol. 2012;763: 85–104.
2. Rizzolo LJ, Peng S, Luo Y, Xiao W. Integration of tight junctions and claudins with the barrier functions of the retinal pigment epithelium. Prog Retin Eye Res. 2011;30:296–323.
3. Rizzolo LJ. Development and role of tight junctions in the retinal pigment epithelium. Int Rev Cytol. 2007;258:195–234.

Classic

4. Antonetti DA, Barber AJ, Khin S, Lieth E, Tarbell JM, Gardner TW. Vascular permeability in experimental diabetes is associated with reduced endothelial occludin content: vascular endothelial growth factor decreases occludin in retinal endothelial cells. Penn State Retina Research Group. Diabetes 1998; 47:1953–1959.
5. Tout S, Chan-Ling T, Holländer H, Stone J. The role of Müller cells in the formation of the blood-retinal barrier. Neuroscience 1993;55:291–301.

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Answers to MCQ's on page 11

1. a. *False*
   b. *True*
   c. *False*
   d. *True*

2. a. *True*
   b. *True*
   c. *False*
   d. *True*
   e. *False*

02

Fluorescein angiography and ICG

PILOTTO E - Italy

MCQ's

1. **About fluorescein angiography (FA):**
   a. Fluorescein binds to serum proteins with a percentage of 40%
   b. The major choroidal vessels are impermeable to both bound and free fluorescein
   c. Fluorescein has excitation at 520 to 530 nm (yellow-green wavelength) and emission spectrum in the blue part of the spectrum
   d. Staining results from the retention of the dye in tissues
   e. Hypofluorescence fully obscures choroid when due to blood retention in the sub-RPE

2. **About indocyanine green (ICG) angiography (ICGA):**
   a. ICG is a water-soluble dye with excitation and emission spectra in the infrared
   b. Most ICG is retained within choroidal vessels because of the size of the molecule
   c. ICG is less suitable for the study of choroidal vasculature, compared to FA
   d. Late phases of ICGA are evaluated at 10 minutes after injection
   e. In ICGA, a "wash out" effect is represented by strong hyperfluorescence in early frames with diffuse hypofluorescence in the late frames

3. **In central serous chorioretinopathy:**
   a. Imaging with ICG is usually not recommended
   b. On FA, a typical pattern is a leaking point and leaking of the dye in the subretinal space
   c. A leaking point may not be detected by FA several days after acute onset of the disease
   d. FA is usually performed to detect dilated choroidal vessels
   e. In chronic or recurrent disease, multiple focal leaks or diffuse areas of leakage may be found

4. **In inflammatory retinochoroidal disorders:**
   a. Combined use of FA and ICGA is usually recommended.
   b. Hypofluorescent spots in ICGA are usually less numerous than those detected on FA
   c. FA is relevant to detect vascular leakage and optic nerve involvement
   d. An acute inflammatory focus is usually hypofluorescent on early frames of both FA and ICGA
   e. Hyperfluorescence in FA of an inflammatory spot in the late frames is almost always a sign of active disease

DESPITE ENORMOUS PROGRESS in investigational procedures for retinal disease, fluorescein (FA) and indocyanine green angiography (ICGA) still remain two essential imaging techniques to accurately evaluate, diagnose, and guide the treatment in patients with retinal vascular, degenerative, and inflammatory disorders. As with any intravenous contrast agent, the use of fluorescein and indo-cyanine green requires precautions because of risk of allergy and severe adverse reactions.

The basic principle is *fluorescence*, which is the property of some molecules to emit light of a longer wavelength when stimulated by light of a shorter wavelength. The use of cameras with specific exciter and barrier filters allows the visualisation of a specified wavelength light. Intravenous injection of molecules with specific absorption and emission spectra – fluorescein and indocyanine green (ICG) – allows visualisation of the retinal vascularisation and registration of the images. The introduction of high-resolution digital fundus cameras and confocal scanning laser ophthalmoscopes (SLO) has progressively improved this imaging technique.

Cameras differ according to the fundus area included in the photographs. Fundus cameras may range from 35° standard to 200° wide-field camera systems. Wide-angle angiography has the advantage of capturing a single image of the retina in high resolution, well beyond the equator, allowing e.g. the acquisition of an excellent clinical picture of non-perfused peripheral retina.

1. Fluorescein angiography (FA)

Fluorescein is an orange water-soluble dye. Once injected intravenously it largely (>70%) binds to serum proteins, particularly to albumin, and is excreted in the urine over 24–36 hours. It has a spectrum of excitation at 465 to 490 nm (in the blue part of the spectrum), and emission at 520 to 530 nm (yellow-green wavelength).

The major choroidal vessels are impermeable to both bound and free fluorescein. Conversely, the walls of the choriocapillaris contain fenestrations through which unbound molecules rapidly escape into the extravascular space, crossing Bruch's membrane. However the intercellular tight junctions (zonulae occludentes) between RPE cells block the passage of fluorescein and constitute the outer blood-retinal barrier.

In the retina, the tight junctions between retinal capillary endothelial cells are main constituents of the inner blood–retinal barrier across which neither bound nor free fluorescein can pass.

The progressive filling of choroidal and retinal vessels consists of different phases: the choroidal filling about 15 s after injection, the arterial phase 1 to 2 s later, the following arteriovenous and venous phases, and the recirculation phase, which occurs about 45 s after the arterial phase.

Hyperfluorescence may result from escape of the dye through the blood-retinal barrier (leakage), retention of the dye in the tissue (staining), pooling of the dye in fluid-filled spaces, or a window defect mainly due to RPE alterations. The two main causes of hypofluorescence are a filling defect and blockage of fluorescence due to the presence of obstacles such as blood or pigment.

2. Indocyanine green angiography (ICGA)

ICG is a water-soluble dye with both excitation and emission spectra in the infrared wavelengths. About 98% of ICG molecules bind to serum proteins. Therefore, as choriocapillaris fenestrations are impermeable to larger protein molecules, most ICG is retained within the choroidal vessels. Moreover, the near-infrared light utilized in ICGA penetrates ocular pigments such as melanin and xanthophyll, as well as retinal exudate and small amounts of subretinal blood, making this technique suitable for the study of choroidal vasculature, unlike FA. Thus ICGA is mainly indicated to study pathology involving the choroidal vasculature, where FA may not be accurete enough.

The main phases of ICGA are: the early phase up to 60 s post-injection; the early mid-phase, 1–3 min; the late mid-phase, 3–15 min; and the late phase, 15–45 min.

Causes of hyperfluorescence may be a window defect and leakage from retinal or choroidal vessels, the optic nerve head, or the RPE, which may give rise to staining or pooling.

Moreover, abnormal retinal or choroidal vessels with an anomalous morphology may exhibit greater fluorescence than normal.

Hypofluorescence may be due to blockage of fluorescence and filling defects. A particular phenomenon to note is that, in contrast to its FA appearance, an RPE detachment will appear predominantly hypofluorescent on ICGA.

3. FA and ICGA in retinal diseases

The use of FA and ICGA involves a multitude of different retinal diseases. Some main pathological features may be identified.

Choroidal neovascularization (CNV) characterises the neovascular form of age-related macular degeneration (wet AMD), but it can be associated also with other pathologic conditions such as degenerative myopia, or it may be idiopathic.

In wet AMD, the FA appearance can be highly variable because of the possible concurrence of haemorrhages, exudates, RPE pigmentary changes, or RPE detachment. Based on the FA, CNV is classified as either classic or occult form. Classic CNV (located between the RPE and the neurosensory retina, also called type 2, according to their appearance on optical coherence tomography [OCT]) is already visible at the onset of the early phase. CNV has hyperfluorescent borders because of a higher density of vessels, and it can be surrounded by outer zones of hypofluorescence, making it easily seen. During the course of the angiographic study, a marked leakage from the vascular membrane becomes evident that causes the margins of the CNV membrane to become increasingly indistinct. In the late phase, diffuse leakage spreads over a broad area. The term occult CNV is used to describe CNV the limits of which cannot be fully defined on FA. Occult CNV is located under the RPE (Type 1 on OCT). Predominantly or minimally classic CNV is present when the classic element is greater or less than 50% of the total lesion, respectively. ICGA visualizes CNV as a focal hyperfluorescent "hot spot" or "plaque". The use of ICGA is

particularly indicated to identify other chorioretinal pathologies, such as polypoidal choroidal vasculopathy (PCV), retinal angiomatous proliferation (RAP) and central serous chorio-retinopathy. Combined use of FA and ICG is usually recommended when approaching them.

PCV is a circumscribed choroidal lesion characterised by a branching vascular network of inner choroidal vessels with multiple terminal aneurysmal protuberances (polyps) that appear to be the source of bleeding and exudation. FA shows leakage in the affected area. ICGA has a key role in the diagnosis, being able to clearly identify it. Hyperfluorescent choroidal nodules, usually associated with a network of large choroidal vessels, appear in the early/mid frames.

RAP is a particular form of wet AMD (Type 3 CNV on OCT) in which the neovascular process originates in the retina. Thus, RAP appears on FA as focal area of intraretinal hyperfluorescence. ICGA is diagnostic in most cases, showing a hot spot in mid frames, late frames, or both, and frequently a perfusing retinal arteriole and a draining venule ("hairpin loop" when these are linked).

In pathologic myopia, CNV is usually well demarcated on FA from the early phases. However, when haemorrhage is present, it is not unusual for FA to fail in correctly identify the CNV. Lacquer crack formation is a possible source of retinal haemorrhage, subretinal bleeding, or both. In ICGA, lacquer cracks appear as hypofluorescent lines in the late frames of the angiogram

Central serous chorioretinopathy can readily be diagnosd on FA and ICG. In fact, FA shows a highly characteristic picture of an early hyperfluorescent spot that gradually enlarges, described as an "ink blot" or, less commonly, forms a vertical column ("smokestack"), followed by diffusion throughout the detached area of neuroretina. An underlying pigment epithelial detachment (PED) may be also demonstrated, when present. In chronic or recurrent disease, multiple focal leaks or diffuse areas of leakage may be found. On ICGA, the early phase may show dilated or compromised choroidal vessels at the posterior pole, and mid stage areas of hyperfluorescence frrom choroidal hyper-permeability. Subclinical foci are commonly visible. CNV must also be ruled out.

Retinal vascular disease such as occlusion and diabetic retinopathy, still represents an important if not essential indication for FA to clearly visualise delayed vascular filling, macular and peripheral areas of augmented vascular permeability or non-perfusions and epiretinal neovascular vessels (visible as quickly progressive hyperfluorescent focal areas). It allows individualised treatments. FA also allows clear distinction between microaneurysms and small haemorrhages, the former being progressively hyperfluorescent, the latter hypofluorescent from masking effect. Moreover, FA can identify leaking microaneurysms that can cause macular oedema.

Macular oedema is characterized by progressive leakage of fluid from the perifoveal capillaries. Fluorescein later collects in fluid filled spaces (cysts), which becomes clearer as the background fluorescence fades. ICGA does not play a significant role in retinal vascular disorders.

Inflammatory retinochoroidal diseases call for routine FA to get good evaluation of inflammation and use it as one follow-up parameter. The most common finding on FA that corresponds to active choroiditis is early hypoflourescence with late hyperflourescence whereas, on ICGA, the hypofluorescent spots identify areas of active involvement, sometimes revealing more extensive involvement as compared to FA. The former often furnishes additional information, otherwise undetectable, bout the choroidal compartment. Several inflammatory choriocapillaropathies (multiple evanescent white dot syndrome [MEWDS], multifocal choroiditis, acute posterior multifocal placoid pigment epitheliopathy [APMPPE], and others) present with minimal signs on funduscopy but with extensive choroidal involvement. Therefore, dual FA-ICGA should be performed for the assessment and follow-up of posterior uveitis.
Moreover, angiography is essential to differente an acute inflammatory focus in the macula from a secondary CNV, e.g. in multifocal chorioretinopathy syndromes. In this case the inflammatory focus will be hypofluorescent, whereas the CNV will be hyperfluorescent through all phases of the ICG angiogram.

Intraocular tumours can, besides its documentary function, be evaluated by FA. The essential clinical importance of FA in the evaluation of choroidal and retinal tumours lies in the differential diagnosis. Usually, FA shows blocking of fluorescence by lesions such as choroidal melanoma or metastases. However, because of the clinical variability in the presentation of these lesions, the FA features also are variable. Sometimes ICGA has the potential to visualize the intrinsic vascular network (dual circulation) of a melanoma that is absent from choroidal metastases. A quite characteristic pattern is that of choroidal haemangioma, which shows a strong hyperfluorescence in early ICGA frames with diffuse hypofluorescence later on (i.e., a "wash out" effect).

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Answers to MCQ's on page 16

1. a. *False*
   b. *True*
   c. *False*
   d. *True*
   e. *False*

2. a. *True*
   b. *True*
   c. *False*
   d. *False*
   e. *True*

3. a. *False*
   b. *True*
   c. *True*
   d. *False*
   e. *True*

4. a. *True*
   b. *False*
   c. *True*
   d. *True*
   e. *False*

OCT: from anatomy to imaging

MIERE A - France

MCQ's

1. **On OCT, the following layers apprear as hyperreflective:**
   a. Nerve fiber layer
   b. Inner plexiform layer
   c. Inner nuclear layer
   d. External limiting membrane
   e. Retinal pigment epithelium;

2. **Swept source OCT:**
   a. Has a shorter wavelength than SD-OCT
   b. Has a longer wavelength than SD-OCT
   c. Has a lower axial resolution than SD-OCT
   d. Allows deeper tissue penetration
   e. Has a better signal to noise ratio

3. **The following statements are true concerning the capillary plexa:**
   a. The superficial plexus is located in the inner nuclear layer
   b. The deep plexus is located on the inner border of the inner nuclear layer
   c. The intermediate plexus is located on the outer border of the inner nuclear layer
   d. The deep plexus is located on the outer border of the inner nuclear layer
   e. The superficial plexus is located in the ganglion cell layer

4. **The following retinal disorders are associated with an increase in choroidal thickness:**
   a. high myopia
   b. central serous chorioretinopathy
   c. advanced age-related macular degeneration
   d. polypoidal choroidal vasculopathy
   e. retinitis pigmentosa

OPTICAL COHERENCE TOMOGRAPHY (OCT) technology has tremendously evolved since it was first described in the 1990's by Huang and colleagues with significant improvement in signal detection, progressing from time-domain (TD) to spectral-domain (SD) and swept source (SS) OCT. This evolution has subsequently allowed more precise and faster study of various retinal and choroidal layers. These structural imaging techniques – SD-OCT and SS-OCT – and the novel OCT angiography (OCTA) are non-contact, non-invasive techniques and provide essentially static information of the normal and pathological retinal and choroidal microvessels (as opposed to conventional angiography that provides dynamic information). The progressive increase in resolution and speed of OCT instruments has generated a paradigm shift in clinical management and evaluation of treatment response in macular disease, from diabetic retinopathy and diabetic macular oedema to retinal vein occlusion and age-related macular degeneration (AMD), t the same time allowing a better understanding of their pathogenesis.

1. The principle of OCT

OCT is based on interferometry and uses light waves to create high-resolution cross-sectional images. Moreover, a Fourier analysis of the fringe pattern, produced by the interference between the light from a reference arm with the light backscattered from different layers, will create a reflectivity profile in depth with a resolution of 5 to 6 µm. Thus, OCT images will consist of alternating bands of hyper- and hyporeflectivity. Unlike SD-OCT, which has a shorter wavelength, a better axial resolution and a better signal to noise ratio, SS-OCT employs a longer wavelength than spectral domain OCT, which enables light penetration to deeper ocular tissues with a better visualisation of the choroid, despite a lower axial resolution and a lower signal-to-noise ratio.

2. Histology-imaging correlations

Given that OCT is often compared to "optical biopsy" that provides cross-sectional images of tissue structure on the µm scale, histology is logically considered as the gold standard for the validation of OCT images. Interestingly, throughout literature, a progressive inclusion of certain anatomic features with each new generation of OCT instruments can be observed. Consequently, histology-imaging correlations on both animal and human eyes reveals an increasing accuracy in the layers detected by means of OCT. In a study from 2011, Curcio and colleagues performed the first graphical representation and thickness database of retinal and choroidal layers in normal human macula, demonstarting good agreement for retinal thickness in OCT and histology.

Proper understanding of normal macular layers plays a central part in interpreting morphological changes in retinal disease. We will address histology-imaging correlations in the normal macula, as well as in retinal disease.

The basics of OCT interpretation include:

Classification of retinal layers on OCT: nuclear layers are in general hyporeflective whereas plexiform layers are in general hyperreflective.

The inner retina contains the three capillary vascular plexi (superficial capillary plexus located in the ganglion cell layer; and intermediate and deep capillary plexus located at the inner and outer border zone of the inner nuclear layer (INL), respectively) and will present morphologic alterations in retinal vascular disease. In retinal arterial occlusive disease, acute ischaemia will generate a thickened, hyperreflective inner retina. Deep capillary ischaemia has the appearance of a hyperreflective deep lesion with defined edges, corresponding to paracentral acute middle maculopathy (PAMM) that has been reported in association with various retinal diseases such as retinal venous occlusion, retinal arterial occlusion, and diabetic retinopathy. Conversely, chronic ischaemia will generate a thinning of the affected retina.

The outer retina will be the most likely location for fluid accumulation (subretinal or intraretinal fluid), usually in the context of macular oedema: diabetes, retinal vein occlusion, inflammation, and choroidal neovascularization. Cystic changes within the outer retina will appear hyporreflective. Outer retinal atrophy may develop in eyes with regression of subretinal drusenoid deposits. Eearly Treatment Diabetic Retinopathy Study (ETDRS) subfield analysis may indicate absolute and relative changes on OCT images during follow-up.

The retinal pigment epithelium (RPE)-Bruch's membrane complex may show an RPE elevation from presence of drusen or from a RPE detachement (PED). The latter will show of a hyporeflective area under the elevated RPE if serous, whereas it will be heterogenous/ mulilaminar/hyperreflective if vascularised (type 1 macular neovascularisation). Hyporeflectivity above the RPE is suggestive of subretinal fluid accumulation, whereas hyperreflectivity above the RPE is suggestive of type 2 macular neovascularisation. Fuzzy hyperreflectivty above the RPE can correspond to subretinal hyperreflective material (SHRM), whereas a well-delineated subretinal hyperreflective, dome-shaped lesion is somewhat suggestive of vitelliform material.

Choroidal thickness measurements using SS-OCT or the enhanced depth imaging (EDI) option of SD-OCT may also generate interesting information. Choroid can be measured on OCT manually perpendicularly from the outer edge of the hyperreflective RPE to the inner sclera (choroid–sclera junction). The choroid is thickest in its subfoveal region and thinner in the nasal and temporal regions. The mean subfoveal choroidal thickness is approximately 300 µm. Increased choroidal thickness and presence of pachyvessels may be suggestive of pachychoroid spectrum disorders, such as pachychoroid pigment epitheliopathy, central serous chorioretinopathy, and polypoidal choroidal vasculopathy. Conversely, eyes with high myopia, AMD or retinitis pigmentosa have thinner than average choroids.

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Answers to MCQ's on page 23

1. a. *True*
   b. *True*
   c. *False*
   d. *True*
   e. *True*

2. a. *False*
   b. *True*
   c. *True*
   d. *True*
   e. *False*

3. a. *False*
   b. *False*
   c. *False*
   d. *True*
   e. *True*

4. a. *False*
   b. *True*
   c. *False*
   d. *True*
   e. *False*

OCT angiography

STAURENGHI G, Italy

For your notes

05

Immune tolerance and its alteration

DICK A - United Kingdom

MCQ's

1. **In the pathophysiology of ocular inflammation:**
   a. Uveitis is caused predominantly by antibody-directed cytotoxicity
   b. The choroid is a potent immunoregulatory environment
   c. There is close link between infection and the expression of non-infectious intraocular (uveitis) inflammatory disease
   d. CD4 T-cells always augment the inflammatory response
   e. Activation of the inflammasome (autoinflammation) generates a potent pro-inflammatory cytokine IL-10

2. **Regulating intraocular inflammatory responses include:**
   a. Secretion of interferon alpha from resident ocular cells
   b. Natural killer T-cells in the eye
   c. Fas-ligand expression in the eye
   d. Secretion of IL-10 from retinal cells
   e. Activation of retinal vascular endothelium

3. **When considering the immune constituent during intraocular inflammation:**
   a. Retinal vasculitis is always associated with ANCA-mediated cytotoxicity
   b. B-cells are plentiful in the uvea of chronic uveitis
   c. TGF beta is a primary mediator of macrophage activation
   d. Chorioretinal granulomas consist principally of macrophages
   e. Microglia are potent antigen presenting cells

4. **When considering the anatomy of the immune system in the eye:**
   a. Rhe retina has a rich network of dendritic cells
   b. No anatomical lymphatic drainage from the retina to regional lymph nodes exists
   c. the inner blood-retinal barrier prevents trafficking of immune cells
   d. The sclera has an abundance of lymphoid tissue
   e. The retinal pigment epithelium secretes complement

THE EYE WAS TRADITIONALLY DEFINED as an immune privileged site. In particular the description adapted from the work of Medawar and corneal immune privilege lay the foundation to under-standing why the eye (or cornea specifically) permitted successful corneal transplantation. We now recognise and understand several facts and clinical features that demonstrate that the eye and the tissues within (cornea, uvea and retina) are immune competent and display active mechanisms to regulate immune responses and, therefore, are highly susceptible to immune-mediated damage. This is either direct through autoimmune responses or indirect via autoinflammatory responses, systemic inflammatory disorders, or both (such as sarcoidosis, Behçet's disease, or cryopyrin-related disorders), immune-mediated pathways activated during ageing and in degeneration (e.g., complement activation and age-related macular degeneration).

1. Immunity and the eye

All tissues of the eye are endowed with a network of immune cells. Whilst it remains the eye does not have an anatomical lymphatic drainage system or directly associated secondary lymphoid tissue, the eye regulates immune responses through regulation of blood-ocular barriers (and this is significantly so for the blood-retinal barriers: retinal vascular endothelium and retinal pigment epithelium), immune regulatory responses of the immune cells (e.g., retinal microglia, corneal dendritic cells, retinal pigment epithelium), and a liquid phase (aqueous and vitreous) that has potent immune suppressive and regulatory molecules (TGF beta, alpha-MSH, VIP).

Whether ocular antigens are sequestered, and autoreactive T-cells are deleted from the thymus during development has been dispelled (at least in mouse!), and ocular antigens are expressed in the thymus. Not surprisingly, therefore, we note in man a significant prevalence of anti-retinal antibodies and autoreactive T-cells in the circulation.

The evidence suggests that in man some uveitic conditions are likely to be T-cell immune-mediated disorders. The T-cell compartment (CD4 and CD8) is plastic but through canonical genes and transcription factors differentiates into three broad classes. Th1 cells (interferon gamma), Th2 cells (IL-4 and IL-13). and Th17 cells (IL-17). All these cells if driven through antigen recognition (e.g., virus, cancer cells, self-antigen) are pathogenic. To combat (or regulate) the potential to develop T-cell mediated or autoimmune inflammation, also T regulatory cells exist that systemically and within the tissue prevent or attenuate such pathogenic responses. As such the term immune tolerance now applies to that derived through auto-reactive T-cell deletion during thymic development (central tolerance) and ongoing in adult life (peripheral tolerance).

Most recently we recognise that the microbiome (particularly the gut) is instrumental to maintain immune health and tolerance.

2. The clinical dilemma

Not surprisingly the eye is a target of immune-mediated damage. The breakdown of the blood -retinal barrier removes a major part of immune privilege as now the eye is open to infiltration of immune cells from the circulation. The choroid is vascular and relatively densely populated with immune cells (macrophages and dendritic cells) as is the anterior uvea, and both tissues are highly susceptible to systemically mediated inflammatory damage (e.g., spondyloarthropathies, sarcoidosis).

The regulatory pathways in the eye are undoubtedly potent (the low incidence of post-operative endophthalmitis), but are perturbed through genetic variants as seen in the complement genes increasing the susceptibility to complement activation and development of neurodegeneration (AMD). If we reflect, we may observe several clinical scenarios (and not an exhaustive list) that demonstrate immune tolerance breakdown (loss of regulation). Firstly, *CFH* gene polymorphisms and AMD susceptibility; secondly, the systemic immune activation that drives inflammation in the eye (Behçet's disease and seronegative spondyloarthropathies, or infectious in tubeculosis -associated uveitis); thirdly, high level of rejection of corneal grafts in vascularised beds and, finally, the panoply of infectious uveitis not confined to immune compromised hosts.

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Answers to MCQ's on page 29

1. a. *False*
   b. *False*
   c. *True*
   d. *False*
   e. *False*

2. a. *False*
   b. *False*
   c. *True*
   d. *True*
   e. *False*

3. a. *False*
   b. *True*
   c *False*
   d *True*
   e. *False*

4. a. *False*
   b. *True*
   c *False*
   d. *False*
   e. *True*

06

Serous retinal detachment

MIDENA E - Italy

MCQ's

1. **About the adhesion between RPE and neuretina:**
   a. Different types of junctions contribute to maintain the adhesion
   b. Under normal circumstances, intraocular fluids flow from the vitreous cavity to the choroid
   c. The interphotoreceptor matrix contributes to the adhesion between the neuroretina and the RPE
   d. The adhesion is maintained exclusively by active transport mechanisms
   e. The neuretina acts as a "water pump".

2. **The choroid:**
   a. Is not involved in the pathogenesis of serous retinal detachment
   b. Has a proper innervation only by sympathetic fibers
   c. Has a proper autoregulation of the blood flow
   d. Its vessels are responsive to molecules such as epinephrine and angiotensin with vasoactive function
   e. The solutes and molecules in the choroidal vessels and interstitium are responsible for osmotic forces involved in the fluids flow

3. **In central serous chorioretinopathy:**
   a. RPE dysfunction has a relevant role
   b. Choroid permeability seems to be reduced
   c. Systemic steroids may influence its development
   d. Leakage of dye is better seen on indocyanine green than fluorescein angiography
   e. It usually involves the mid periphery

4. **Serous (exudative) retinal detachment**
   a. May develop secondary to choroidal tumours because of a dysregulation of the retinal inflammatory and reactive mechanisms
   b. Among inflammatory diseases, is rare in Vogt-Koyanagi Harada syndrome
   c. Cannot be directly caused by a systemic condition
   d. May characterise a distinct phenotype of macular edema
   e. Whatever its cause, steroid injections have proved to reduce this type of detachment

SEROUS RETINAL DETACHMENT (SRD) may appear in many ocular and systemic conditions, but even if it appears similar in each of them, it may be completely different in pathophysiology with similarly different targeted therapeutic strategies. A brief anatomic and functional recall is essential to understand how the interrelations of the neurosensory retina with the RPE, the Bruch's membrane and the choroid are maintained in physiologic conditions, and to understand the consequences of ocular diseases where these mechanisms fail.

1. Maintenance of retinal adhesion

A complex interaction of forces keeps the neuroretina perfectly adherent to the RPE: the balance between active and passive forces keeps the anatomical retinal relationships intact. The correct adhesion between neuroretina and RPE is necessary to maintain the neuronal activity. Under normal conditions, there is a continuous balance between hydrostatic, osmotic, and active transport mechanisms in order to keep the apposition between the retinal layers (neuroretina) and the RPE. The RPE is also responsible for the Ph control and it produces several molecules implicated in angiogenesis, vessel dilation, and neuroprotection.

In humans, many types of junctions are usually needed to attach cells to each other. Nevertheless, the retina represents an exception to this rule. In fact, because of the embryologic mechanisms, the apical surface of the neuroretina is in contact with the apical RPE and these cells adhere to each other without cell-to-cell junctions. Under normal circumstances, intraocular fluids flow from the vitreous cavity to the choroid. The retinal tissue offers a mechanical resistance to this flow of fluids, while the RPE, through passive and active forces and phagocytosis behaves as a "water pump".

The apical surface of RPE cells is characterised by numerous microvilli. The microvilli interdigitate between the outer segments of photoreceptors whereas a specialised extracellular matrix, the interphotoreceptor matrix, fills the virtual space between them and contributes to the adhesion between the neuroretina and the RPE.

Conversely, the lateral surface of RPE cells is characterised by the presence of junctions, such as desmosomes, zonulae adherentes and zonulae occludentes that maintain adhesion between cells and represent the outer blood-retinal barrier. They also prevent the free diffusion of fluids, ions and molecules, controlled by the RPE through active channel- and pumps-regulated mechanisms.

Another important role in the pathogenesis of SRD is played by the choroid. It has an innervation by sympathetic and parasympathetic fibers. Moreover, it shows autoregulation of blood flow, and its vessels respond to selected molecules such as epinephrine and angiotensin with vasoactive function. The solutes and molecules in its vessels and interstitium are responsible for osmotic forces reinforcing the currents of fluid from the vitreous to the choroid itself.

2. Clinical conditions presenting with SRD

Central serous chorioretinopathy **(CSC)** is a condition characterised by a serous detachment of the neurosensory retina with or without a concomitant localised RPE detachment. It usually affects the posterior pole with foveal involvement and, consequently, visual discomfort that

most often affects young and middle-aged adults. The RPE is thought to play the most relevant role in the pathophysiology of CSC as it maintains the integrity of the outer blood-retinal barrier. A RPE loss of activity has been hypothesised as RPE could be susceptible to increased hydrostatic pressure in the choroid, an ischemic insult, or inflammatory and hormonal influences. In acute CSC, leakage of dye usually occurs from a precise point, seen when performing fluorescein angiography. This point is thought to be the site of fluid flow from the choroid to the subretinal space. However, some authors demonstrated that in the site of the focal RPE defect, an outflow from the subretinal compartment toward the choroidal space can also be observed. In fact, it was recently hypothesised that choroidal circulation also plays a significant role in the pathogenesis of CSC. Choroidal hyperpermeability has in fact been documented, particularly using indocyanine green angiography. It may be a consequence of several mechanisms such as vascular stasis, inflammation, or ischemia. The corresponding increase in hydrostatic pressure in the choroidal compartment could overwhelm the pump functions of the RPE and, in accordance with a simple mechanical theory, lead to progressive fluid accumulation in the subretinal space. Anyway, the exact causes leading to vascular hyperpermeability remain unclear. A self-regulation of the choroidal circulation exists, and in CSC it seems influenced by the level and activity of steroid molecules, catecholamines and sympathomimetic agents. This retinal disease seems therefore to be multifactorial in its pathophysiology, leading to a variability in current therapeutic strategies of this retinal disorder and in clinical response to treatments.

Vascular malformations (e.g., haemangioma) may lead to SRD because of an increased hydrostatic pressure in the choroid that overwhelms the reabsorption mechanisms of the RPE. **Choroidal tumours** (e.g., choroidal melanoma, choroidal naevus) may have increased hydrostatic pressure within the tumour tissue, consequently affecting the perilesional choroid and RPE. Moreover, the presence of a tumour may alter the normal retinal environment, causing a dysregulation of the retinal inflammatory and reactive mechanisms with hyperproduction of inflammatory cytokines. The production of proinflammatory mediators may promote the development of the SRD and, after radiation treatment, the damaged tumour cells and healthy retinal cells may enhance these phenomenons in so called "tumour toxic syndrome".

Impaired outflow through the sclera (i.e., uveal effusion syndrome) causes SRD because of the excessive accumulation of fluid. **Inflammatory conditions** of the choroid and posterior sclera (e.g., Vogt-Koyanagi Harada syndrome, posterior scleritis) may induce a SRD secondary to diffuse vascular hyperpermeability and RPE disfunction due to inflammation. **Venous vascular diseases** are characterised by significant vascular leakage, leading to fluid accumulation.

Systemic conditions (e.g., malignant hypertension, praeeclampsia, pro-thrombotic conditions) may lead to SRD secondary to a combination of mechanisms such as hyperpermeability, ischemia and tissue necrosis.

In retinal disease such as diabetic maculopathy and venous occlusions, SRD may be a specific clinical feature associated with macular oedema. In these conditions, SRD seems to characterise a distinct phenotype of macular oedema associated with inflammation (higher concentration of inflammatory cytokines) and choroidal hyperpermeability, providing relevant elements for the therapeutic approach.

The manifestations of different conditions leading to the appearance of SRD are highly variable. It is therefore recommended to perform a complete multimodal retinal imaging (including in particular spectral domain optical coherence tomography, fluorescein and indocyanine green angiography) and systemic investigations, when needed, before starting a therapeutic approach. Treatment is highly dependent on the origin of the detachment and on the amount of fluid present under the neuroretina, and the strategy may differ widely between the different conditions. Treatment can consist of a systemic and a local approach, including subthreshold micropulse laser, photodynamic therapy, steroid intravitreal injections, etc, depending on the main pathophysiologic mechanisms involved.

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Answers MCQ's page 34

1. a. *False*
   b. *True*
   c. *True*
   d. *False*
   e. *False*

2. a. *False*
   b. *False*
   c. *True*
   d. *True*
   e. *True*

3. a. *True*
   b. *False*
   c *True*
   d *False*
   e. *False*

4. a. *True*
   b. *False*
   c *False*
   d. *True*
   e. *False*

07

Atrophy of the retina

CREUZOT C, France

MCQ's

1. **Concerning the retina:**
   a. The macula measures 5 mm in diameter
   b. The umbo is a small depression, 150 µm diameter
   c. In the fovea, there is an increased density of pigment
   d. Bruch's membrane is made of two different layers
   e. In the inner nuclear layer, horizontal, bipolar and amacrine cells can be found

2. **Concerning SD-OCT:**
   a. The resolution of current SD-OCT is almost 5 µm
   b. Swept source OCT is capable to assess choroidal layers
   c. Interdigitation zone is immediately underneath external limiting membrane
   d. Ganglion cell layer is the most superficial layer in the retina
   e. Normal central retinal thickness is 250 µm whatever the SD-OCT brand

3. **Fundus autofluorescence:**
   a. Its principle is based on macular pigment (lutein and zeaxanthin) detection
   b. Fundus fluorescence is emitted through a broad band from 500 to 800 nm
   c. The normal autofluorescence decreases from the center toward the periphery
   d. Is impacted by media opacity
   e. Can easily localise the foveal center

4. **In dry AMD:**
   a. Drusen can exhibit normal, hypo- and hyperautofluorescent pattern
   b. Pigmentary changes typically appear as focal or linear hyperautofluorescent areas
   c. Reticular pseudodrusen typically look like macular hyperfluorescent round areas
   d. Measurement of lesion size by FAF shows low to intermediate reproducibility
   e. Progression of geographic atrophy is slower in eyes without surrounding hyperautofluorescent patterns

ATROPHY OF THE RETINA is the result of many conditions unlike macular oedema that is clearly defined as a thickening of the retina that in most cases esults from a breakdown of blood-retinal barriers, The following is a non-exhaustive list of circumstances where an atrophy of the retina can be found:

- Essentially physiological (e.g., in myopia)
- Linked to a non-retinal disease (e.g., in glaucoma)
- Linked to age-related diseases (e.g., dry age-related macular degeneration [AMD])
- Associated with hereditary dystrophies
- Miscellaneous (injury, vascular disease, retinal detachment, inflammatory disease…)

To just consider that retinal atrophy as a "thinning" of the retina does not take into account which level of the retina is involved and what is the pathogenesis of the disease. Moreover, an abnormal vitreoretinal interface can modify the automated measurement, masking a real "thinning" of the retina. Finally, one should remind that glial cells – not directly involved in the subtle mechanisms of vision – represent almost one fifth of the total normal thickness of the retina and are implicated in all biochemical features involved in vision.

1. Pathogenesis

As mentioned above, because atrophy of the retina can result from many different diseases, no single pathophysiological mechanism results in atrophy. For instance, in dry AMD, where the underlying mechanisms are still not very well understood, retinal pigment epithelium (RPE), photoreceptors and choriocapillaris all play a role. What remains unknown is the exact order of the impairment cascade leading to atrophy. A hallmark of ageing retina is the accumulation of lipofuscin in the cytoplasm of the RPE cells (making possible the early identification of the dysfunction of the phagocytosis of shed photoreceptors with fundus autofluorescence imaging), and atrophy could be considered a progressive degenerative process. However, even in age-related diseases that result in macular atrophy, other active mechanisms like inflammation and oxidative stress probably play an important role. Finally, all diseases involving vessels in the nerve fiber layers can result finally in atrophy with additional pathophysiological mechanisms, adding even more actors.

2. Diagnosis

Clinical diagnosis. The condition of the patient at presentation is crucial: uni- or bilateral; with familial history of visual impairment or not; acute or progressive; with or without visual loss.Atrophy of the retina can be suspected by an abnormal thinning of the retina but, contrary to macular oedema, it is almost impossible to detect it with biomicroscopy, except in glaucoma where the optic nerve head neural rim can be a surrogate of ganglion cell and fiber layer loss. This is why, in acute vascular disease like central retina arterial occlusion, after the initial whitening and oedema of the retina, the fundus appears almost normal, except sometimes for artery diameter. In high myopia, dry AMD, and more generally in all diseases involving RPE, the diagnosis of "atrophy" is made through the well demarcated areas of absent RPE allowing choroidal vessels to be seen rather than observing reduced retinal thickness. The associated

features like drusen, haemorrhages, lacquer cracks, subretinal scars will help to characterise the retina and, finally, to make the diagnosis. This is why retinal photographs, taken close to clinical examination, remain recommended in clinical trials.

Imaging. Multimodal imaging has changed dramatically diagnostics of retinal atrophy. Spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) imaging are probably the first-line exams to be considered when facing with an atrophy of the central retina. Indeed, SD-OCT will provide cross-sectional morphology of the retina resembling histological assessment. It can identify which level of the retina is involved, especially when a patient complains of a sudden visual loss that took place a long time ago. Moreover, it will provide the physician with a quantitative assessment of the atrophy (retinal thickness and RPE atrophy). FAF exhibits diffuse homogeneous autofluorescence in the normal fundus, whereas retinal blood vessels and optic nerve appear black. In diseases associated with RPE atrophy, dark hypoautofluorescent patches can be identified. In eyes with intermediate AMD, spots of increased or decreased autofluorescence can be found. Other imaging techniques can be useful depending on the suspected cause of retinal atrophy: infrared imaging, fluorescein or indocyanin green angiography, OCT angiography, and also visual field examination or electroretinography, based on initial clinical exam at presentation (see Figures 1 to 5 at the and of the text).

3. Atrophy in AMD

While a dramatic improvement in outcomes has been observed with anti-vascular endothelial growth factor (VEGF) treatments for "wet" exudative AMD, "dry" AMD – so called because of absence of exudative features – remains untreatable. Dry AMD corresponds to a wide range of fundus signs, from drusen and pigmentary changes to well demarcated atrophy of the retina called geographic atrophy. Reticular pseudodrusen, known as a predictor of increased risk of progression to exudative AMD, can be identified as multiple clustered small areas of hypoautofluorescence.

As dry AMD is a progressive disease, visual acuity measurement is not discriminative enough to assess progression of atrophy. A classification has been proposed to describe abnormalities found in early and intermediate AMD. Moreover, different patterns of hyperautofluorescence surrounding the central hypoautofluorescence from atrophy of RPE have been described with different risks for AMD progression (focal, patchy, linear, lace-like or speckled hyperauto-fluorescence). In clinical trials, these aspects as well as the total area of hypoautofluorescence have been recognised as validated primary endpoints. Dry AMD can convert to the neovascular form. The detection of a haemorrhage associated with some exudation on the OCT is very often present before any visual loss reported by the patient. However, in some cases the patient reports on visual loss without exudative complications, simply due to the fact that atrophic zone now involves the central point of fixation. Finally, OCT angiography is a novel technique that can quantify the vascular network. It is a promising imaging device not only for diagnosis but also for better understanding of the pathophysiology.

Differential diagnosis can be challenging when facing a patient with macular atrophy. Macular dystrophies like areolar choroidal dystrophy and Stargardt's disease can be suspected from family history. Examination of the peripheral retina and the results of electrophysiology examination can help to differentiate these diseases. Chronic central serous chorioretinopathy and late-onset pseudovitelliform dystrophy can also exhibit some common features with AMD. Finally, some drug toxicity may resemble dry AMD. All theses circumstances underline the interest to multimodal imaging in central retinal atrophy.

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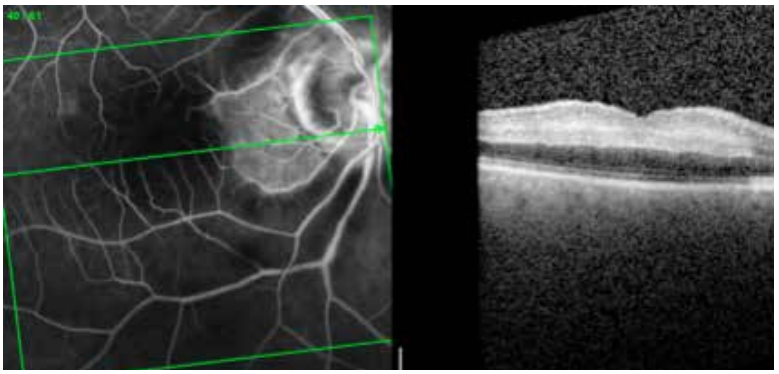
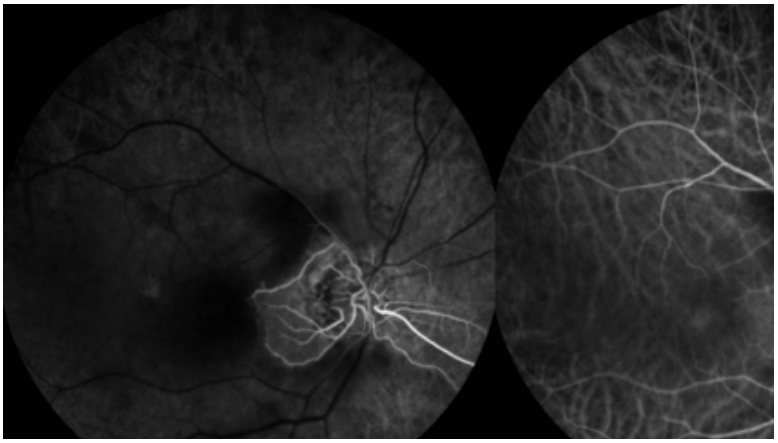
Figures

a





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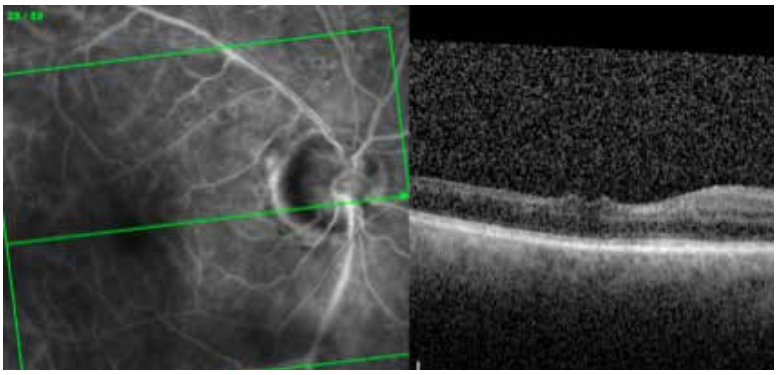


Figure 1 : Central artery retina occlusion: a Angiogram and corresponding OCT; b 1 month later, atrophy of the retina.

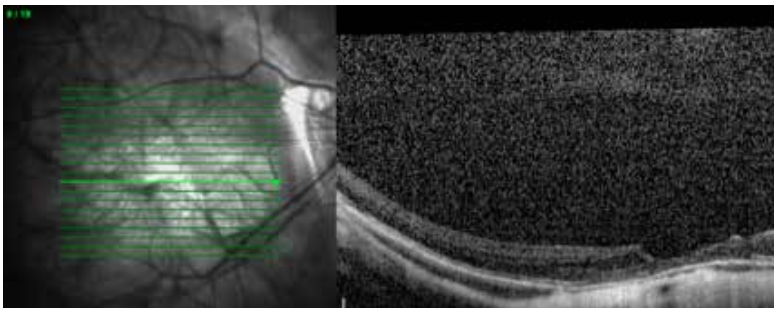
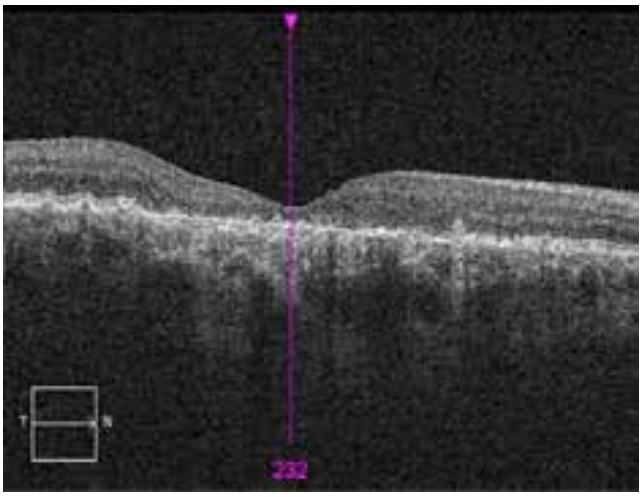


Figure 2 : Atrophy of the retina in a myopic patient (SD-OCT)

a 

Figure 3 : Dry AMD
a. geographic atrophy on colour retinophotography
(continues)

b



c

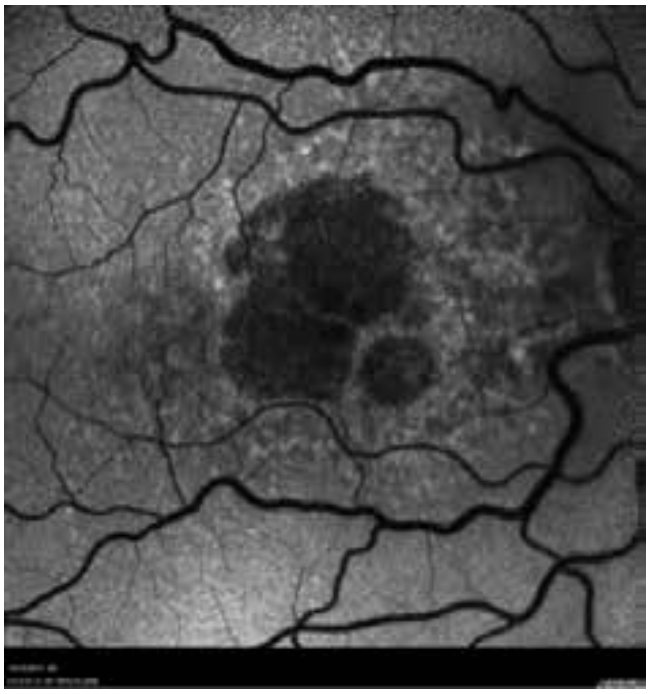
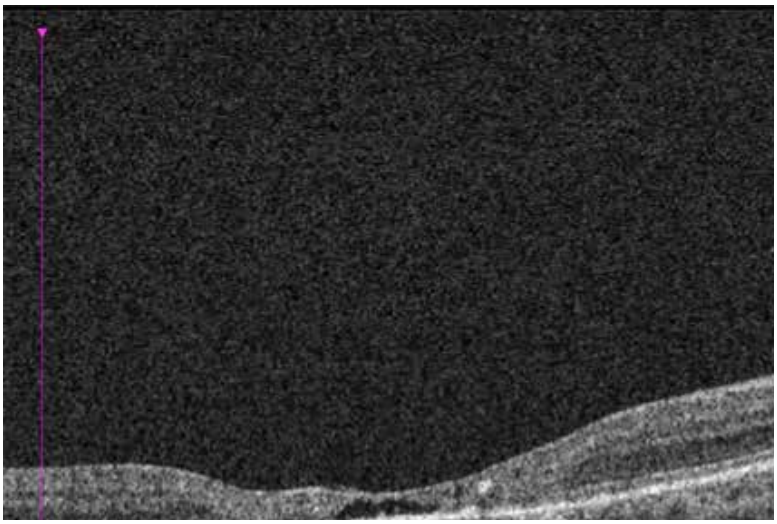


Figure 3 (continued) : Dry AMD
b SD-OCT; c Fundus autofluorescence with well-limited central hypoautofluorecence

a



b

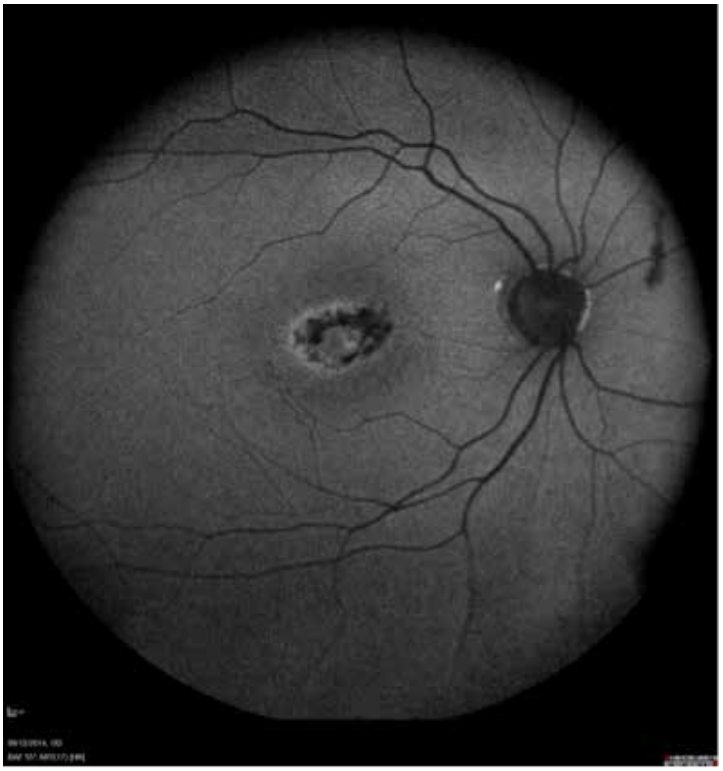


Figure 4 : Atrophy of the retina linked to type 2 macular telangiectasia a SD-OCT; b FAF

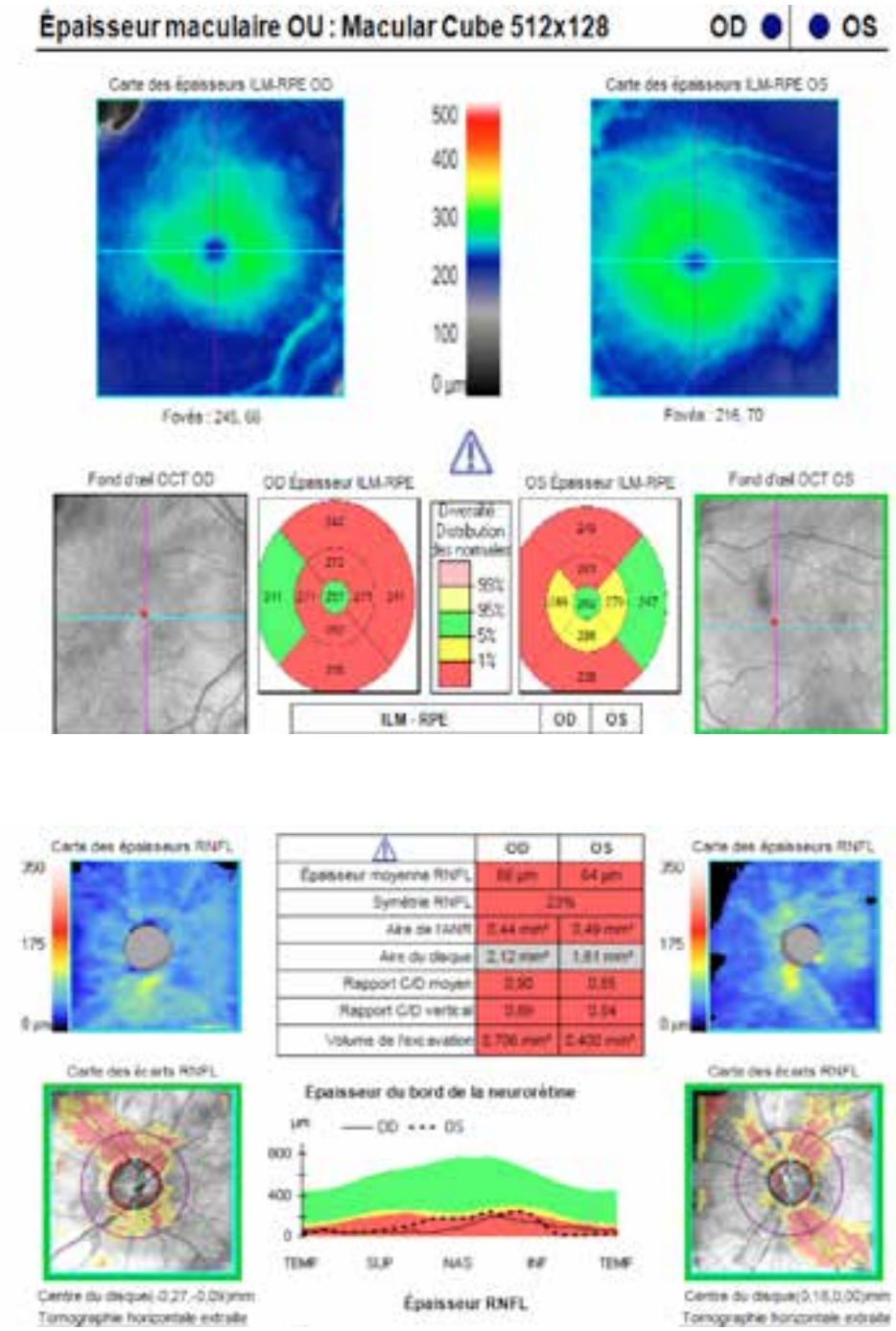


Figure 5 : Patient with severe glaucoma and retina atrophy linked to the loss of nerve fiber layer

Answers to MCQ's on page 40

1. a. *True*
   b. *True*
   c. *True*
   d. *False*
   e. *True*

2. a. *True*
   b. *True*
   c. *False*
   d. *False*
   e. *False*

3. a. *False*
   b. *True*
   c. *True*
   d. *True*
   e. *False*

4. a. *True*
   b. *True*
   c. *False*
   d. *False*
   e. *True*

08

Detachment of pigment epithelium

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PIGMENT EPITHELIAL DETACHMENT (PED) is defined by a collection of fluid or material between the basement membrane of the retinal pigment epithelium (RPE) and the inner collagenous layer of Bruch's membrane. Fluidic PEDs can be either serous or haemorrhagic. Solid PEDs can result from accumulation of drusenoid material or neovascular tissue. PEDs can vary in size, from small drusenoid PEDs to large exudative detachment. They also can vary in number, being either isolated or multiple. A large spectrum of diseases is associated with PED occurrence. However, three main ocular etiologies are responsible for most cases: age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV), and central serous chorioretinopathy (CSC).

1. Pathogenesis

While detachment of the retinal pigment epithelium (RPE) was first described by Gass in 1966, pathophysiological mechanisms resulting in PED occurrence are still debated today. In AMD, for Gass and many other authors, PED would result from the growth of type 1 choroidal eovascularisation (CNV) within Bruch's membrane and CNV-associated active leakage that would be responsible for a local increase in hydrostatic pressure, finally causing PED. The same phenomenon would occur in PCV. In type 3 CNV, retinal angiomatous proliferation (RAP), the neovascularization starts from the inner retina and it has been proposed that the often present serous PED could be related to RPE invasion by the neovascular complex. However, for other authors, PED would precede CNV occurrence and be responsible for CNV development because of PED-associated Bruch's membrane damage. As for CSC, PEDs are present in 70-100% of cases and are thought to be a consequence of dysregulation of fluid reabsorption by the RPE along with increased choroidal vascular permeability. In some cases, a CNV can be associated.

2. Clinical detection

Clinical presentation of PEDs is variable. Functionally, patients can remain asymptomatic or they report blurred vision, metamorphopsia, or both. At fundus examination, except serous PED that can be present without other visible retinal signs, haemorrhagic, drusenoid or neovascular PED is often associated with other retinal lesions guiding the diagnosis. Multimodal imaging allows now better definng PED content, identifying its cause and anticipating its potential evolution.

Drusenoid PED is secondary to RPE failure to clear fluid and debris from the sub-RPE space. At fundus examination, drusenoid PED is associated with early AMD signs and it cannot be clearly distinguished from large soft or confluent drusen with scalloped borders and slightly irregular surface. On OCT images, hyperreflective RPE band appears detached with a hyporeflective area beneath RPE. Neither intraretinal nor subretinal fluid is associated. According to the content of PED, drusenoid PED can either be iso- or hyperautofluorescent. No or few staining is observed when angiography is performed. Anatomical and visual outcomes of drusenoid PEDs are better than those of other types of PED. However, risk of secondary RPE atrophy is high.

Serous PED is due to fluid accumulation. At fundus examination, it appears as circular posterior elevation. On OCT, serous PED is a characteristic well-demarcated, dome-shaped elevation. The choroid is typically thickened. Serous PEDs are hyperautofluorescent with hypoautofluorescent borders. When angiography is performed, serous PEDs disclose an early hyperfluorescence with late pooling without associated leakage, and the borders stay well-defined during the entire sequence. Serous PEDs are hypocynanescent on indocyanine green (ICG) angiography. Their spontaneous evolution towards RPE atrophy is frequent in CSC.

Vascularised PED related to AMD is mostly associated with type 1 CNV but it can also occur with type 3. At fundus examination, vascularised PED is seen as an irregular elevation of the RPE that can be associated with haemorrhages, intraretinal exudates, or both. OCT images show a solid hyperreflective elevation of the RPE band. OCT angiography (OCT-A) often allows to identify an abnormal vascular network. Due to their content, such PEDs are mostly hyperautofluorescent. On fluorescein angiography, vascularised PED is typically hyperfluorescent in the early phase with a late staining as in serous PED, but due to the associated vascularisation, a late-phase leakage can be seen. On ICG angiography, a late hyperfluorescent area allows to identify the associated occult CNV (hot spot or plaque according to the diameter). Risk of vision loss is high and vision can drop suddenly in case of haemorrhage or RPE tear. RPE tear occurs in approximately 10% of cases and can be accelerated after anti-vascular endothelial growth factor (VEGF) injection.

PED associated with PCV show hard exudates and marked haemorrhages are often associated. On OCT scans, the PED is visible and associated with double-layer sign, thickened choroid and sometimes focal choroidal excavation. Presence of subretinal and intraretinal fluid are markers of active exudation and often correlate with an area of leakage on fluorescein angiography. ICG angiography helps in the localization of polyps. These are inconstantly seen on OCT-A.

3. Treatment

Therapeutic management of PEDs mainly depends on the cause. Anti-VEGF intravitreal injections remain the gold standard for AMD-related vascularized PEDs. In PCV, resistant lesions can be managed by a combination of anti-VEGF and verteporfin photodynamic therapy (PDT). As for CSC, treatment of PED is not necessary in patients with good visual acuity or those who remain asymptomatic or paucisymptomatic, because exudative signs can resolve in a few months without any treatment. In other cases, verteporfin PDT or mineralocorticoid receptor antagonist medication can be proposed. When active CNV is associated with CSC, anti-VEGF treatment is required.

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09

Black & white dots

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IN 1969 ALEX KRILL AND CO-AUTHORS used the term "multifocal choroiditis" (MFC) to describe a non-infectious choroidal disease that appeared similar to the "presumed ocular histoplasmosis syndrome" (POHS). Few years later, in 1973, Nozik and Dorsch described a similar chorioriditis that presented with anterior uveal inflammation with chorioretinal lesions resembling POHS. The main difference between these two diseases was the presence of vitreous and anterior chamber inflammation, but no evidence of a possible infectious trigger was reported. These patients, were classified as MFC with panuveitis (MFCPU).

A decade later, in 1984, Dreyer and Gass collected a large series of MFCPU: 28 cases gave them the right to identify a clinical entity distinct from POHS. In the same year, Watzke nd colleagues described for the first time ten myopic women with MFC but smaller chorioretinal lesions that were prevalently located at the macula. The authors called it "punctate inner choroidopathy" (PIC). They considered PIC as a distinct entity, because this new multifocal choroiditis presented with small yellow-gray dots in the posterior pole with no signs of ocular inflammation that develop into atrophic chorioretinal scars and become progressively more pigmented with time. Only in 1990, Joondeph and Tessler used for the first time the terms MFC and PIC as inflammatory disorders distinct from POHS. On the other hand, there has been no evidence to support MFC and PIC as separate entities: their clinical course and treatment are similar, and both conditions are idiopathic.

Recently, an extensive debate has been raised on the classification of the so called "white dot syndromes". The term does not have a clinical meaning *per se*, but it has to be interpreted as a description of a group of different uveitis entities that present with multiple foci involving the chorioretinal tissue.

Although multifocal choroiditis of unknown etiology has been extensively studied now for many years, the classification has been recently discussed in order to simplify the nomenclature used in the past. This process can be compared to the so-called Occam's razor: a problem-solving principle according to which the simplest solution tends to be the right one.

In the past, MFC was described by using many different names: MFC with panuveitis, MFC without panuveitis, PIC, POHS, recurrent MFC, progressive subretinal fibrosis and multifocal inner choroiditis, among the others. All the previous entities are now identified under the umbrella term "idiopathic multifocal choroiditis".

The aim is to explain the clinical meaning of the white and black dots in the field of uveitis, by providing the fundamentals and suggestions on how to interpret them.

1. White dot syndromes

In light of recent discussion on MFC, white dot syndromes can be classified as follows:

- Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
- Multiple evanescent white dot syndrome (MEWDS)
- Serpiginous or ampiginous choroiditis
- Birdshot chorioretinopathy
- Acute zonal occult outer retinopathy (AZOOR)
- Acute macular neuroretinopathy
- Acute retinal pigment epitheliitis
- Acute idiopathic unilateral maculopathy (AIUM)

These diseases primarily involve the posterior uveal tract and present primarily with multiple white inflammatory lesions that affect the choroid, retina, and retinal pigment epithelium (RPE).

It is appropriate to clarify that some of these conditions, such as APMPPE, were supposed to have a self-limited course with a good visual prognosis and preservation of central vision, but these characteristics are still under discussion as well as the need for a prompt treatment. Others, such as idiopathic MFC, can have a relentless progressive course, require treatment with corticosteroids and corticosteroid-sparing immunomodulatory agents, and can lead to severe visual impairment.

Although several possible triggers have been associated with many of these conditions, such as viral infections, these entities otherwise have no identifiable cause. Among them, serpiginous choroiditis has been strongly associated with *Mycobacterium tuberculosis* (TB) infection and it is considered secondary to this disease until proven otherwise. If TB is ruled out, serpiginous choroiditis is considered idiopathic. In addition, suspicion of TB is raised when the posterior pole involvement does not present the typical serpiginous pattern, but rather multifocal macular lesions with serpiginous-like shape. This disease is then called ampiginous choroiditis.

It is almost generally agreed that the different diseases included among the white dot syndromes might represent different phenotypic manifestations of a single agent, differing in appearance only because of the underlying genotype of the individual affected. On the other hand, as previously stated, the term white dot syndrome describes just the clinical picture of the disease and cannot exclude other possible multifocal lesions secondary to other systemic diseases, such as sarcoidosis, or even malignancies, like primary vitreoretinal lymphoma (PVRL).

The majority of these conditions may be associated with serious retinal or choroidal sequelae, such as choroidal neovascularization (CNV) or macular scars that could result in delayed visual loss even after the original disease process has become inactive.

2. Black dots

The black dots in the retina are mainly associated with malignancy and less frequently with inflammation of the retina, uveal tract, or both.

Imaging of the retina can effectively and more precisely reveal tissue involvement. Very often, the white dots look like black dots on angiography, even though recently new techniques, such as optical coherence tomography angiography (OCT-A) have been introduced to study the vascular structure of the eye.

The precise assessment of the disease leads the physician towards the correct decision making, by providing essential clinical details. The different techniques used for the treatment of these diseases depend on the degree of severity, the onset and the clinical characteristics.

In conclusion, white and black dots are descriptive terms used to define the clinical characteristics of a series of different retinal inflammations and cannot be considered a real terminology used for a clinical classification. On the other hand, their characteristics can help the physician to assess the patient appropriately. Multimodal imaging represents the first step of the flow chart for their management.

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10

Vasculitis

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RETINAL VASCULITIS is a sight-threatening inflammatory eye disease that involves the retinal vessels. It may occur as a complication of infective or neoplastic disorder, in association with systemic inflammatory disease, or as an isolated idiopathic ocular condition.

1. Clinical features

Retinal vasculitis may manifest with blurring or loss of vision, floaters, or visual field defects. It may be asymptomatic, particularly when it is located in the peripheral retina and not associated with vitritis or macular oedema. A sudden decrease in vision due to vitreous haemorrhage may reveal retinal vasculitis in some patients. Ocular symptoms may be uni- or bilateral. Slit-lamp examination may show features of anterior uveitis. Vitritis, which is variable in severity, is present in almost all patients with retinal vasculitis.

The diagnosis of retinal vasculitis is based on careful dilated fundus examination and fluorescein angiography (FA) that is an essential tool in the evaluation. Active vasculitis is characterized by focal, multifocal, or diffuse fluffy white sheathing or cuffing of blood vessels. In later stages, the affected vessels show well-defined gliotic sheathing. An extreme form of sheathing of the vessels, resembling tree branches in winter, is called frosted branch angiitis. Kyrieleis arteriolitis (after late German ophthalmologist Werner Kyrieleis) refers to the accumulation of periarterial nodular exudates or plaques classically seen in toxoplasmosis, but also in other infectious disorders. Dense perivascular exudates with an appearance of "candle-wax drippings" are typical of sarcoidosis.

Retinal vasculitis affects predominantly veins (phlebitis, periphlebitis). It may also affect arteries (arteritis, periarteritis) or capillaries (capillaritis). Retinal vasculitis affecting predominantly the veins has been described in association with Behçet's disease, tuberculosis, sarcoidosis, multiple sclerosis, pars planitis, and human immunodeficiency virus (HIV) infection. Certain diseases are associated with a predominantly arterial involvement including systemic lupus erythematosus, polyarteritis nodosa, polyangiitis with granulomatosis, and Susac syndrome.

Funduscopic signs of retinal vasculitis may include cotton wool spots, retinal haemorrhages, and retinal oedema. Other vascular changes that may accompany retinal vasculitis include telangiectasiae, vascular anastomoses, microaneurysms, macroaneurysms, and optic disc or preretinal neovascularisation. Associated inflammatory posterior segment changes can occur, including vitreous snowballs, snowbanks, retinal infiltrates, necrotising retinitis, choroidal lesions, and optic disc swelling. They may provide clues to the diagnosis of retinal vasculitis.

2. Ocular Imaging

Conventional FA remains the gold standard imaging tool for the appraisal of retinal vasculitis. FA is routinely used in the diagnosis, monitoring of therapy, and management of complications. Characteristic features seen with FA in active vasculitis include staining of the blood vessel wall with fluorescein and leakage of dye due to breakdown of the inner blood-retinal barrier. Such leakage may be focal, as seen in sarcoidosis or multiple slerosis, or more diffuse, as seen in Behçet's disease and tuberculous retinal vasculitis. Diffuse retinal capillary leakage is also a common finding in many specific conditions including Behçet's disease and birdshot chorioretinopathy. FA is a more sensitive technique and will frequently show that the vasculitis

is more extensive than the clinical examination suggests. FA is very useful to delineate areas of capillary non-perfusion and neovascularisation with or without associated retinal ischemia. It is also very valuable in diagnosing an inflammatory branch retinal vein occlusion. Other angiographic findings include cystoid macular oedema and optic disc leakage.

***Ultrawide field fundus fluorescein angiography (UWF-FA)*:** With the advent of ultra wide field retinal imaging, a much broader view of the retinal periphery in a single frame is now possible, which translates to earlier disease recognition, identification of progression, and initiation of therapeutic intervention. UWF-FA helps to identify and document the entire extent of areas of vascular leakage, retinal capillary non-perfusion and neovascularisation, and to detect disease activity that could be missed on conventional FA.

***Optical coherence tomography*:** Spectral domain optical coherence tomography (SD-OCT) is a useful modality for the detection, classification, quantification, and follow-up of retinal structural changes associated with retinal vasculitis including macular oedema, serous retinal detachment, epiretinal membranes, macular hole, and macular atrophy.

***OCT angiography (OCT-A)* :** Compared to FA, OCT-A is a non-invasive modality that may provide greater details of the altered perfusion of the superficial and deep capillary plexuses in eyes with posterior segment inflammation associated with retinal vasculitis.

3. Differential diagnosis

Retinal vascultis may occur as a complication of a wide variety of infective or neoplastic disorders, in association with systemic inflammatory disease, or as an isolated idiopathic ocular condition. The most common and relevant entities are discussed below.

3.1. Infectious retinal vasculitis

Tuberculosis: The most common manifestations of ocular tuberculosis include granulomatous anterior uveitis, choroiditis, and retinal vasculitis. Retinal periphlebitis with a marked tendency to peripheral retinal capillary closure and neovascularisation is common in ocular tuberculosis.

Syphilis: A sexually transmitted disease (STD) caused by the spirochete *Treponema pallidum*. Because of the protean manifestations of the disease, it has been called the "great imitator". Syphilis, therefore, needs to be excluded in all patients with retinal vasculitis. Posterior segment complications include vitritis, chorioretinitis, retinal vasculitis, venous and arterial occlusive disease, serous retinal detachment, macular oedema, neuroretinitis, optic neuritis, optic atrophy, choroidal neovascularisation, and pseudoretinitis pigmentosa

Toxoplasmosis: The hallmark of ocular toxoplasmosis is focal necrotising retinochoroiditis, ultimately resulting in characteristic atrophic scars. Reactivation is frequently located adjacent to an old atrophic scar with hyperpigmentation along its borders, indicating an old infection (satellite formation). Anterior uveitis, which may be granulomatous, and a secondary rise in intraocular pressure may also be noted. There may be an associated retinal vasculitis, which may be either near to or distant from the focus of active retinochoroiditis. In rare cases, the vasculitis may be occlusive, resulting in retinal infarction and consequent visual field defects.

Acute retinal necrosis: Acute retinal necrosis is caused by multiple members of the herpes family including varicella zoster, herpes simplex 1 and 2, and, rarely, cytomegalovirus. The prominent features of acute retinal necrosis include peripheral necrotising retinitis, retinal arteritis, and a prominent inflammatory reaction in the vitreous and anterior chamber. Optic neuritis occurs in many affected eyes, and severe rhegmatogenous retinal detachments are often encountered as a late complication.

3.2. Retinal vasculitis associated with systemic inflammatory disease

Behçet's Disease: The ocular manifestations of Behçet's disease include recurrent anterior uveitis with or without hypopyon, cellular infiltration and opacification of the vitreous, retinal vasculitis, retinal infiltrates and haemorrhages, cystoid macular oedema, and optic disk hyperaemia. Retinal vascultis may present in the form of diffuse vascular sheathing mainly involving veins, gliotic sheathing in advanced disease, diffuse retinal capillary leakage in a "fern-like" pattern, and retinal vascular occlusive complications.

Sarcoidosis: Characteristic findings in posterior segment involvement include non-occlusive retinal periphlebitis presenting with typical segmental cuffing or more extensive sheathing and perivenous exudates, which are usually indicated as "candle wax drippings". Retinal vasculitis may be subclinical, only visible on FA. Vitritis with snowballs and peripheral mulfifocal choroiditis are frequently seen in association with retinal vascultis.

Systemic lupus erythematosus (SLE): The retinopathy generally consists of cotton wool spots with or without retinal haemorrhages and it may occur in the absence of hypertension. By contrast, a less common but more severe retinal vaso-occlusive disease characterised by diffuse arteriolar occlusion with extensive capillary nonperfusion and telangictasiae can occur. Patients with SLE and raised anti-phospholipid antibodies have a higher risk of developing occlusive retinal vascular disease.

Granulomatosis with polyangiitis (prefered term, previously known as Wegener's granulomatosis): The ocular manifestations include orbital involvement secondary to paranasal granulomata, nasolacrimal duct obstruction, episcleritis, scleritis, corneal ulceration, retinal vasculitis, optic nerve vasculitis, retinal artery occlusion, and choroidal ischemia.

Multiple sclerosis (MS): Various ocular inflammatory changes have been described in patients with MS and may be the presenting sign of the disease. They include nongranulomatous and granulomatous iridocyclitis, intermediate uveitis, retinitis, and optic neuritis. Retinal periphlebitis has been described as a common manifestation of MS.

Microangiopathy of the brain, retina, and cochlea (Susac Syndrome): Microangiopathy affecting the arterioles of the brain, retina, and cochlea, giving rise to the classic triad of encephalopathy, branch retinal arterial occlusions, and sensorineural hearing loss. The underlying process is believed to be a small-vessel vasculitis causing microinfarcts of the retina, brain, and cochlea.

3.3. Local retinal vasculitis without systemic disease

Frosted branch angiitis: Occurs in young, healthy individuals who typically have acute bilateral (sometimes unilateral) visual loss, associated with anterior and posterior segment inflammation. The retinal findings include swelling of the retina and severe sheathing of retinal venules, creating the appearance of frosted tree branches. Additional findings include intraretinal haemorrhages, hard exudates, and serous detachments of the macula and peripheral retina. The disease usually responds rapidly to systemic corticosteroids with rapid resolution of vascular sheathing. The visual prognosis is usually good, and there is no recurrence in most patients. The differential diagnosis include frosted branch angiitis secondary to infectious disease, systemic non-infectious disease, and malignancies.

Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN): A rare entity characterised by bilateral retinal arteritis, numerous aneurysmal dilatations of the retinal and optic nerve head arterioles, peripheral retinal vascular occlusion, neuroretinitis, and uveitis

4. Diagnostic evaluation

The search for a cause in patients with retinal vasculitis involves a multidisciplinary approach and laboratory investigations. The exclusion of a masquerade syndrome and the discrimination between infectious and non-infectious etiology of retinal vasculitis are essential for management and outcome. Laboratory workup of a patient with retinal vasculitis should follow a differential diagnosis derived from a detailed history, review of systems, and physical examination. If the patient's medical history, review of systems, or ocular examination suggests an underlying systemic disease, then the diagnostic workup should be tailored for that disease. In the absence of any diagnostic clues from history, clinical examination and ocular imaging, a minimum work-up is recommended including complete blood count, erythrocyte sedimentation rate, C-reactive protein, syphilis serology, tuberculin skin test, Quantiferon, and a chest X-ray. A diagnosis of idiopathic retinal vasculitis is made in patients with negative evaluation.

5. Management

The goal of management in any clinical scenario, whether infectious or non-infectious, is control of intraocular inflammation and prevention of blinding complications of retinal vasculitis. Patients with infectious retinal vasculitis are treated with appropriate systemic and, if needed, intraocular antimicrobial therapy, usually in combination with corticosteroid therapy. Non-infectious retinal vasculitis requires treatment with corticosteroids, conventional immunosuppressive drugs, or biologics. Laser or surgical treatment may be required for the management of specific complications. Because the clinical course of each of the diagnoses associated with inflammatory retinal vascular changes can vary broadly, treatment should be targeted as much as possible.

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11

Inflammatory macular oedema

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MACULAR OEDEMA THAT MAY BE CYSTOID (CMO) is a very common accompaniment to uveitis. In the Manchester Uveitis Clinic it is seen experienced by over 20% of patients, and in over 40% of those registered it is a factor in visual handicap registration. It is one of the most common, and arguably the most difficult complication of uveitis to manage.

1. The context: uveitis activity and location

In assessing a patient with macular oedema, the context is of crucial importance. Firstly (and perhaps obviously): is the uveitis active, and if so, is it only in the anterior segment, or does it involve the posterior segment? Active anterior uveitis may cause CMO in a minority, but in those cases the oedema is almost always treated in tandem with the uveitis itself; intensive topical steroids alone may suffice. If they do not, then either periocular or systemic steroid may be necessary. In contrast, if active posterior segment inflammation (intermediate, posterior or panuveitis) is present, then the oedema will not reliably settle unless adequate intraocular or systemic steroid is used.

The Manchester Uveitis Clinic occasionally sees referred patients who have received multiple intravitreal injections of anti-VEGF for inflammatory macular oedema, in the erroneous belief that this is adequate treatment. It is not; the untreated uveitis also causes other complications including epiretinal membranes and macular ischaemia, the macular oedema is inadequately treated, the eye is exposed to the unnecessary risk of frequent injections. Permanent damage may ensue.

If the uveitis is active but the attack is single and probably self-limiting, then a single depot injection or short course of oral steroid may suffice. However, chronic uveitis requiring significant steroid dosage may be better treated with oral immunosuppression; in this way, suppression of inflammation is usually followed by resolution of the oedema.

2. The extent, chronicity and type of macular oedema

Macular oedema may be of several physical types. *Central petalloid* CMO is the most common, and in its early stages tends to respond very well to treatment; recurrence and chronicity is the problem. However, macular oedema may be only part of a more widespread retinal oedema, especially in birdshot retinochoroidopathy or retinal vasculitis with panuveitis. In this case, more potent and long-lasting treatment is frequently needed. Some patients with severe CMO are also seen to have subretinal fluid. In these cases the prognosis is guarded, but having established that there is no evidence of central serous chorioretinopathy (which can be worsened by steroid treatment), high-dose oral or repeated intravitreal steroid may be successful.

Vitreroretinal traction is commonly seen in association with macular oedema in uveitis. To some extent, the oedema may respond to anti-inflammatory treatment and in some cases there is spontaneous resolution of traction. However, if traction is persistent or increasing, or if incipient macular disruption is seen, surgery is necessary.

3. Medical and surgical treatment

In eyes with no underlying uveitis (for instance following cataract surgery), CMO may respond to oral nonsteroidal anti-inflammatory drugs (NSAID), or in minor cases to topical NSAID. However, that is not the case in eyes with active uveitis. To supplement anti-inflammatory treatment, acetazolamide can add effect, and in some cases it can be used temporarily as the sole measure. However, it can never safely be a long-term solution. We do not find topical dorzolamide to be effective.

It is the guideline of the Manchester Uveitis Clinic that in any new patient with non-infective uveitis and CMO, steroid is the first-line treatment. If the uveitis is unilateral and not severe, a single periocular steroid injection is used. If incompletely effective, intravitreal steroid is used. If the inflammation is bilateral, oral steroids are used, followed by oral immunosuppression if tapering leads to recurrent inflammation and CMO at an unreasonable dose. This clinic uses intravitreal triamcinolone 2-4 mg by preference and has shown sustained visual acuity (VA) gain and reduced retinal thickness at 6 months after injection. There is as yet inadequate evidence on the long-term efficacy of the Iluvien® fluocinolone implant.

These general guidelines may need to be modified in steroid intolerance (raised intraocular pressure, systemic complications, etc) and anti-VEGF injections may be used to supplement anti-inflammatory treatment. For tractional macular elevation with oedema, and in unilateral substantial uveitis with CMO, vitrectomy and ERM with or without ILM peel may be effective in removing CMO.

Various new developments are under investigation including several steroid delivering implants and a suprachoroidal microstent, and early results of tocilizumab suggest efficacy in inflammatory CMO.

Key Points:

1. Treat macular oedema early. Do not leave it to progress or become chronic.
2. Treat aggressively enough to clear it, or if not possible, to demonstrate maximal treatment efficacy and VA change
3. Significant chronic inflammation always requires long-term anti-inflammatory treatment as baseline, if necessary supplemented with local or additional treatment for CMO
4. Longstanding, undertreated CMO develops permanent retinal structural change with gross disruption of architecture, ischaemia and unresponsiveness to steroid. Even if removed, visual acuity may not improve and damage is permanent. Do not leave it this long!

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12

Pigmented tumour

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MCQ's

1. **RPE hamartomas associated with familial adenomatous polyposis that should lead to a thorough family history and a referral to colonoscopic screening are:**
   a. Multifocal rather than solitary
   b. Uniformly jet black
   c. Scattered anywhere in the fundus
   d. Large as compared to CHRPE
   e. Growing lesions

2. **Orange pigment, one of the five TFSOM features that help to predict growth of a small pigmented choroidal tumour:**
   a. Is a special type of lipid-containing residue of lysosomal digestion
   b. Is often associated with leakage of subretinal fluid, another TFSOM feature
   c. Is more frequently found over peripheral pigmented tumours
   d. Appears black rather than orange in colour when the tumour is amelanotic
   e. Is found on the surface of 6 to 10 percent of small choroidal melanomas

3. **Regarding fundus autofluorescence imaging of pigmented choroidal tumours:**
   a. CHPRE is hyperautofluorescent, except for its atrophic patches
   b. Hypoautofluorescence over a naevus may translate to RPE insufficiency
   c. Newly leaked subretinal fluid causes hypoautofluorescence by shadowing
   d. Orange pigment is hyperautofluorescent
   e. Autofluorescence imaging can differentiate a naevus from a melanoma

4. **When should you refer a patient with a small pigmented choroidal tumour:**
   a. It has any of the five TFSOM features
   b. It has not been mentioned in previous exams, even if has no TFSOM features
   c. The patient is older than 50 years of age
   d. New symptoms that likely are related to the naevus have developed
   e. Growth is documented at a follow-up examination

5. **Regarding review of a choroidal naevus without any of the five TFSOM features:**
   a. Regular review should begin when the patient reaches 50 years of age
   b. A fundus photograph for comparison should be taken at baseline
   c. The review interval may be adjusted to the age of the patient
   d. The review interval may be adjusted to the size of the naevus
   e. Approximately 1 in 400 naevi will transform into a malignant melanoma

COMPREHENSIVE OPHTHALMOLOGISTS will encounter pigmented tumours regularly when they perform ophthalmoscopy. If they do not, they should worry. More and more widespread use of fundus photography further increases the chances of finding tumours. At least one in twenty Caucasians has a choroidal naevus, and one in hundred a congenital hypertrophy of the retinal pigment epithelium (CHRPE). Two inevitable questions arise: How can I be confident that this tumour is benign? Should I refer my patient to a specialist?

The initial differential diagnosis between a choroidal naevus and a melanoma is based on clinical examination with the slit lamp and indirect ophthalmoscope followed by optical coherence tomography (OCT) and fundus autofluorescence (FAF) imaging, which now are widely available, followed if necessary by ultrasonography. Large to medium-sized melanomas are quite reliably diagnosed using these methods. The challenge lies in smaller lesions.

1. Is it a CHPRE?

A typical CHPRE is easy to recognize once you have diagnosed your first patient. It has a very sharp border, as if it had been drawn with a pencil. Frequently, this outline is doubled by a thin whitish line just outside the lesion itself. Its shape is roundish, but it can be undulating. In a young patient, the lesion is jet black. Over time, it develops white atrophic patches, and eventually may be almost entirely white and scar like. Most of them are found anterior to the equator. They are flat. About 2 percent are bilateral. By OCT, the overlying retina becomes atrophic from loss of outer retinal layers, the RPE is hyperreflective. The lesion is hypoautofluorescent. The atrophic patches are iso- or hyperautofluorescent.

Three less frequent RPE lesions must be excluded before diagnosing CHRPE. *Congenital grouped pigmentation* refers to many small CHRPE-like lesions scattered in one meridian, indicating genetic pigmentary mosaicism. *Torpedo maculopathy* refers to a torpedo ray -shaped, horizontally ellipsoid, variably pigmented congenital RPE lesion of unknown genesis located immediately temporal to and pointing toward the macula. *RPE hamartomas associated with familial adenomatous polyposis* (FAP) are multiple in more than half of the cases, either in one or both eyes, haphazardly distributed, and smaller and irregularly pigmented as compared to CHRPE, frequently with an pale atrophic tail.

2. If not, judge by TFSOM

Unlike CHRPE, choroidal naevi have soft margins. Most of them are elevated. They are variably pigmented, some being amelanotic and cream-coloured. A most useful mnemonic "To Find Small Ocular Melanomas" reminds the ophthalmologist to look for five distinct risk features for growth: tumour Thickness over 2 mm, subretinal Fluid, visual Symptoms, Orange pigment, and tumour Margin relative to the optic disk. Each feature approximately doubles the likelihood of growth.

Thickness is estimated by imagining that the optic disc is tilted upward. Tumours that equal the imaginary vertical disk approach 2 mm limit in thickness. Dioptric difference in direct ophthalmoscopy can also be used, and if the lesion is not higher than 1 mm and not heavily pigmented, it can be measured with OCT. Use the enhanced depth imaging (EDI) option.

Subretinal fluid at the top, or adjacent to, a choroidal tumour is detected stereoscopically at the slit lamp. Small amounts of subretinal fluid leaks from 5 to 15 percent of presumed non-growing naevi, because of a breakdown of the retinal pigment epithelial barrier. These tumours typically show hypoautofluorescence from atrophy of the overlying RPE. Lack of hypoautofluorescence should rise alarm. If the leakage is recent, raising alarm, the detached area is hyperautofluorescent. If it is longstanding, favouring a naevus, the detached area may be hypoautofluorescent from atrophy.

Symptoms from a small choroidal melanocytic tumour are visual and usually are due to extension of either the tumour or subretinal fluid to the fovea, causing blurred vision, altered colour perception, metamorphopsia, or a central visual field defect. The presence or appearance of symptoms suggests recent change in the tumour.

Orange pigment, a special type of lipofuscin, frequently coexists with subretinal fluid. It is located on the outer surface of the detached retina typically in the posterior pole and is not detected over peripheral tumours. The flecks vary in size and shape, they can form a meshwork, and will appear black if the tumour is amelanotic. They are always hyperautofluorescent. Orange pigment is found on 6 to 10 percent of non-growing naevi, but is much more commonly seen over small melanomas.

Margin of the tumour relative to the optic disk originally referred to tumour touching the disk margin but in more recent publications it sometimes refers to tumour margin within 3 mm from the disk. The association between tumour growth and the margin of the tumour close to the optic disk is likely to be a statistical rather than a biological one.

On ultrasonography, a naevus is medium to highly reflective. A low reflective acoustic profile should rise alarm, although not all such lesions grow on follow-up.

Choroidal naevi like their cutaneous counterparts generally are present from childhood and with time the RPE over them often develops drusen, atrophy and patches of proliferation. The presence of such features suggests that the lesion is longstanding. Not all naevi develop them, however. Drusen are found in about 60 percent and atrophy or hyperplasia of the RPE in about 10 percent of naevi in patients over 50 years of age. The thicker the naevus, the more likely it develops RPE changes. These features do not exclude a malignant change in a pre-existing naevus, especially when they are absent from a part of the tumour.

3. Counsel the patient

CHPRE, grouped pigmentation, and torpedo maculopathy are innocent stable lesions that do not call for review. Although a CHRPE will often slightly enlarge over time, it exceedingly rarely turns into an RPE adenoma and even more rarely to an adenocarcinoma that is not known to metastasise. Whenever the finding is consistent with RPE hamartomas associated with FAP, however, a complete family history and referral to screening colonoscopy are advisable.

It is advisable to refer a patient with a small choroidal melanocytic tumour for second opinion if it has any of the TFSOM features. Some centres recommend a needle biopsy of suspicious

small pigmented tumours, but this is not yet standard of care. Diagnostic errors from different cell lines in different parts of some tumours remain a possibility, especially if the tumour is a transformed naevus. Intraocular biopsy involves the risk of vitreous haemorrhage, retinal detachment, and other complications.

Other patients with a presumed naevus should be made aware of their lesion and ideally be provided with a copy of the fundus photograph.

4. Review periodically

How often a comprehensive ophthalmologist should review a naevus without any TFSOM features is not universally agreed. Most often, it is recommended that naevi should be observed periodically for life. The patient should be told to return immediately if they ever develop visual symptoms in the naevus eye.

Of uveal melanomas diagnosed, from 6 to 20 percent have developed from a previously identified presumed naevus. The smaller a melanoma is, the harder it is to tell from a naevus. Thus, no naevus is small enough not to warrant review. The smallest melanomas can only be diagnosed by relatively rapid growth. Benign naevi can grow slowly, particularly in adolescence: 31 percent of presumed naevi grew 0.2 to 3.0 mm in diameter over a mean follow-up of 15 years. The annual growth varied from 0.01 to 0.36 mm with a median of 0.06 mm, which translates to a 0.5 mm increase in 8 years. The proportion growing was 54 percent in patients aged less than 40 years and 19 percent after the age of 60 years. Younger age was the only factor that predicted growth by multivariate analysis.

An increase in size faster than is typical for a naevus, asymmetric growth, or appearance of any TFSOM feature should lead to referral for second opinion. In the absence of any TFSOM feature this is likely to occur in 1 in 400 to 500 patients over lifetime. This risk is age-related, being smallest before the age of 45 years, when a 2 to 3-year interval may be appropriate, decreasing to 1 to 2 years thereafter, and eventually to one year. The larger the naevus, the shorter the interval. If the patient has previously been examined without a naevus being mentioned, start with an interval of 3 to 6 months. If no change is observed, the interval can gradually be extended. The review should be based on fundus photographs taken at baseline. Suspected growth should be verified with a new photograph.

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Answers to MCQ's on page 66

1. a. *True*
   b. *False – they are variably pigmented unlike typical CHRPE*
   c. *True*
   d. *False – they are smaller than an average CHRPE*
   e. *False – they are typically stationary*

2. a. *True*
   b. *True*
   c. *False – it is almost never found over peripheral lesions*
   d. *True*
   e. *False – that is frequency over naevi, more common over small melanomas*

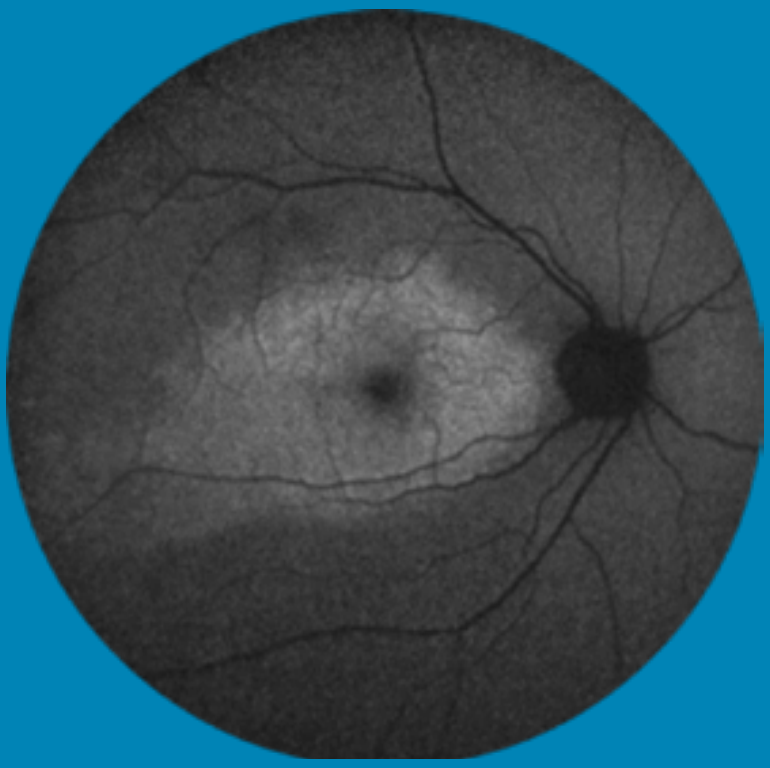
3. a. *False – It is hypoautofluorescent, atrophic patches may hyperautofluoresce*
   b. *True*
   c. *False – It causes hyperautofluorescence from RPE distress*
   d. *True*
   e. *False – It is a useful adjunct in differential diagnosis, but not diagnostic*

4. a. *True*
   b. *False – naevi are surprisingly often missed on routine examination: observe*
   c. *False – age is no criterion for referral, but may influence review interval*
   d. *True*
   e. *True*

5. a. *False – review is indicated, but the review interval can be longer*
   b. *True*
   c. *True*
   d. *True*
   e. *True*

RT1

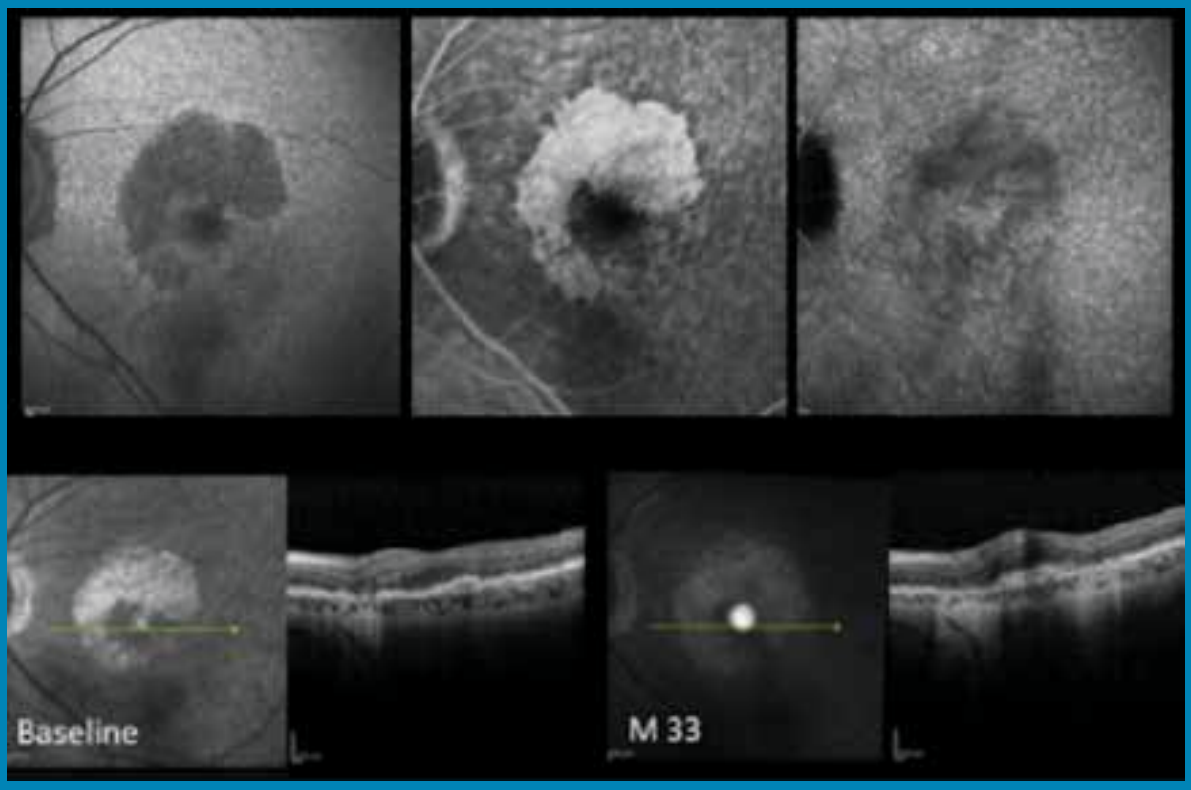
Round table 1: How do you diagnose these cases?
Case BAILLIF S



A 54-year-old male with a sudden decrease in right visual acuity. He has no past medical history. The anterior segment (both eyes) was unremarkable. His right retinal fundus disclosed a large, yellowish, placoid lesion. The lesion was hyperautofluorescent. Fluorescein angiography showed progressive hyperfluorescence in the area of the lesion with leopard spotting. Indocyanine green angiography showed hypofluorescent dots localized within the same area. Spectral domain optical coherence tomography revealed a small amount of subretinal fluid, irregular hyperreflectivity of the RPE with prominent nodular elevations, disruptions ofthe ellipsoide zone, and hyperreflective dots in the choriocapillaris layer.

RT1

Round table 1: How do you diagnose these cases?
Case MIERE A



Adapted from Am J Ophthalmol. 2017;182:45-55.

An 84-year-old patient from our department. Fundus autofluorescence showed sharply demarcated areas of hypoautofluorescence, surrounded by a slightly hyperautofluorescent ring, with foveal sparing. Fluorescein angiography revealed a well-demarcated area of increased fluorescence due to a window defect, as well as an ill-defined hyperfluorescent lesion without leakage of dye in the late phase. Indocyanine green angiography showed a late plaque like lesion. Spectral domain optical coherence tomography revealed an irregular elevation of the retinal pigment epithelium with no intraretinal or subretinal fluid.

RT1

Round table 1: How do you diagnose these cases?
Case KIVELÄ T

A 51-year-old healthy woman with one year-long decrease in visual acuity of the left eye was referred to a retinal specialist by a comprehensive ophthalmologist with suspected atypical macular degeneration. The right eye had 20/20 (1.0) vision and was unremarkable. The best corrected vision of the left eye was 20/50 (0.4) with cyl –0.5 ax 150°. The anterior segment and vitreous were unremarkable. A whitish yellow thickening of the choroid to 500 µm (spectral domain optical coherence tomo-graphy using enhanced depth imaging) together with mixed atrophic and proliferative changes in the macular retinal pigment epithelium were noted. Fundus autofluorescence imaging showed mixed hypo-, hyper- and isoautofluorescence. A fluorescein angiogram revealed no active choroidal neovascular membrane (CNV). The outer retinal architecture was disturbed. lesion was thought to repersent subretinal fibrosis after a previous CNV. Although not found at the first visit, intraretinal cystic oedema was noted after three months and she subsequently received 6 monthly injections of bevacizumab for suspected reactivation. By 10 months, the fundus changes remained largely unchanged, but another retinal specialist dismissed the diagnosis of macular degeneration. She referred the patient to the ocular oncology service.

RT1

Round table 1: How do you diagnose these cases?
Case KHAIRALLAH M

VA : 20/32 (0.63)

AC: 1+ cells

IOP: 13 mmHg

2+ vitreous cells

VA: 20/50 (0.4)

AC: 1+ cells

IOP: 15 mmHg

2+ vitreous cells

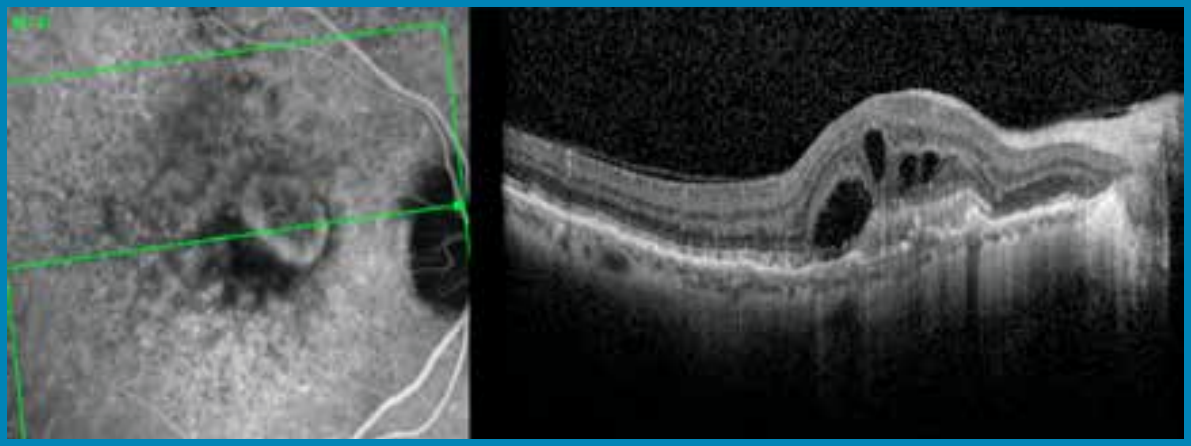
A 25-year-old obese woman persents with bilateral optic disc swelling associated with headache She ahs a history of headache followed by progressive decrease in vision of both eyes. Brain MRI is normal. She has been treated by her physician with oral acetazolamide.

Differential diagnosis?

Work-up ?

RT1

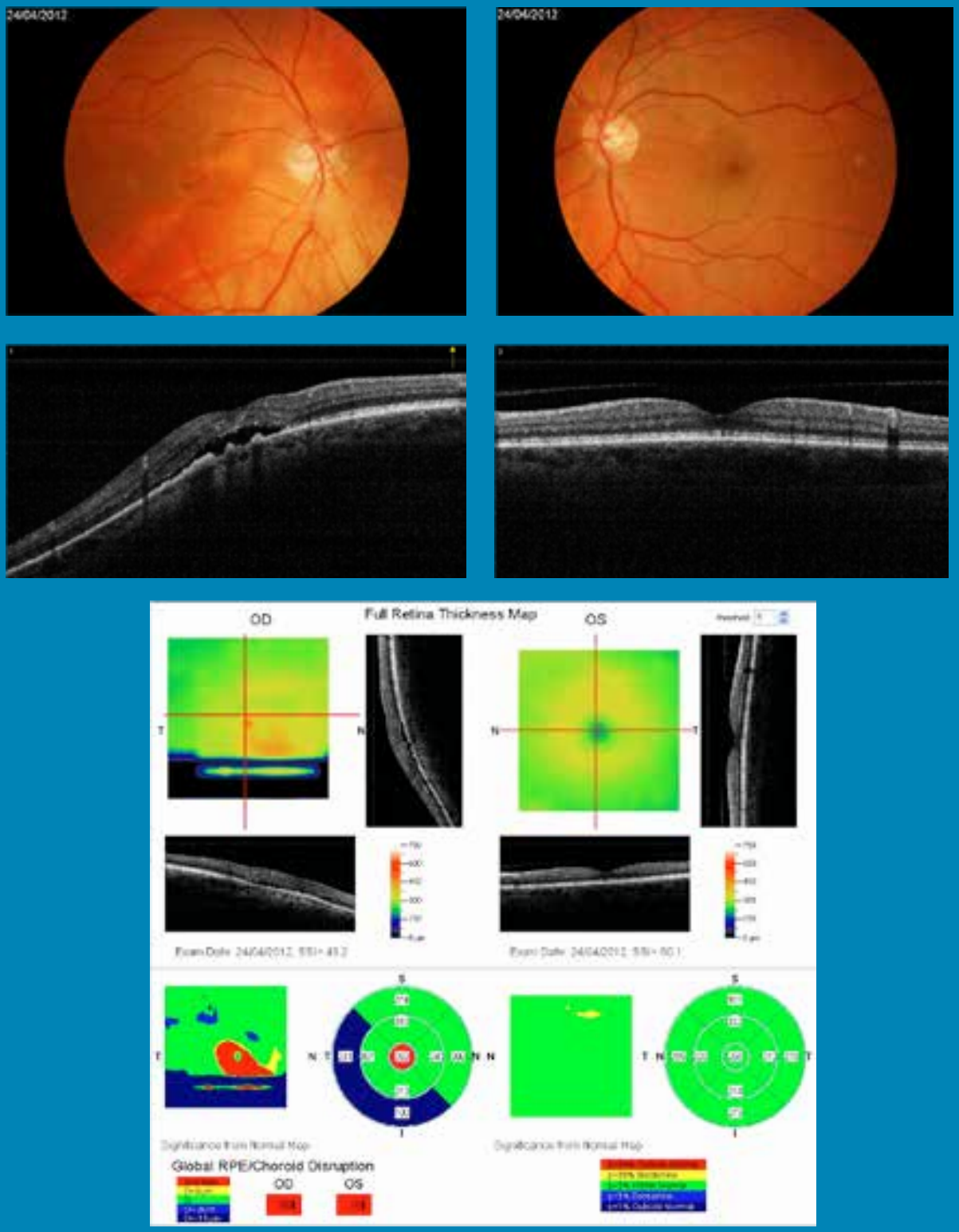
Round table 1: How do you diagnose these cases?
Case 1 – CREUZOT C



Case 1: A man with visual loss in his right eye since 3 days. Past medical history for diabetes. Visual acuity of the right eye is 20/200 (0.1) with a central scotoma. The acuity of the fellow eye is 20/20 (1.0). Intraocular pressure is 15 mmHg, OD, and 16 mmHg, OS.

RT1

Round table 1: How do you diagnose these cases?
Case 2 – CREUZOT C

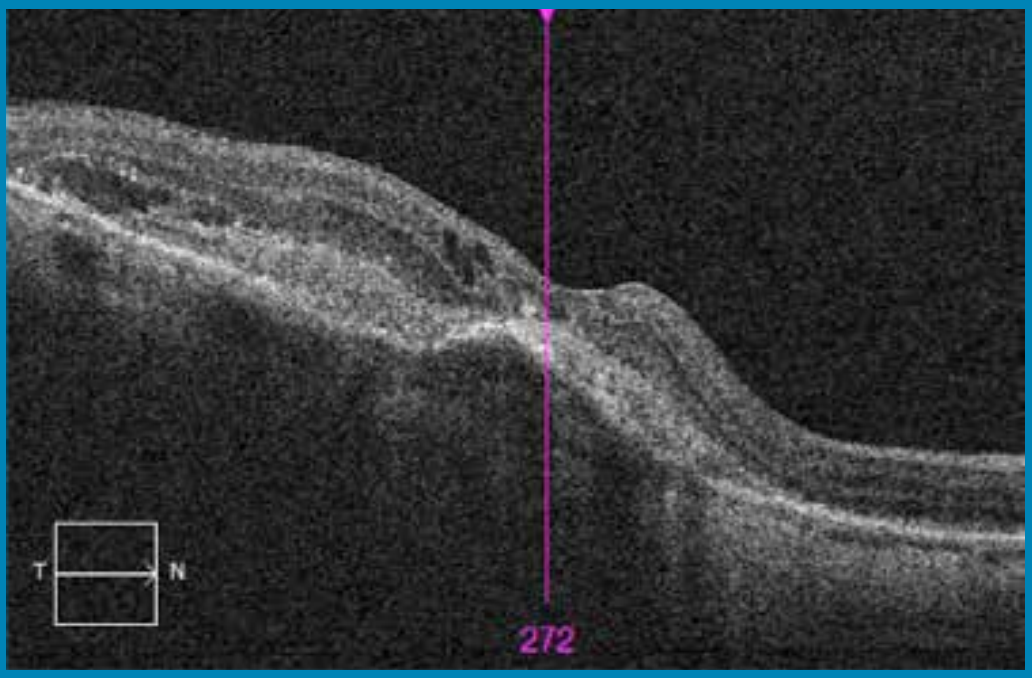


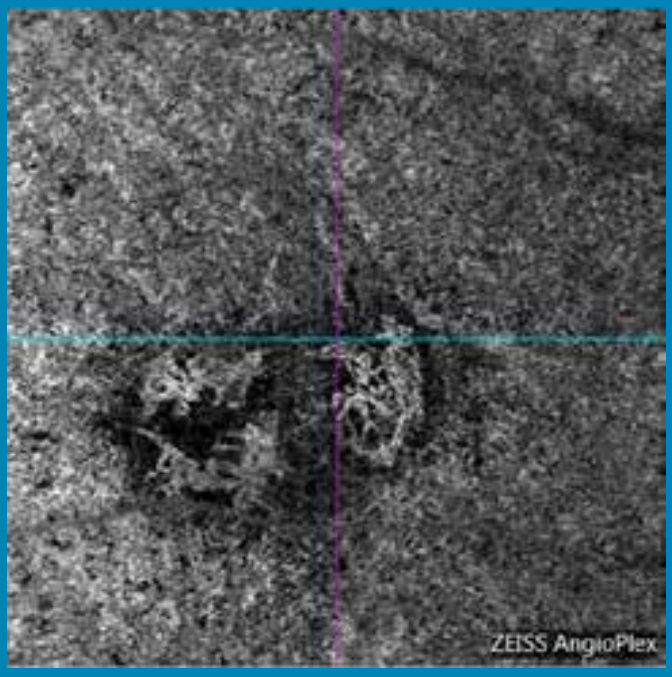
Case 2: A myopic male patient, refraction – 2.0 D. Visual loss n the right eye to 20/40 (0.5). Visual acuity of the fellow eye is 20/20 (1.0).

Visual loss RE 20/40 LE 20/20

RT1

Round table 1: How do you diagnose these cases?
Case 3 – CREUZOT C

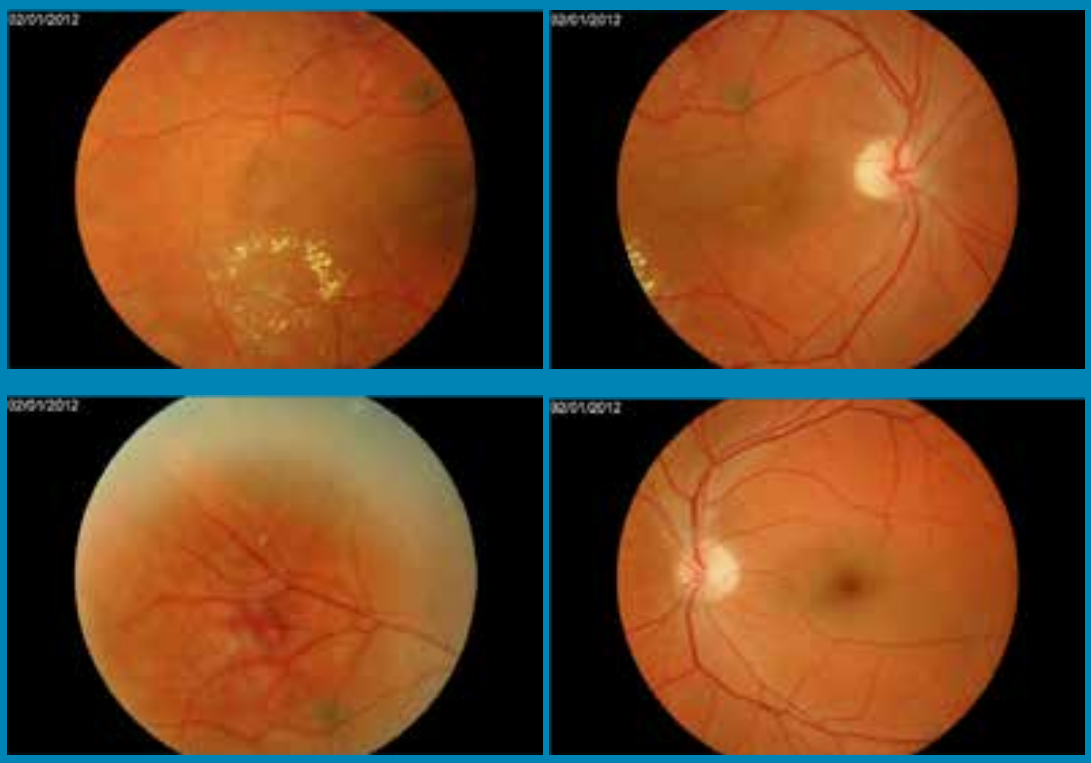


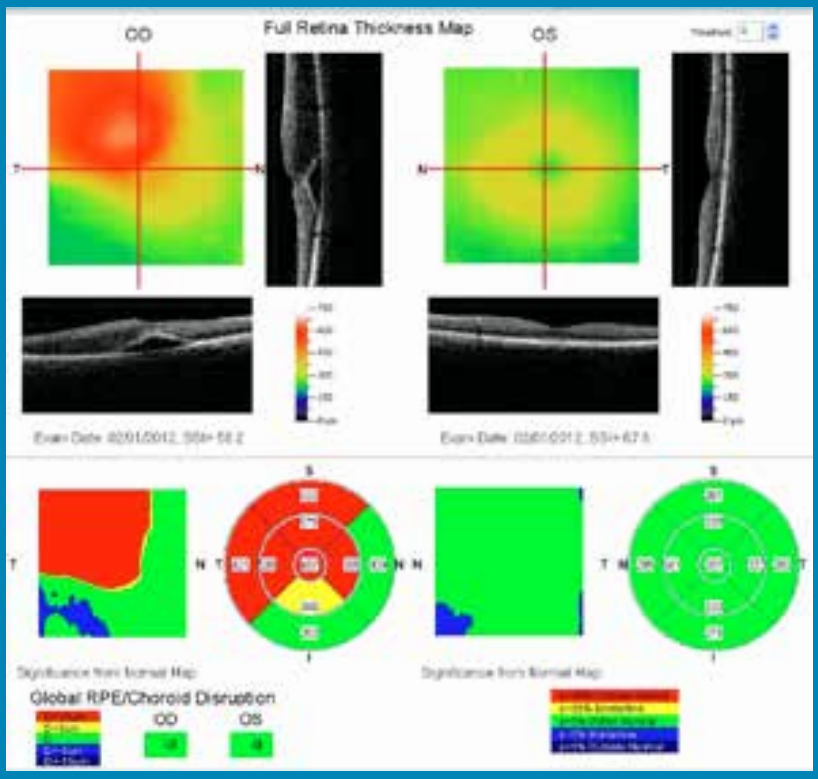


Case 3: Patient with visual loss to 20/70 (0.3) in the right eye. The acuity of the fellow eye is normal.

RT1

Round table 1: How do you diagnose these cases?
Case 4 – CREUZOT C





Case 4: A man with poor vision in his right eye, visual acuity 20/200 (0.1).

13

Anti-VEGF

GRZYBOWSKI A, Poland

MCQ's

1. **Which condition is an indication for intravitreal anti-VEGF treatment:**
   a. Wet age-related macular degeneration
   b. Neovascular glaucoma
   c. Diabetic background retinopathy
   d. Vitreous haemorrhage in selected cases

2. **Which VEGF isoform is mainly responsible for pathological angiogenesis in adult eyes:**
   a. VEGF-A
   b. VEGF-B
   c. VEGF-C
   d. VEGF-D

3. **The VEGF-receptor 1:**
   a. Activation is responsible for most of the VEGF activity
   b. Binds sVEGFR-1
   c. No significant cellular activity is associated with VEGFR-1
   d. Binds VEGFf

4. **VEGFf:**
   a. Is a result of proteolytic processing of VEGF-B to smaller fragments
   b. Is increased at sites of tissue injury or inflammation
   c. Leads to increased binding of VEGF to VEGFR-1
   d. Leads to increased binding of VEGF to VEGFR-2

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) - is responsible for growth of blood vessels. Despite its physiological action (particularly in the neonatal period and childhood), VEGF has a role in many retinal diseases with neovascular growth, increased leakage and retinal oedema.

The family of VEGF proteins includes the following isoforms:

- **VEGF-A -** responsible for angiogenesis (increasing migration and mitosis of endothelial cells, matrix metalloproteinase activity, creates blood vessel lumens and induces fenestration), has chemotactic activity for macrophages and granulocytes, and induces vasodilation (indirectly, by nitric oxide release)
- **VEGF-B -** responsible for embryonic angiogenesis in the myocardial tissue
- **VEGF-C -** takes part in lymphangiogenesis
- **VEGF-D -** takes part in development of lymphatic vasculature surrounding lung bronchioles
- **VEGF-E -** selectively binds to VEGF receptor-2, carrying a potent mitogenic activity without affinity to heparin
- **VEGFf** (VEGF fragments) - result of proteolytic processing of VEGF-A

Human isoforms (referred by the number of amino acids) are 121, 145, 165, 189, 206.

VEGF action is induced by binding to VEGF-receptors (VEGFR). VEGFR-1 is produced by endothelial cells and monocytes. The affinity of a VEGF particle is ten times greater for VEGFR-1 than VEGFR-2. Nevertheless, no cellular activity associated with VEGFR-1 activation is noted. Activation of the VEGFR-2 receptor results in its dimerization and activation. Subsequently, migration, proliferation of endothelial cells, as well as vasodilatation is observed. VEGF-A, VEGF-C, VEGF-D, VEGF-E and VEGF-F are ligands for VEGFR-2. VEGFR-3 does not bind VEGF-A, and its activity is related to fetal angiogenesis. Finally, soluble VEGF receptors (sVEGFR-1 and sVEGFR-2) modulate VEGF activity by binding free VEGF particles.

VEGFf is a result of proteolytic processing of VEGF-A to smaller fragments the presence of which might have a significant effect on the binding distribution of VEGF. Excess of VEGFf, due to proteolytic damage at sites of tissue injury or inflammation, can lead to increased binding of VEGF to VEGFR2 through VEGFf binding to VEGFR1 and to subsequent liberation of neuropilin-1.

Anti-VEGF agents inhibit VEGF activity. Currently several anti-VEGF agents are available:

- *pegaptanib* (Macugen®) - the first commercially available agent. It is an aptamer binding specifically only to one VEGF-A isoform
- *bevacizumab* (Avastin®) - a monoclonal antibody, binds all VEGF-A isoforms
- *ranibizumab* (Lucentis®) - a monoclonal antibody fragment, binds all VEGF-A isoforms with a higher affinity than bevacizumab
- *aflibercept* (Eylea®) and *zib-aflibercept* (Zaltrap®) - bind VEGF-A with a higher affinity than ranibizumab. It also binds VEGF-B and PlGF.

Common indications for anti-VEGF agents include:

- Myopic choroidal neovascularisation (CNV)
- Wet age-related macular degeneration (AMD)
- Macular oedema
- Severe diabetic retinopathy
- Vascular occlusions
- Neovascular glaucoma
- Vitreous haemorrhage from vascular lesions

Other indications in the anterior segment include:

- Iris neovascularisation
- Pterygium
- Trabeculectomy (modulating wound healing)
- Before keratoplasty (to reduce corneal neovascularisation)

Other indications in the posterior segment include:

- Retinopathy of prematurity
- Eales' disease
- Refractory pseudophakic cystoid macular oedema
- Coats' disease

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Answers to MCQ's on page 80

1. a. *True*
   b. *True*
   c. *False*
   d. *True*

2. a. *True*
   b. *False*
   c. *False*
   d. *False*

3. a. *False*
   b. *False*
   c. *True*
   d. *True*

4. a. *False*
   b. *True*
   c. *False*
   d. *True*

14

Steroids

WILLERMAIN F, Belgium

THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE in 1950 was awarded jointly to Edward Calvin Kendall, Tadeus Reichstein and Philip Showalter Hench. Two years earlier, Hench was the first rheumatologist to treat a rheumatoid arthritis patient with cortisone. A tremendous clinical effect was found and reproduced on other patients, but soon all started to experience severe side effects. Almost 70 years later steroids remain the first line therapy for most clinicians treating inflammatory diseases, including ophthalmologists. Obviously, considerable progress has been made in our understanding of their mechanism of action and in a search to decrease their side effects.

1. Mechanisms of action

Glucocorticoids (GCs) are a class of lipophilic hormones produced in the adrenal cortex that bind to glucocorticoid and mineralcorticoid receptors. Today, the clinically used prednisolone, and methylprednisolone, or fluorinated GCs dexamethasone and betamethasone, have less mineralocorticoid activity and stronger anti-inflammatory properties. GCs bind to a specific intracellular GC receptor and enter the nucleus where some of their effects are mediated through transactivation (after binding to GC responsive elements on the DNA) and transrepression (after interacting with different transcription factor, such as NFkB). The common view is that most of the immunosuppressive effect of GCs are mediated through transrepression, whereas transactivation would be responsible for important adverse effects. However, this view might be too simplistic and does not for example explain some very fast effects of GCs. Non-genomic effects have been described in this context, involving other mechanisms such as effect on the cytosolic membrane or mediated by the cytosolic or membrane bound receptor.

2. Cellular and metabolic effects

GCs modulate the phenotype of immune and non-immune cells with a plethora of different cellular effects explaining their immunosuppressive properties and side effects. GCs generally decrease release of cytokines, chemokines and prostaglandins, and the expression of adhesion molecules and major histocompatibility complex (MHC) molecules. In addition, GCs will also interfere with the regulation of glucose, protein and fat in the body. The latter is believed to mediate some side effects of GCs. Those are numerous, and every physician should be able to explain them to their patients.

3. Optimisation of GC use in clinical practice

Different non-exclusive strategies have been developed in order to decrease the GC side effects. First, the dosage is very important and has been divided in three main categories. Low-dose refers to treatment with prednisone equivalent less than 7.5 mg per day. At this level GC receptors are saturated at 40% to 50%. It is associated with less adverse effects and might be used in certain circumstances as maintenance therapy. Some authors even suggest that the safety profile of daily doses below 5 mg is very good. Medium, high or very high doses (prednisone equivalent of 7.5-30 mg, 30-100 mg, or >100 mg, respectively) can only be used for short term.

Local delivery is a very attractive option to limit GC side effects. In ophthalmology, three main routes are commonly used, topical, periocular (subconjunctival, sub-Tenon or retrobulbar) and intravitreal. Interestingly, local approach has also a benefit from development of new GC compounds. Today, four GCs are used intravitreally: triamcinolone acetonide, a lipophilic suspension acting as a depo of sustained release; Ozurdex®, a biodegradable extended-release intraocular implant of dexamethasone, and Retisert and Iluvien that are intraocular extended- release implants that deliver fluocinolone acetonide. Unfortunately, even if a local approach will protect the patient from systemic side effects, all are associated with ocular adverse events. Cataract and elevated intraocular pressure are of particular concern with the local approach, especially as regards the fluocinolone acetonide implants. Interestingly, although the association between systemic CG administration and central serous retinopathy is robust, it has been rarely reported with local ocular GC administration.

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15

Laser

LARSEN LM, Denmark

MCQ's

1. Which of the following statements characterize the effect of thermal photocoagulation on the retina?

a. Photocoagulation scars in the fundus are immediately visible and stay the same for the remainder of the patient's lifetime.
b. On rare occasions thermal photocoagulation that hits a large retinal blood vessel can cause it to bleed.
c. The yellow flash that the treating physician sees during 532 nm photocoagulation not the result of leakage of 532 nm light through the barrier filter.
d. Thermal photocoagulation effects in the outer retina differ fundamentally depending on whether the laser light is blue, green or yellow.
e. It is normal and intended when you hear a popping sound at the moment the thermal laser effect appears on the retina.

2. Which of the following statements characterize photodisruption of the vitreous for the treatment of floaters and/or Weiss rings?

a. The treatment is made using an argon laser.
b. The treatment is made using a Neodymium-YAG laser.
c. The treatment is associated with risk of damage to the lensr.
d. The treatment has been thoroughly validated in high evidence-level studies.
e. In most countries the treatment does not require regulatory approval because it is a surgical treatment.

3. Which of the following statements are true for experimental subthreshold nanosecond (micropulsed) laser treatment for dry AMD according to the LEAN study?

a. Sub-threshold nanosecond laser treatment was applied to AMD with drusen and geographic atrophy.
b. In the primary analysis of the total study population sub-threshold nanosecond laser (SNL) treatment did not reduce the progression from intermediate to late AMD compared to sham treatment.
c. A subgroup analysis of eyes without reticular pseudodrusen (subretinal drusenoid deposits) showed reduced progression to late AMD after laser compared to sham.
d. The investigators recommend immediate clinical implementation of sub-threshold nanosecond laser treatment in drusen-only AMD.
e. Positive outcomes in post-hoc subgroup analysis are accepted as evidence that can in themselves lead to approval of new medicinal treatments in the European Union.

4. In the DRCR.net Protocol S study of panretinal photocoagulation versus intravitreal ranibizumab for proliferative diabetic retinopathy, the 5-year outcomes were characterized by

a. A continued clear superiority of ranibizumab in visual acuity outcomes after 5 years.
b. The 5-year follow-up included more than 90 % of the randomized patients.
c. Lower rates of retinal detachment and diabetic macular edema were seen in the ranibizumab arm than in the photocoagulation arm over 5 years.
d. After 2 years patients in the ranibizumab arm could receive photocoagulation and vice versa. True
e. After 2 years photocoagulation could be applied in the ranibizumab arm and visual field loss was evident from then on. True.

There are different types of vitreoretinal laser interventions. **Thermal laser** is the classic, continuous-wave light source, applied over intervals from 0.02 to 1.0 seconds per burn. The effect is fundamentally the same as that of conventional light sources such as sunlight or incandescent light. Lasers are compact and efficient sources of light, however, that can be fed into an optic cable. The common photocoagulation lasers produce visible radiation. **Pulsed lasers** that operate on a nanosecond or femtosecond scale produce fundamentally different effects that are non-linear, meaning that the effect can switch from nothing to dramatic at a sharply defined threshold of light flux. The classic use in ophthalmology is in the non-invasive production of microexplosions inside the eye. The most common example is in nanosecond Nd-YAG capsulotomy. A recent application of even faster pulses is femtosecond cataract surgery. In the retina, nanosecond pulses are used in a different manner, namely in the form of trains of nanosecond pulses with thermal effects that are more narrowly confined to the retinal pigment epithelium, so that collateral damage to the photoreceptors and the choriocapillaris can be minimized. The proposed retinal indications of such **micropulsed lasers** are in the treatment of central serous chorioretinopathy, diabetic macular edema and intermediate AMD. Numerous explorative but few definitive clinical intervention trials have been made with micropulsed retinal lasers.

This update of the field of vitreoretinal laser therapy includes trial highlights on photocoagulation versus intravitreal anti-VEGF medication in proliferative diabetic retinopathy, micropulsed laser for intermediate dry AMD without geographic atrophy and laser vitreolysis for Weiss ring floaters.

The 5-year results of the DRCR.net Protocol S study were published recently. While the primary endpoint was defined prospectively and set at two years after initiation, the 5-year outcomes are also of considerable interest to clinicians. The fraction of randomized patients available for the 5-year follow-up was 61 %. There was no significant difference between visual acuity outcomes in the two arms after 5 years and visual field loss began to appear in the ranibizumab arm after 2 years, after which time panretinal photocoagulation could be used to supplement the anti-VEGF treatment. Photocoagulation was given between 2 and 5 years in 14 % of the patients in the ranibizumab arm. Vitreous hemorrhage and neovascular glaucoma rates were comparable, whereas the ranibizumab arm had fewer retinal detachments and fewer vitrectomies. The investigators propose that both treatment options are justifiable. It is important to note that patients in the laser arm received approximately a quarter of the injections that were given in the photocoagulation arm. The total number of anti-VEGF injections giver over 5 years were 19.2 and 5.4, respectively. Thus, combination therapy was available and widely used in both arms.

The randomized, sham-controlled LEAD study of sub-threshold nanosecond laser in AMD evaluated the safety and efficacy in slowing progression of intermediate AMD in a 36-month trial with 292 participants with bilateral large drusen, but no geographic atrophy. Laser or sham treatment was administered at six-monthly intervals. Overall, progression to late AMD was not significantly retarded by laser, but a subgroup analysis found retardation after treatment in participants **without** reticular pseudodrusen (subretinal drusenoid deposits) at baseline and

acceleration in participants **with** reticular pseudodrusen. A new trial in the former type of patients is expected.

A recently published trial of YAG laser vitreolysis versus sham vitreolysis for symptomatic Weiss ring floaters – but no other type of floater – found that after 6 months duration there was subjective improvement in a considerable proportion of vitreolyzed patients. This was supported by validated questionnaires. The investigators were careful to include only patients whose Weiss ring was found at safe distances from the retina and the lens. The study is one of very few adequately controlled trials, it was restricted to Weiss ring floaters and follow-up was short. The results cannot be generalized to other types of vitreous opacity.

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Answers to MCQ's on page 88

1. *a. False*
   b. True
   b. True
   d. False
   e. IFalse

2. *a. False.*
   b. True
   c. True
   d. False
   e. True

3. *a. False*
   b. True
   c. True
   d. False
   e. False

4. *a. False*
   b. False (it was only 66 % excluding deaths)
   c. True
   d. True
   e. True

16

PDT

PARODI MB, Italy

MCQ's

1. **Which of the following are valid PDT treatment protocols:**
   a. Full-fluence, verteporfin 6 mg/m^2, 600 mW/cm^2 for 83 s
   b. Full-fluence, verteporfin 6 mg/m^2, 300 Mw/cm^2 for 166 s
   c. Half-fluence, verteporfin 6 mg/m^2, 300 mW/cm^2 for 83 s
   d. Half-fluence, verteporfin 3 mg/m^2, 600 mW/cm^2 for 83 s
   e. Half-fluence, verteporfin 3 mg/m^2, 50 mJ/cm^2 for 83 s

2. **Which of the following indications are suitable for PDT:**
   a. Diffuse choroidal haemangioma
   b. Choroidal metastasis
   c. Fovea-sparing diabetic macular oedema
   d. Central serous chorioretinopathy
   e. Neovascularisation elsewhere (not at optic disk) in proliferative diabetic retinopathy

3. **Regarding light source parameters in PDT:**
   a. Verteprofin can be stimulated also by infrared light
   b. Verteporfin is selectively stimulated by light at 689 nm
   c. Verteporfin can be stimulated also by light at 532 nm
   d. Once stimlulated verteporfin emits light at 532 nm
   e. Verteporfin is photosensitized only by monochromatic laser light

4. **Which of the following statements apply to the anatomo-clinical effects of PDT:**
   a. Histopathological studies showed choroidal vessel obliteration after full-fluence therapy
   b. Optical coherence tomography angiography showed focal ischemia of the superficial capillary plexus after half-fluence therapy
   c. Optical coherence tomography angiography showed preservation of choriocapillaris after half-fluence therapy
   d. Optical coherence tomography angiography showed focal ischemia of the deep capillary plexus after half-fluence photodynamic therapy
   e. Retinal pigment epithelial atrophy and choroidal ischaemia are possible side effects

PHOTODYNAMIC THERAPY (PDT) is a selective vaso-occlusive mode of treatment involving the use of a photosensitive intravenous drug that produces tissue damage when activated by a low power and long duration red light with minimal damage to adjacent normal structures.

Early models of PDT were developed in the early 1900's, and the first beneficial evidence was derived from treatment of dermatological cancers. PDT was introduced in ophthalmology in the 1990's to treat neovascular age-related macular degeneration (AMD) using the what is now known as the "standard" protocol (see below). Treatment indications later expanded, including a range of other chorioretinal conditions such as choroidal haemangioma, central serous chorioretinopathy (CSC), polypoidal choroidal vasculopathy (PCV), and peripapillary choroidal neovascularization. Various "safety-enhanced" PDT protocols have been devised to optimize treatment outcomes and minimize adverse effects, which include transient vision loss, transient multifocal electroretinogram (ERG) bnormalities, retinal pigment epithelial (RPE) atrophy, RPE tears, secondary choroidal neovascular membrane (CNV), choroidal ischaemia, and choroidal infarction.

1. Mechanism of action

PDT causes release of free radicals when the verteporfin is activated by laser energy. Verteporfin accumulates in the abnormal blood vessels and, when stimulated by nonthermal 689 nm red light in the presence of oxygen, produces highly reactive short-lived singlet oxygen and other reactive oxygen radicals, resulting in local damage to the endothelium and thrombosis. In case of CNVs, this process serves to induce regression.

The "standard" full-fluence protocol is verteporfin 6 mg/m^2, fluency 50 J/cm^2 (600 mW/cm^2) for 83 sec. Evolved proposed protocols include a reduced drug dose (3 mg/m^2) or reduced fluence (25 J/cm^2), generally indicated as "half" or "low-fluence" PDT.

2. Fields of applications

2.1. Choroidal haemangioma

PDT is a valid treatment for haemangiomas that threaten vision by serous retinal detachment. Verteporfin is sequestered in the abnormal, large caliber vessels with limited accumulation in normal choriocapillaris, therefore achieving a selective targeting of the tumour with minimal damage to the overlying neurosensory retina. Choroidal haemangiomas can be effectively treated using the "standard" PDT protocol. Alternative protocols have been reported, generally involving higher laser fluence (100 J/cm^2, that is 600 mW/cm^2 for 166 s). The maximum laser spot size generated by most laser systems is around 7000 µm. Treatment of larger choroidal hemangiomas may require multiple, partially overlapping laser spots (administered during the same treatment session). More than 80% of subjects obtain resolution of the retinal detachment (and tumour regression) with one session, reaching >95% with two sessions.

2.2 Capillary haemangioma

Ability to treat retinal capillary haemangioma with PDT has been shown in different series, but some authors prefer standard thermal laser. Definitive evidence between the two strategies are lacking and results are not as consistent as in treating choroidal haemangiomas.

2.3. Malignancies

For primary malignant tumours, such as choroidal melanoma, PDT does not offer local tumour control rates that are equivalent to or better than those achieved with plaque or proton radiation therapy. On the other hand, it may be able to obtain a complete tumour regression of a small amelanotic choroidal melanoma, with no major effect on visual acuity. For choroidal metastases, PDT can be applied as a palliative treatment.

2.4. Central serous corioretinopathy

Evidence is growing that PDT is an effective treatment option for CSC. Selection of patients for PDT should be guided by factors such as duration, visual impairment and location of leakage site(s) relative to the fovea. Half-fluence PDT can rapidly reduce choroidal hyperpermeability and obliterate the leaking points, leading to a prompt resolution of subretinal fluid (SRF) without significant complications. PDT has been shown to reduce the subfoveal choroidal thickness.

Recently, optical coherence tomography angiography (OCT-A) has demonstrated absence of changes in both choriocapillaris and Sattler & Haller layers of the choroid following half-fluence PDT. Conversely, histopathological studies have found signs of choriocapillaris vascular damage (obliteration and thrombosis). These two observations are in agreement, suggesting that half-fluence PDT exerts its action without permanent significant choroidal damage.

The PLACE trial proved that half-dose PDT provides superior outcomes compared with high-density subthreshold micropulse laser treatment (HSML) with a significantly higher proportion of patients with complete resolution of SRF and functional improvement. The rationale may be found in the fact that PDT targets directly the choroid, primarily affected in CSC, while HSML seems to target the RPE, stimulating its pumping function (without visible damage to the retina).

2.5. Polypoidal choroidal vasculopathy

PDT was investigated in the past for treatment of neovascular AMD, specifically for subfoveal CNV. Randomized protocols such as TAP (Treatment of AMD with Photodynamic Therapy) and VIP (Verteporfin in Photodynamic Therapy) supported its use as compared to placebo. The MONT BLANC trial investigated the role of PDT combined with anti-VEGF in wet AMD, highlighting the non-inferiority of the combined treatment in comparison to ranibizumab monotherapy. Despite positive results, at present the gold standard for typical foveal and extrafoveal CNV in wet AMD is intravitreal anti-VEGF monotherapy.

Nevertheless, PDT maintains a significant role in treatment of a specific subtype of wet AMD: PCV. Indocyanine green angiography (ICGA) -guided PDT treatment of active (leaking) polyps can resolve macular oedema and SRF through direct occlusion of the polyps. One to two treatments are usually performed to achieve the regression. PDT treatment for PCV may be complicated by subretinal haemorrhage, a potential sight-threatening event. Limitation of the spot size to include only active polyps and spare the branching vascular network, and half-fluence PDT can decrease the incidence of haemorrhage.

Anti-VEGF alone also has been found to be beneficial in the treatment of PCV, effectively reducing macular oedema. Considering its limited and variable effect on direct polyp regression, anti-VEGF role has been investigated in conjunction with PDT. The EVEREST trial indeed found that PDT with 0.5 mg ranibizumab (or PDT only) was superior to ranibizumab monotherapy in achieving complete regression of polyps in patients with PCV.

2.6. Dome-shaped macula

Dome-shaped macula, particularly when associated with high myopia, is a controversial and challenging condition for which no specific treatment algorithm is available. Literature suggests that myopic eyes associated with a dome-shaped macula and foveal fluid may be responsive to PDT, even showing total resolution of fluid and functional improvement. The beneficial effect is limited to eyes where baseline ICGA shows evidence of a limited hypocyanescent macular area.

3. Conclusions

PDT played a strategic role in the clinical management of a variety of neovascular disorders in the "pre anti-VEGF era", such as wet AMD or myopic CNV. At present, PDT is used as a second-line therapy in wet AMD patients not responding to any anti-VEGF agent, or in whom the treatment burden of monthly injections is too heavy. Additional to this, it is still virtually the only effective treatment for PCV patients. Furthermore, emerging strong evidence supports the use of PDT for persistent or recurring forms of CSC. It seems to give promising results when applied for benign vascular tumours, such as circumscribed choroidal haemangioma.

Increased knowledge concerning the pathogenesis of neovascular-based diseases would likely result in gradual development of more selective photosensitizers and of combination strategies with improved therapeutic benefits for patients, and increased potential for long-term vision improvement.

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Answers to MCQ's on page 93

1. a. *True*
   b. *False*
   c. *True*
   d. *True*
   e. *True*

2. a. *True*
   b. *True*
   c. *False*
   d. *True*
   e. *False*

3. a. *False*
   b. *True*
   c. *False*
   d. *False*
   e. *False*

4. a. *True*
   b. *False*
   c. *True*
   d. *False*
   e. *True*

17

Radiotherapy

PARROZZANI R, Italy

MCQ's

1. **Regarding cell death mechanisms induced by radiation therapy:**
   a. Senescence is a condition of permanent cell cycle arrest and occurs following extensive cellular stress induced by radiation
   b. Apoptosis is the major cell death mechanism by which haematopoietic tumours respond to radiotherapy
   c. Mitotic catastrophe is the major cell death mechanism by which solid tumours respond to radiotherapy
   d. Mitotic catastrophe is the major cell death mechanism by which haematopoietic tumours respond to radiotherapy

2. **Which of the following statements correctly characterizes radiation side effects:**
   a. The radiosensitivity of the lens is higher compared to that of the sclera
   b. Radiosensitivity is the relative susceptibility of cells, tissues, organs or organisms to the harmful effect of ionising radiation
   c. The radiosensitivity of the lens is lower compared to that of the retina
   d. Radiation retinopathy is characterised by vascular occlusion, leakage, oedema, and lipid exudation

3. **Regarding the mechanism of action of radiotherapy in oncology:**
   a. The type of cell death is determined by the type and the dose of radiation, and by the molecular profile of the target cells
   b. The damage in the cell DNA causes deprivation of cancer cells of their reproductive potential
   c. The loss of the reproductive potential of a tumour cell is biologically equivalent to cell death
   d. The survival of a tumour cell after irradiation, even with no reproductive potential, is a failure of the radiotherapy purpose

4. **Regarding radiation side effects in ocular structures:**
   a. Radiation optic neuropathy mainly occurs as an indirect effect secondary to radiation-induced optic nerve vasculopathy
   b. Radiation optic neuropathy is a result of a direct effect of radiation to the lamina cribrosa
   c. Scleral necrosis often occurs even after low dose radiotherapy of the globe
   d. Multiple factors (e.g., age, condition of tissue, local and systemic disease) can affect the incidence and the severity of ocular side effects

RADIOTHERAPY IS A MAIN TREATMENT MODALITY against human cancer. The type of cell death is determined by the type and the dose of radiation, and by the molecular profile of the target cells. Ionising radiation displaces electrons from atoms to produce ion pairs, consisting of positive and negative electrons, which damage molecular bonds. Ionising radiation also interacts with water to produce free radicals that have unpaired electrons. Ionising radiation may damage cells directly, by disrupting chemical bonds in molecules, and indirectly, by the formation of toxic-free radicals. The damage in the cell DNA causes the deprivation of cancer cells of their reproductive potential, through cell death mechanisms.

1. Mechanism of action of radiotherapy

The major cell death mechanisms induced by radiotherapy (RT) are:

- Apoptosis (for haematopoietic tumours and, rarely, tumours originating from epithelial cells)
- Senescence (for solid tumours)
- Mitotic catastrophe (for solid tumours)

Apoptosis is the main cell death modality observed in response to irradiation of cells naturally prone to apoptosis, such as haematopoietic cells and their malignant counterparts. The cells are typically programmed for rapidly induced apoptotic death occurring within hours after exposure to radiation. Conversely, in solid tumours apoptosis only plays a modest role, because these neoplastic cells typically lose their pro-apoptotic mechanisms during progression. Therefore, in solid tumours other cell death modalities play a more relevant role, including radiation-induced senescence, a form of proliferative cell death, and radiation-induced mitotic catastrophe. The inactivation of p53 that modules apoptosis, seems to promote rather than repress the induction of mitotic catastrophe.

1.1. Apoptosis

Tumours originating from tissues highly susceptible to apoptosis more commonly respond to radiation with the induction of p53-dependent apoptosis. Suppression of p53 in these tumours results in resistance to treatment. Protein p53 is the guardian of the genome that controls the target genes that influence cell cycle arrest, DNA repair, apoptosis, and senescence. Following irradiation, activation of p53 promotes cell survival by growth arrest and DNA damage repair. However, depending on the extent of damaged DNA and the cell type, p53 can also activate elimination routes for damaged cells by apoptosis or senescence. The way p53 turns on or off genes depends on many co-factors that differentially regulate the ability of p53 to bind specific subsets of target genes.

Radiation-induced apoptosis is characterized by pyknosis, cell shrinkage, and internucleosomal breakage of chromatin, all hallmarks of apoptotic death. Execution of apoptosis is closely linked to the activation of caspase-3, caspase-6, and caspase-7. These caspases are crucial for the demolition phase of apoptosis, and their targets include mediators and regulators, structural proteins, cellular DNA repair proteins, and cell cycle proteins. Radiation can induce apoptosis

also through another pathway that involves mitochondrial outer membrane permeabilisation that disrupts the mitochondrial function. Following radiation, p53 activates transcription of pro-apoptotic genes (the Bax-like family and the BH3-only proteins). The anti-apoptotic genes (the Bcl-2 family) block the apoptosis. So p53 can mediate the transcriptional repression of anti-apoptotic genes.

1.2. Mitotic catastrophe

Mitotic catastrophe is a cell death mechanism that occurs during or as a result of aberrant mitosis. It is generally considered a consequence of premature or improper entry of a cell into the mitotic phase, and can be induced by a multitude of DNA-damaging agents, including radiation. Aberrant mitosis produces an atypical chromosome segregation and cell division, and leads to formation of giant cells with aberrant nuclear morphology, multiple nuclei, and several micronuclei.

There are two mechanisms for the induction of mitotic catastrophe: first, a mitotic catastrophe may be the consequence of DNA damage and deficient cell cycle checkpoints. Checkpoint inactivation is frequently a consequence of mutation/inactivation of p53. In cells with impaired p53, a premature entry into mitosis because of a compromised G2/M checkpoint, will occur. The second mechanism is hyperamplification of centrosomes. During normal mitosis, centrosomes make bipolar mitotic spindles, and they are important for accurate chromosome segregation. Hyperamplification of centrosomes may result in a multipolar mitotic spindle, which causes an abnormal chromosome segregation and generates cells with multiple micronuclei or binucleated giant cells followed by mitotic catastrophe. These cells can continue through several cycles of cell division, acquiring an increasing amount of chromosomal aberration, finally causing cell death. Centrosome hyperamplification has been reported to occur as a result of DNA damage and compromised DNA repair mechanisms. The activity of the CDK2-cyclin A/E complex is critical for the initiation of centrosome amplification and is regulated by p53. Activation of p53 inhibits CDK2 activity, blocking centrosome duplication. Consequently, centrosome hyperamplification is frequently observed in cells lacking functional p53.

The mitotic catastrophe is characteristic of most non-haematopoietic tumour cells in response to ionising radiation. It is the major cell death mechanism by which solid tumours respond to radiotherapy. This process is a delayed type of cell death starting days after treatment, which can explain why clinical regression of solid tumours is usually slow.

1.3. Senescence

Senescence is a condition of permanent cell cycle arrest and occurs following extensive cellular stress. It is a radiation-induced mechanism that inhibits tumour growth. Senescent cells display characteristic phenotypic traits as they enlarge and flatten with an increased granularity. The marker for senescence is the staining for senescence-associated -galactosidase of lysosomal compartments in the perinuclear region of cells. Senescent cells acquire extensive alterations in gene expression, including inhibition of genes involved in cell proliferation and induction of several intracellular and secreted growth inhibitors. Replicative senescence depends on the activation of two major tumour suppressor pathways controlled by p16/pRB and p53/

p21. Both signalling pathways can initiate, but are also important for, the maintenance of the senescence-associated growth arrest. Senescence induced in tumour cells in response to radiation treatment is promoted by p53 and it is generally accompanied by expression of p21. When p53 signalling is impaired, radiation-induced senescence may be abolished and has been linked to a loss of cytotoxic effect of radiation on cancer cells. Senescent cells do not divide (biological death), but may remain metabolically active.

2. Radiosensitivity of ocular structures

Radiosensitivity is the relative susceptibility of cells, tissues, organs, and organisms to the harmful effect of ionising radiation. Each ocular and orbital structure have its own radiosensitivity: some tissues have a higher resistance to radiation (for example the sclera), whereas other tissues (for example the lens) are more radiosensitive. Even if is not possible to determinate an exact dose-response relationship for ophthalmic side effect, mainly because multiple factor (e.g., age, condition of tissue, local and systemic disease) can affect the incidence and the severity of radiation oculopathy, the following table shows the doses after which side effects usually appear.

Organ at risk	*Total dose (Gy)*
Eyelids and lashes	10-30 Gy
Lacrimal apparatus	30-40 Gy
Lens	2-8 Gy
Sclera	60 Gy
Iris	10-40 Gy
Retina	30-45 Gy
Choroid	45-60 Gy
Optic nerve	60 Gy

2.1. Retina

After radiation, retinal blood vessels become depleted of endothelial cells with thickening of their basement membranes. Small vessels develop outpouchings, fusiform dilatation, and microaneurysms. These changes result in vascular occlusions, leakage, oedema, and lipid exudation. Narrowing of capillary lumens and localised closure causes ischaemia and infarction. Exudative retinal detachment can occur as a result of increased vascular permeability.

2.2. Retinal pigment epithelium (RPE)

Irradiated RPE develops atrophy, melanin loss, lipofuscin accumulation, and areas of hyperplasia. Clinically, these RPE changes appear as scattered areas of hyper- or hypopigmentation.

2.3. Choroid

Radiation effects on the choroid are predominantly vascular, and include beading, telangiectatic-like dilatations, microaneurysms, sclerosis, closure, and neovascularisation.

2.4. Optic nerve

Radiation optic neuropathy mainly occurs as an indirect effect secondary to radiation-induced optic nerve vasculopathy. Glial cells show demyelination and neurons degeneration. Optic nerve blood vessel changes cause infarction and gliosis. As a result, the nerve shows areas of necrosis with lymphocytic infiltrates.

2.5. Iris

Direct effects of radiation include atrophy, reduced thickness, and loss of cellularity. Principal indirect effect is rubeosis that may lead to neovascular glaucoma.

2.6 .Lens

Radiation damages the DNA of proliferative lens epithelial cells that become rounded and bladder-like. Lens fibres become deformed and debris accumulates in the sub-capsular regions.

2.7. Sclera

Scleral necrosis can occur after high-dose radiotherapy because of ischemia and inflammation, aggravated by tumour necrosis.

RECOMMENDED READING

Recent

1. Seregard S, Pelayes DE, Singh AD. Radiation therapy: posterior segment complications. Dev Ophthalmol. 2013;52:114-23.
2. Mendez CA1, Singh AD. Radiation therapy: anterior segment complications. Dev Ophthalmol. 2013;52:102-113.
3. Groenewald C. Konstantinidis L. Damato B. Effects of radiotherapy on uveal melanomas and adjacent tissues. Eye 2013;27:163-171.
4. Eriksson D. Stigbrand T. Radiation-induced cell-death mechanisms. Tumour Biol. 2010;31: 363-372.

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Padova, Italy

Answers to MCQ's on page 99

1. a. *True*
   b. *True*
   c. *True*
   d. *False*

2. a. *True*
   b. *True*
   c. *False*
   d. *True*

3. a. *True*
   b. *True*
   c. *True*
   d. *False*

4. a. *True*
   b. *False*
   c. *False*
   d. *True*

18

Immunosuppression and biologics

BODAGHI B, France

MCQ's

1. **Adalimumab:**
   a. Is an anti-IL6 drug
   b. Is administered subcutaneously
   c. May be used in patients with Behçet's disease
   d. Is contraindicated in children with uveitis
   e. Should not be used more than 2 years

2. **Which of the following may be proposed to a patient with severe sympathetic ophthalmia:**
   a. Enucleation
   b. Systemic corticosteroids
   c. Azathioprine
   d. Cyclophosphamide
   e. Methotrexate

3. **Regarding methotrexate :**
   a. Therapeutic indication are limited, especially in children with intermediate uveitis
   b. The drug is administered daily
   c. Dosage is usually between 10 to 20 mg/week
   d. Gastroiintestinal tolerance may be a limitation
   e. Gain of weight may occur

4- **Regarding TNF alpha inhibitors:**
   a. Tuberculosis must be excluded before initiation
   b. Brain MRI may be mandatory in cases of intermediate uveitis
   c. The drug is usually administered every 4 weeks
   d. The drug should be combined with low dose methotrexate in all cases
   e. Inefficacy may be due to anti-anti-TNF antibodies

5- **Which of the following entities require immediate immunosuppression or immunomodulation in most cases:**
   a. Behçet's disease with posterior segment involvement
   b. Sympathetic ophthalmia
   c. Birdshot retinochoroidopathy
   d. Intermediate uveitis
   e. Non-occlusive retinal vasculitis

I - Treatment objectives
- a. Strict control of ocular inflammation with and without associated active systemic disease
  - i. Corticosteroids
  - ii. Corticosteroids sparing agents
    1. Conventional immunosuppressors
       - a. Local
       - b. Systemic
    2. Biologic agents
- b. Prevention and control of inflammatory complications
  - i. Macular edema
  - ii. Subretinal detachment
  - iii. Choroidal neovascularization
  - iv. Retinal fibrosis

II - Modalities of action
- a. Conventional immunosuppressors
  - i. Mechanisms of action
  - ii. Antimetabolites
    1. Folic acid analogues
       - a. Methotrexate
    2. Purine analogues
       - a. Azathioprine
  - iii. Inhibitor of Inosine-5′-monophosphate dehydrogenase
    1. Mycophenolate mofetil
  - iv. Alkylating agents
    1. Cyclophosphamide
  - v. Drugs acting on immunophilins
    1. Ciclosporin
    2. Tacrolimus
    3. Sirolimus
- b. Biologic agents
  - i. Mechanisms of action
  - ii. Monoclonal antibodies
    1. TNF-alpha inhibitors
    2. Anti-IL6
    3. Anti-IL1
    4. Anti-CD20
  - iii. Interferon alpha
  - iv. Others

III - Treatment initiation and monitoring
- a. Initiation
  - i. Selected cases
  - ii. After excluding contraindications: tuberculosis or other infections, multiple sclerosis
  - iii. In collaboration with internists and rheumatologists
- b. Monitoring
  - i. Efficacy
    1. Clinical scores
    2. Multimodal imaging
    3. Anti-drug antibodies
  - ii. Tolerance
    1. Complete blood cell count
    2. Liver function

IV - Which treatment for which disease?

A- Anterior
- a. JIA and B27 uveitis with macular edema

B- Intermediate
- a. Idiopathic

C- Posterior
- a. Birdshot retinochoroïdopathy
- b. White dot syndromes
  - i. CMF +/- panuveitis
  - ii. ABISE
  - iii. APMPPE
  - iv. Serpiginous choroiditis
  - v. AZOOR

D- Panuveitis
- a. Behçet's disease
- b. Sarcoidosis
- c. Vogt-Koyanagi-Harada disease
- d. Sympathetic ophthalmia

RECOMMENDED READING

1. Jabs DA. Immunosuppression for the uveitides. Ophthalmology. 2018;125:193-202.
2. Dick AD, Rosenbaum JT, Al-Dhibi HA, et al. Fundamentals of Care for Uveitis International Consensus Group. Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis: Fundamentals Of Care for UveitiS (FOCUS) initiative. Ophthalmology. 2018;125:757-773.
3. Goto H, Zako M, Namba K. Adalimumab in active and inactive, non-infectious uveitis: global results from the VISUAL I and VISUAL II trials. Ocul Immunol Inflamm. 2018:1-11; doi: 10.1080/09273948.2018.1491605. [Epub ahead of print]
4. Ozguler Y, Leccese P, Christensen et al. Management of major organ involvement of Behçet's syndrome: a systematic review for update of the EULAR recommendations. Rheumatology (Oxford). 2018; doi: 10.1093/rheumatology/key242
5. Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group, Kempen JH, Altaweel MM, Holbrook et al. Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. JAMA. 2017;317:1993-2005.
6. Diwo E, Gueudry J, Saadoun D, et al. Long-term efficacy of interferon in severe uveitis associated with Behçet disease. Ocul Immunol Inflamm. 2017;1-8; doi: 10.1080/09273948.2017.1332768. [Epub ahead of print]

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Answers to MCQ's on page 106

1. a. *False*
   b. *True*
   c. *True*
   d. *False*
   e. *False*

2. a. *False*
   b. *True*
   c. *True*
   d. *True*
   e. *False*

3. a. *True*
   b. *False*
   c. *True*
   d. *True*
   e. *False*

4. a. *True*
   b. *False*
   c. *False*
   d. *False*
   e. *True*

5. a. *True*
   b. *True*
   c. *False*
   d. *False*
   e. *False*

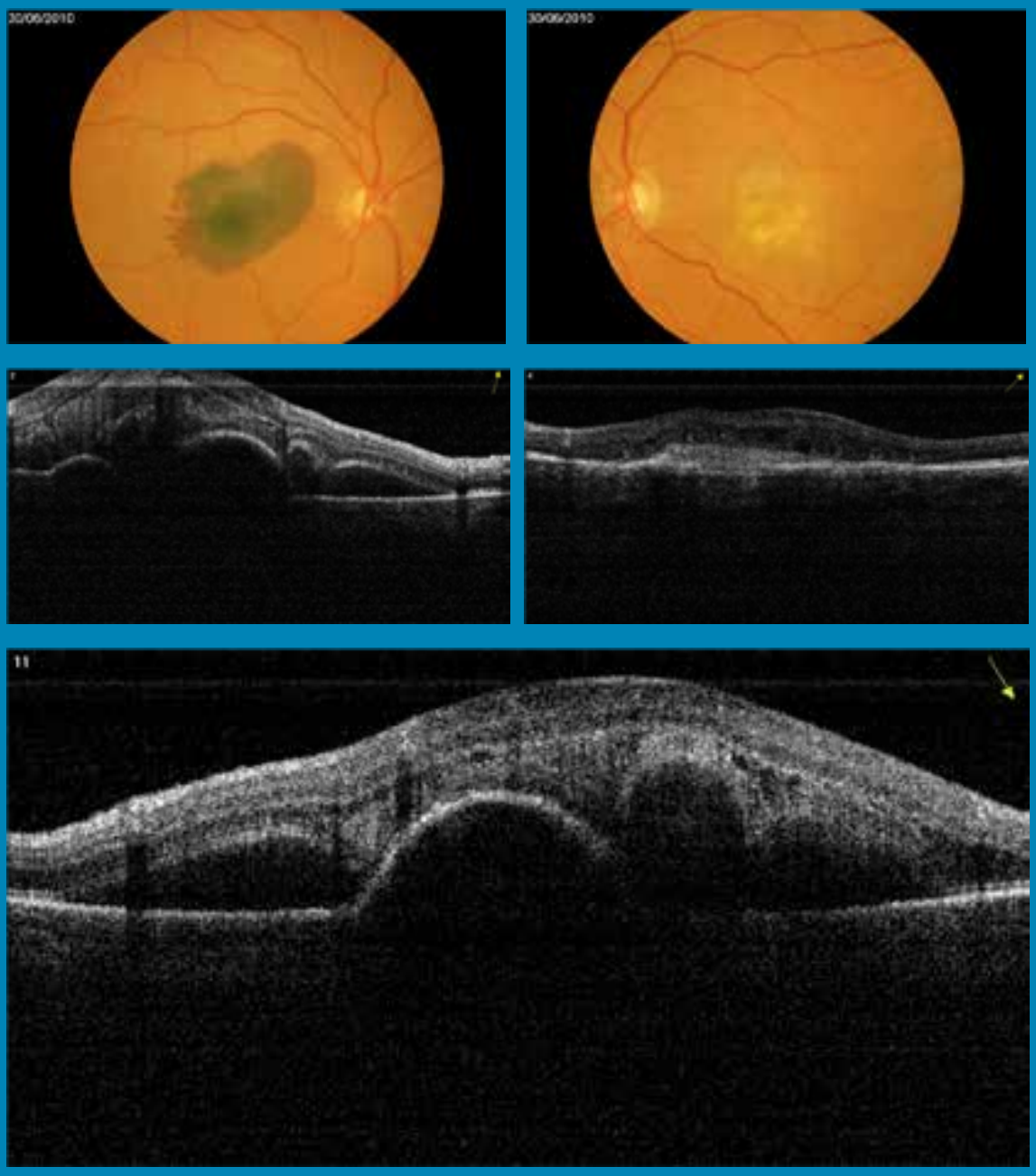
RT2

Round table 2: How do you treat these cases?
Case PARODI MB

A 55-year-old previously healthy man was referred with gradual vision decrease, relative central scotoma, and metamorphopsia in his left eye since 3 months. His best corrected visual acuity was 20/20 in the right eye and 20/63 in the left one. Multimodal imaging including multicolour and infrared scanning laser ophthalmoscopy, blue light autofluorescence, indocyanine green angiography and spectral domain optical coherence tomography found a serous neuroepithelial detachment with irregularity of the ellipsoid zone and retinal pigment epithelium involving the macular area, with focal signs of leakage. Optical coherence tomography angiography showed a hyperreflective tissue at the choriocapillaris level.

RT2

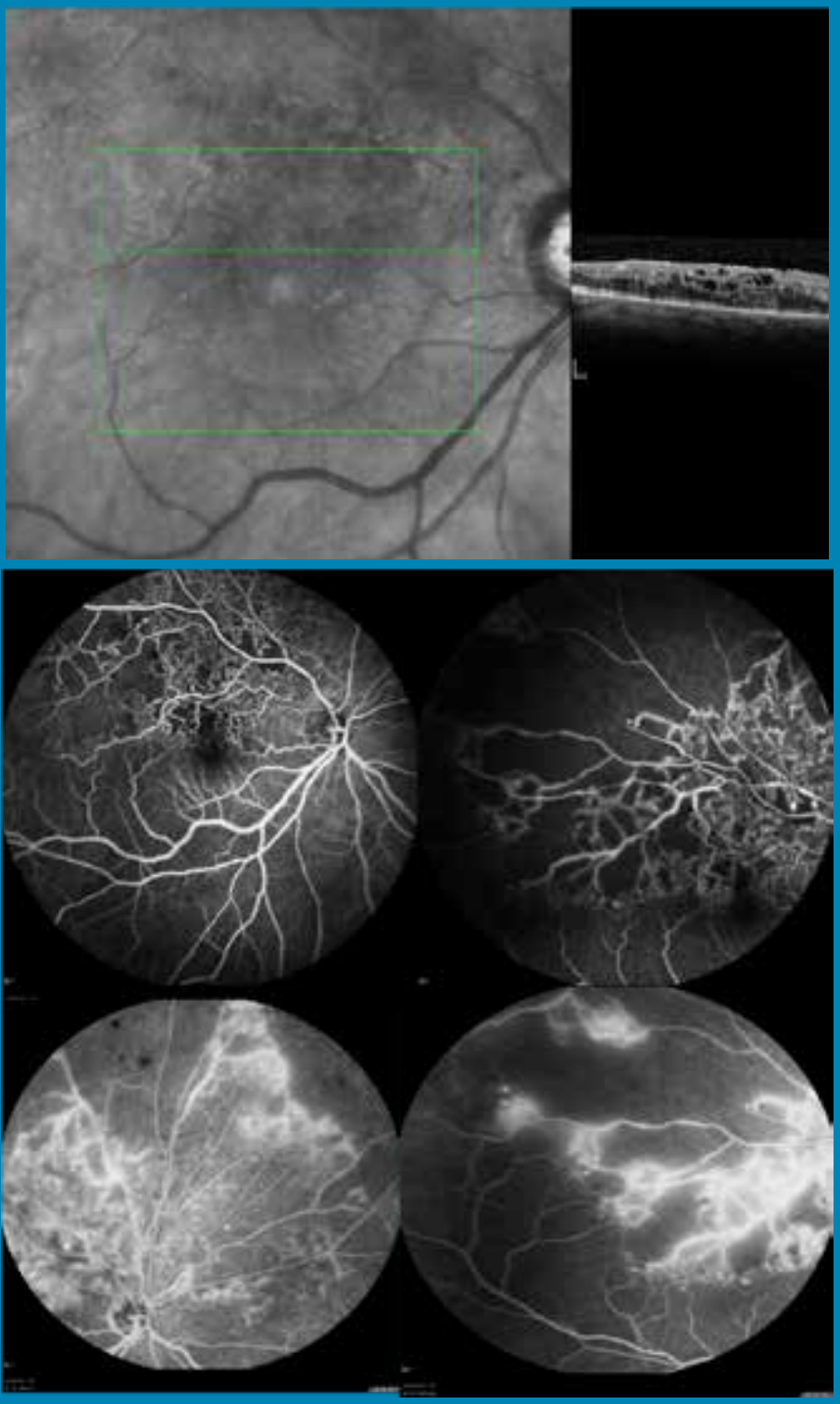
Round table 2: How do you treat these cases?
Case 1 – CREUZOT C



Case 1: A 78-year-old woman with a history of visual loss in her left eye from exudative age-related macular degeneration. acute loss of vision from the right eye.

RT2

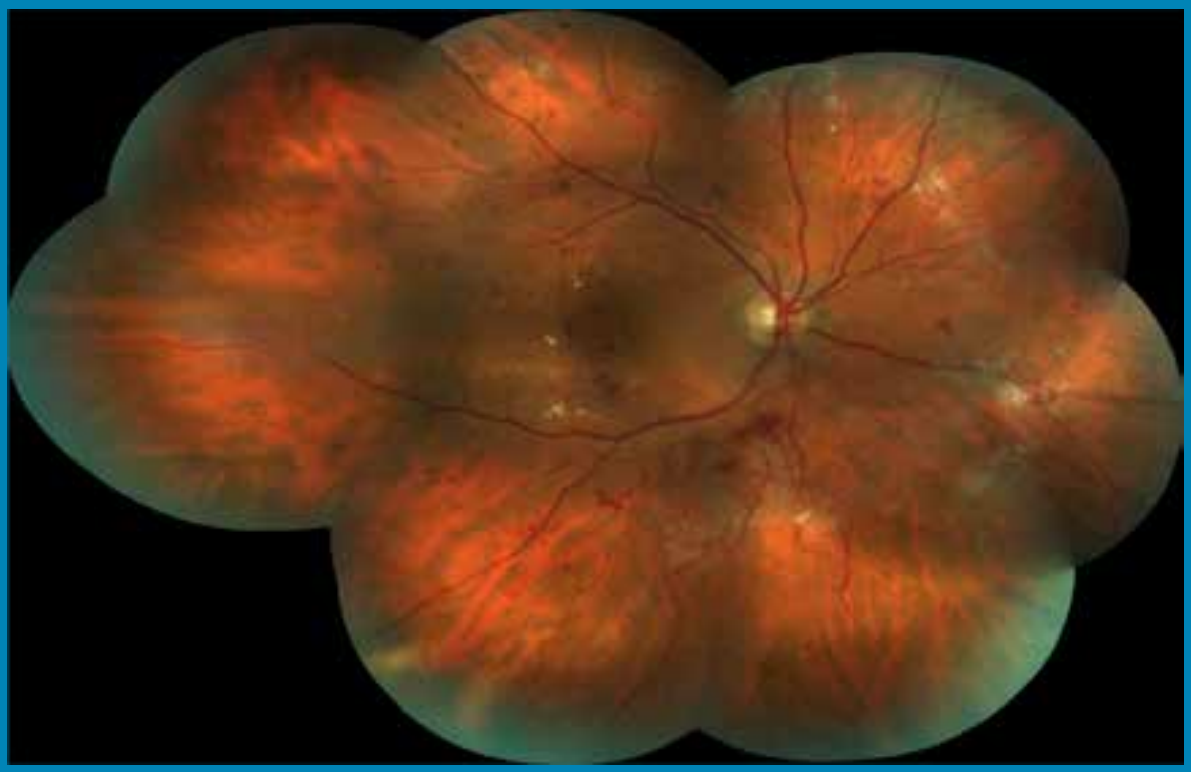
Round table 2: How do you treat these cases?
Case 2 – CREUZOT C

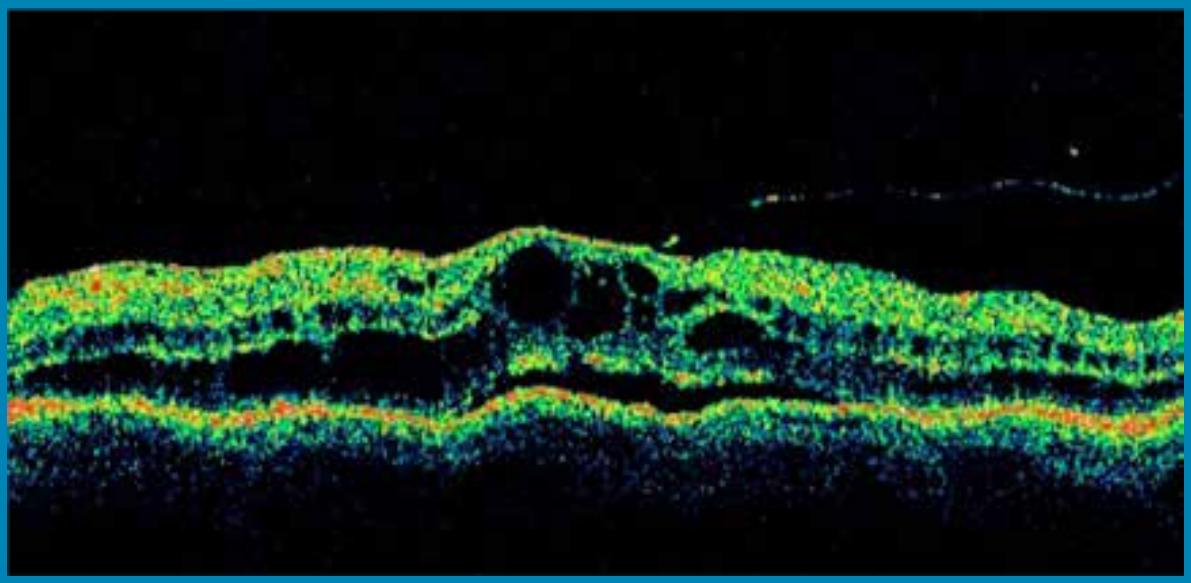


Case 2. A 44-year-old woman with visual loss in her right eye. The visual acuity score is 46 letters on the ETDRS chart (approximately 0.16).

RT2

Round table 2: How do you treat these cases?
Case 3 – CREUZOT C

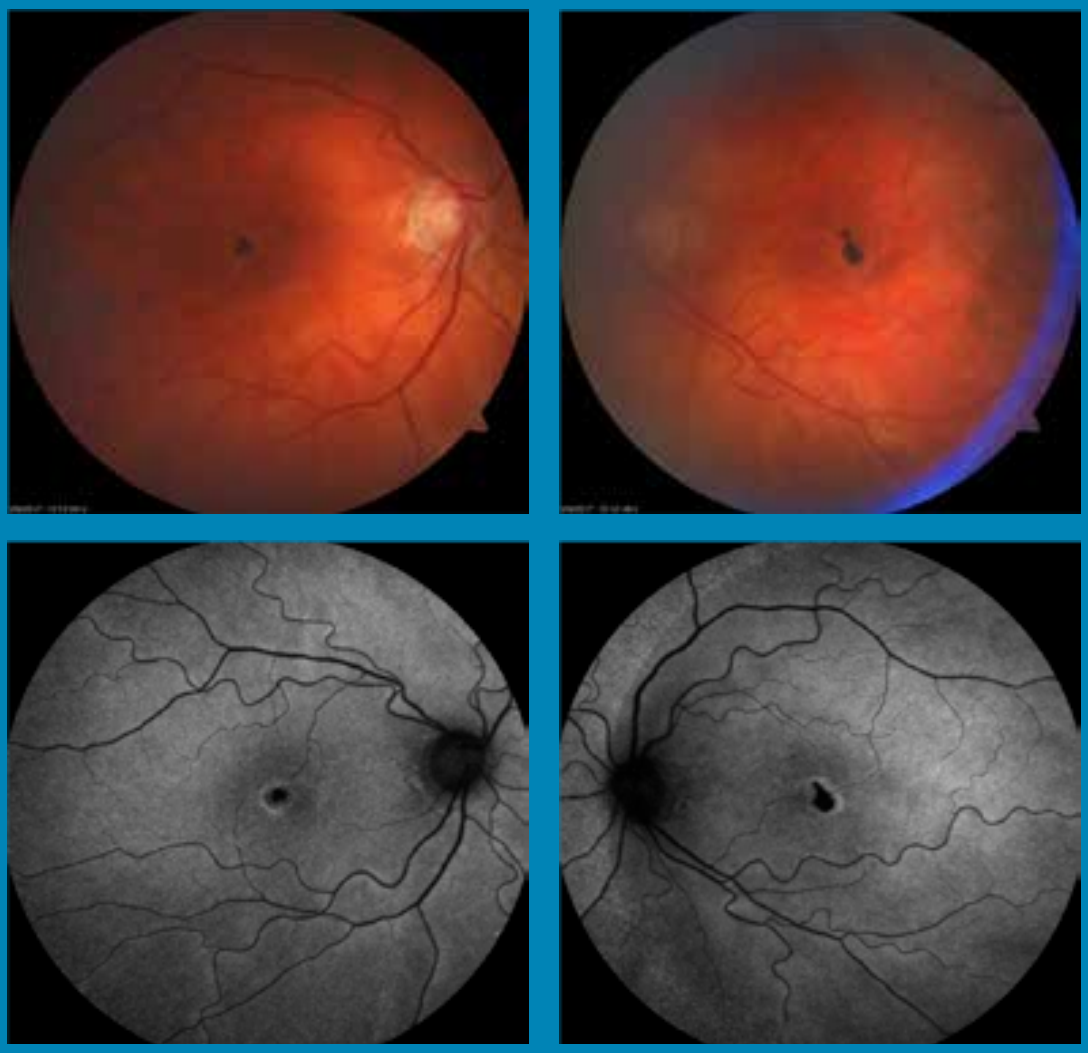




Case 3: A 60-year-old diabetic patient. Recent HbA1c level 9% and blood pressure 165/90 mmHg. Visual acuity of the right eye is 20/70 (0.3).

RT2

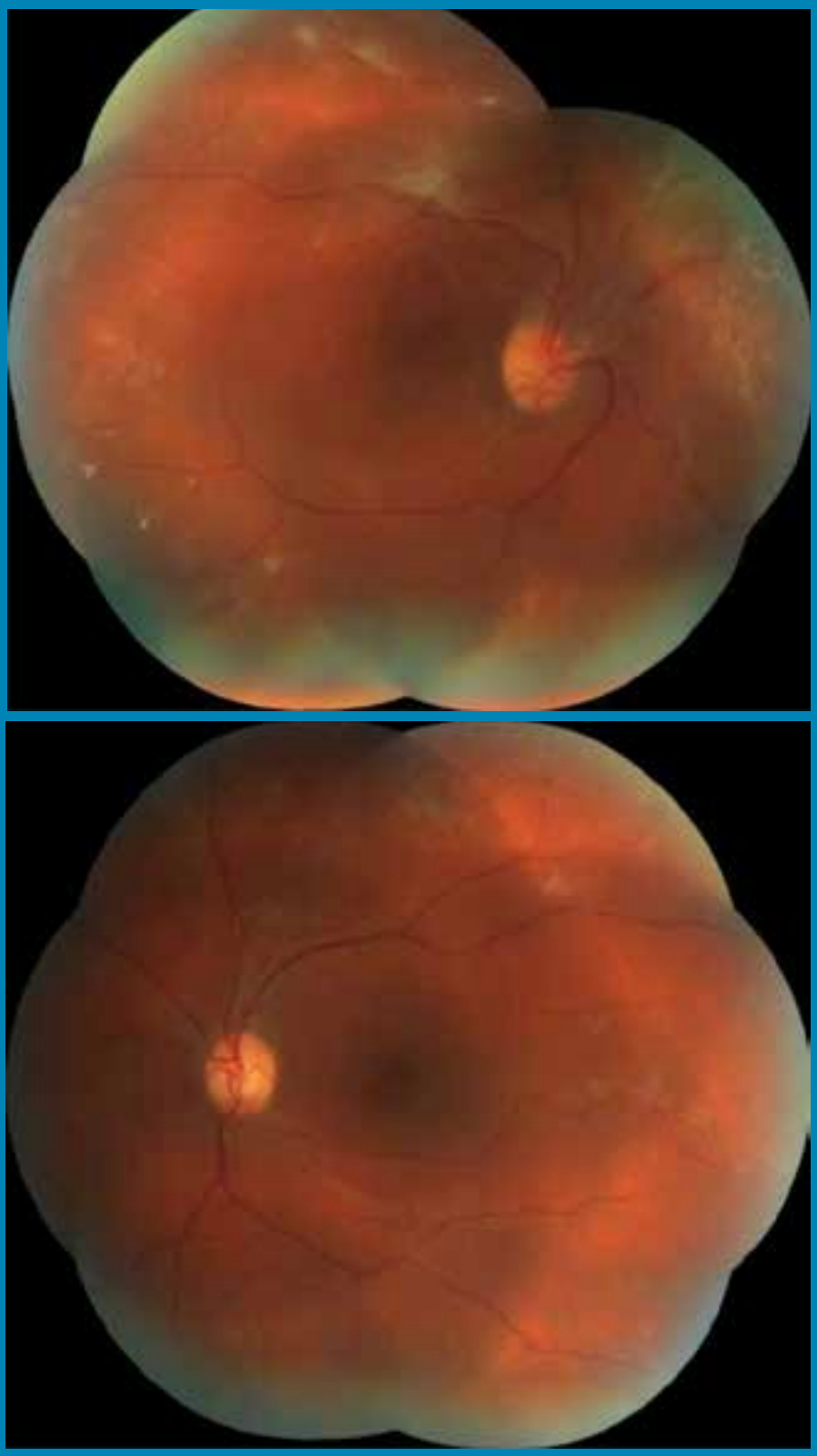
Round table 2: How do you treat these cases?
Case 4 – CREUZOT C



Case 4: An 86-year-old woman with a bilateral macular abnormality.

RT2

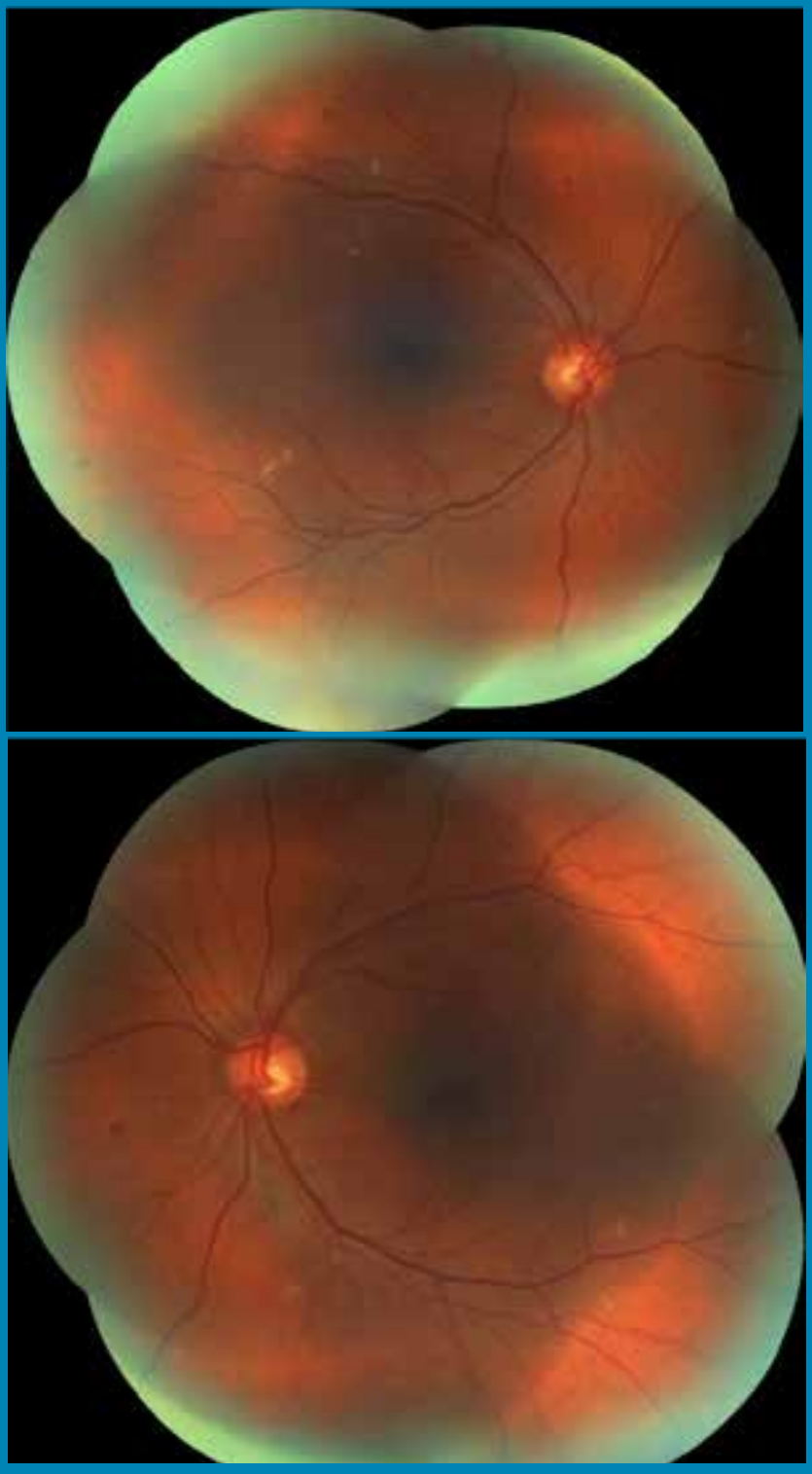
Round table 2: How do you treat these cases?
Case 5 – CREUZOT C



Case 5: A 34-year-old woman with type 1 diabetes has been pregnant or 2 months. Her HbA1c level is 7,5%. Her visual acuity is 20/25 (0.8) in both eyes.

RT2

Round table 2: How do you treat these cases?
Case 6 – CREUZOT C

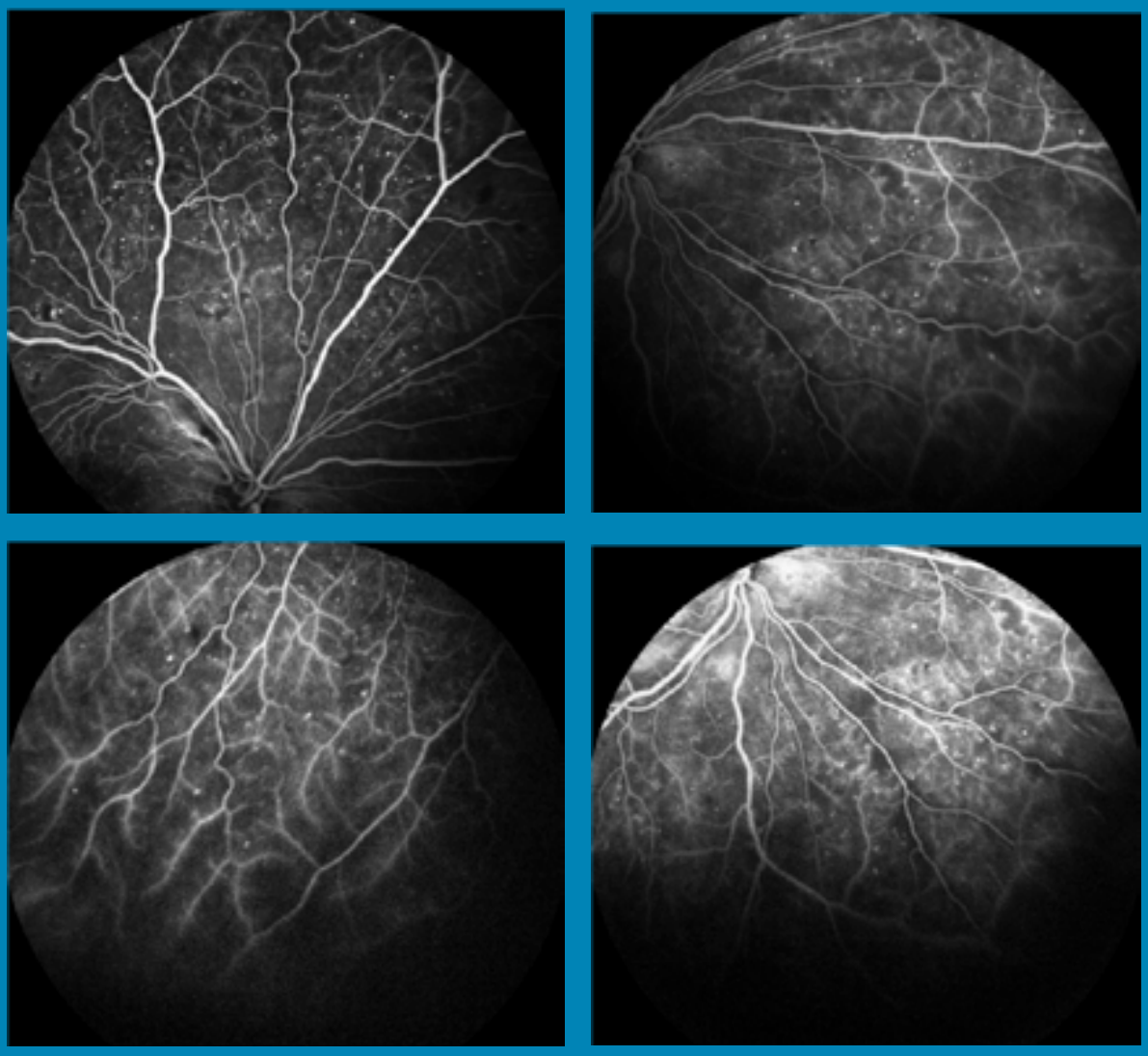


Case 6: A patient with type 1 diabetes, HbA1c: level 10% and blood pressure 135/80 mmHg. Visual acuity is 20/20 (1.0) for both eyes.

(continues…)

RT2

Round table 2: How do you treat these cases?
Case 6 – CREUZOT C

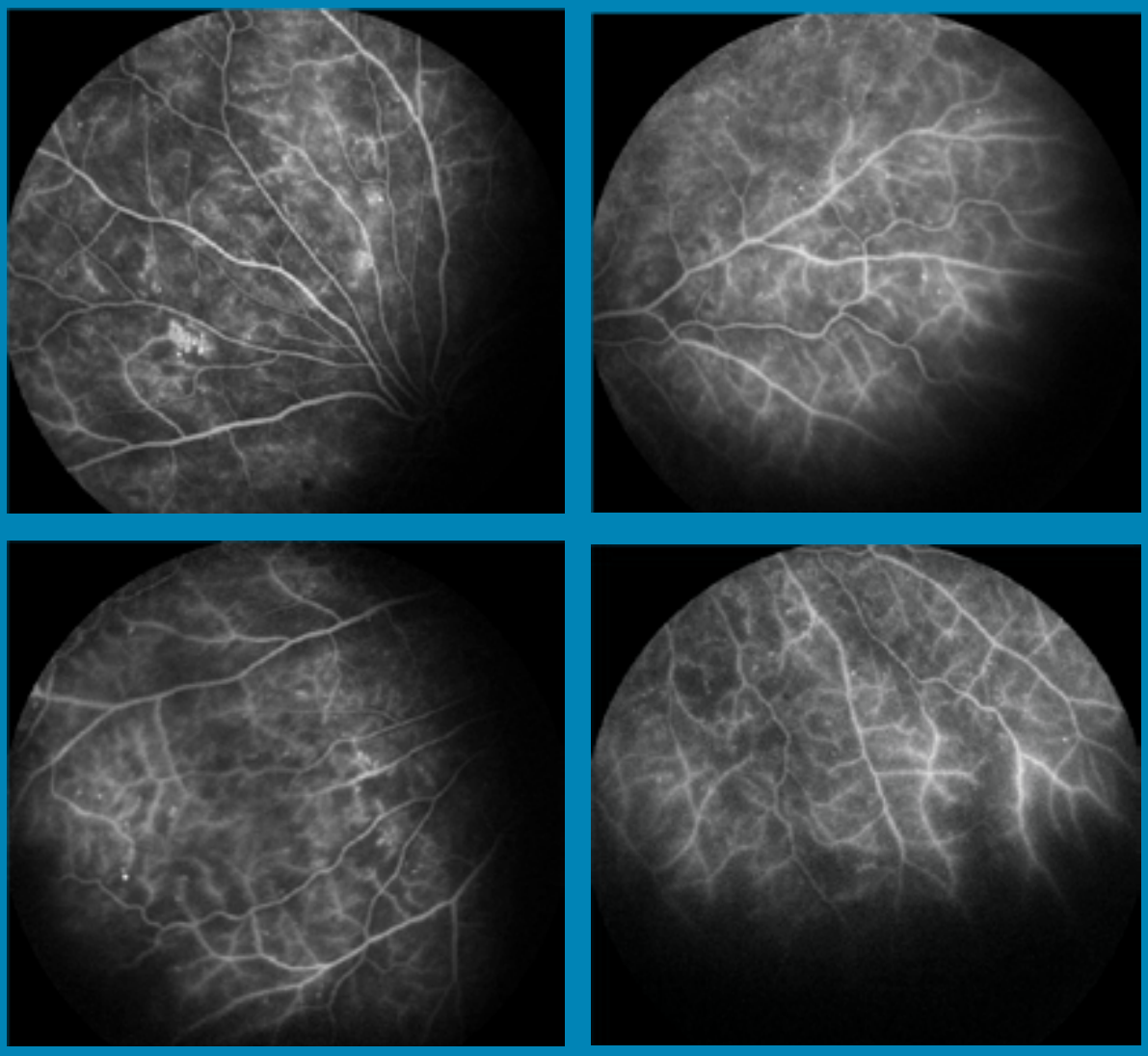


Case 6 continues: Fluorescein angiogram of the right eye.

(continues…)

RT2

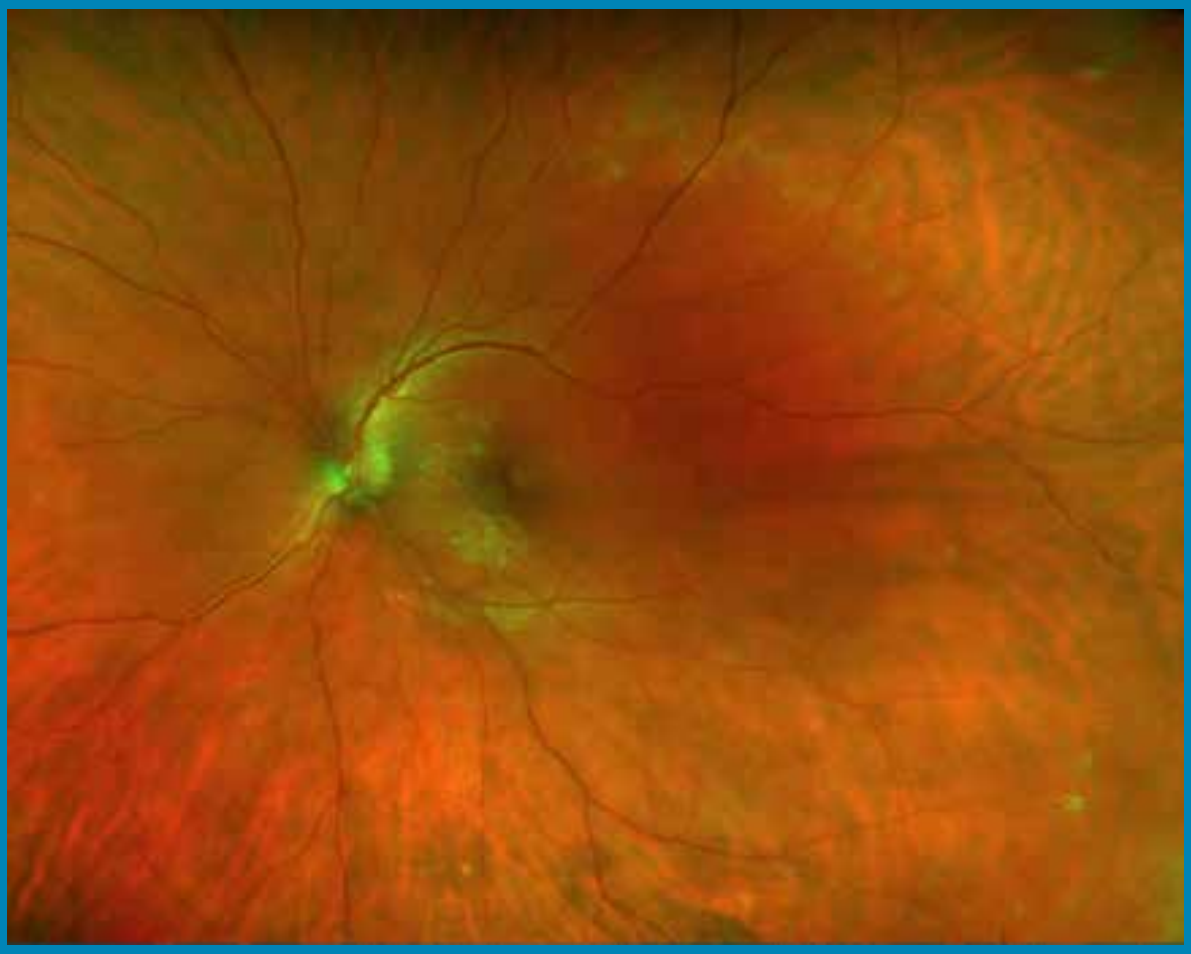
Round table 2: How do you treat these cases?
Case 6 – CREUZOT C



Case 6 continues: Fluorescein angiogram of the left eye.

RT2

Round table 2: How do you treat these cases?
Case 1 – JONES N



Case 1: A 24-year-old man presented with subacute central visual loss of his left eye. He was diagnosed at his local eye unit (images unavailable) with APMPPE and presecribed prednisolone 60 mg/day. After 2 weeks and slight visual improvement he was referred to the uveitis clinic. He was fit, active and usually worked overseas doing voluntary work, most recently for several months in Sri Lanka. He recalled a viral-type illness a few weeks before the onset of visual symptoms. He had no illnesses abroad and could not recall insect bites. He was in regular contact with cats, dogs, and monkeys. He denied sexually transmitted infections, and had no significant history.

On presentation 6 weeks after the onset of symptoms (Optomap above) his white blood cell count was 15.5 and he was lymphopenic at 0.4. He had a slightly raised ALT 45 and a slightly raised bilirubin 32. Renal function was normal, erythrocyte sedimentation rate was 45, and CRP was 8. His visual acuity was 0.0 logMAR (1.0), OD, and 0.4 (0.4), OS. The right eye was entirely normal. The left eye was quiet with no cells in anterior chamber or vitreous.

Differential diagnosis?
Risk factors?
Further investigations?

RT2

Round table 2: How do you treat these cases?
Case 2 – JONES N

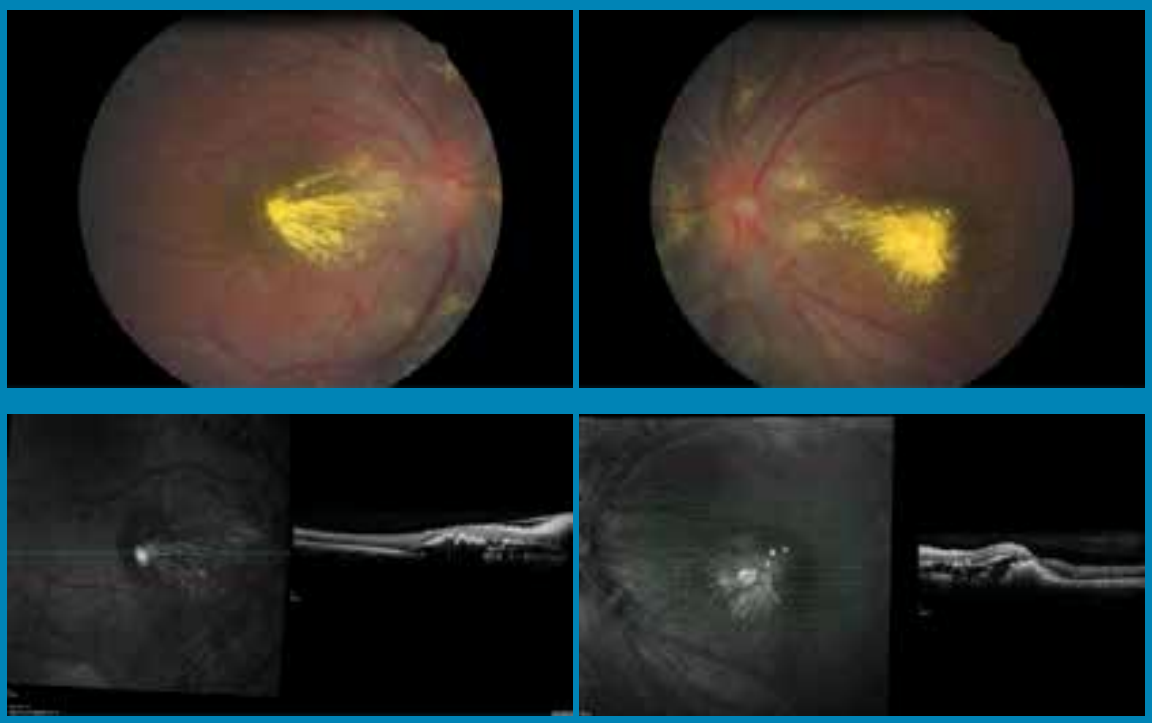
Case 2: A 56-year-old man presented with a 3-week-long history of central visual blur in his left eye. He had no associated systemic symptoms and no prodrome; specifically, he had no headache, no fever, no skin rash, no cough or respiratory symptoms, and no weight loss. Two years previously he had been found to be HIV-positive. He was fit and well on highly active antiretroviral therapy (HAART) with normal blood count and no known infections. He had recently returned from a visit to India. He was an alcoholic, but denied drug abuse.

At presentation (Optomap above) his visual acuity was 0.2 logMAR (0.6), RE, and 0.5 (0.3), OS. The right eye was entirely normal. The left eye was quiet and had no cells in anterior chamber or vitreous. Full blood count, and liver and renal function tests were normal. The erythrocyte sedimentation rate was 50, CRP 3, ACE 49, and chest X-ray normal.

What can you see?
What is your differential diagnosis?
What further imaging and investigations would you arrange?

RT2

Round table 2: How do you treat these cases?
Case 1 – BODAGHI B

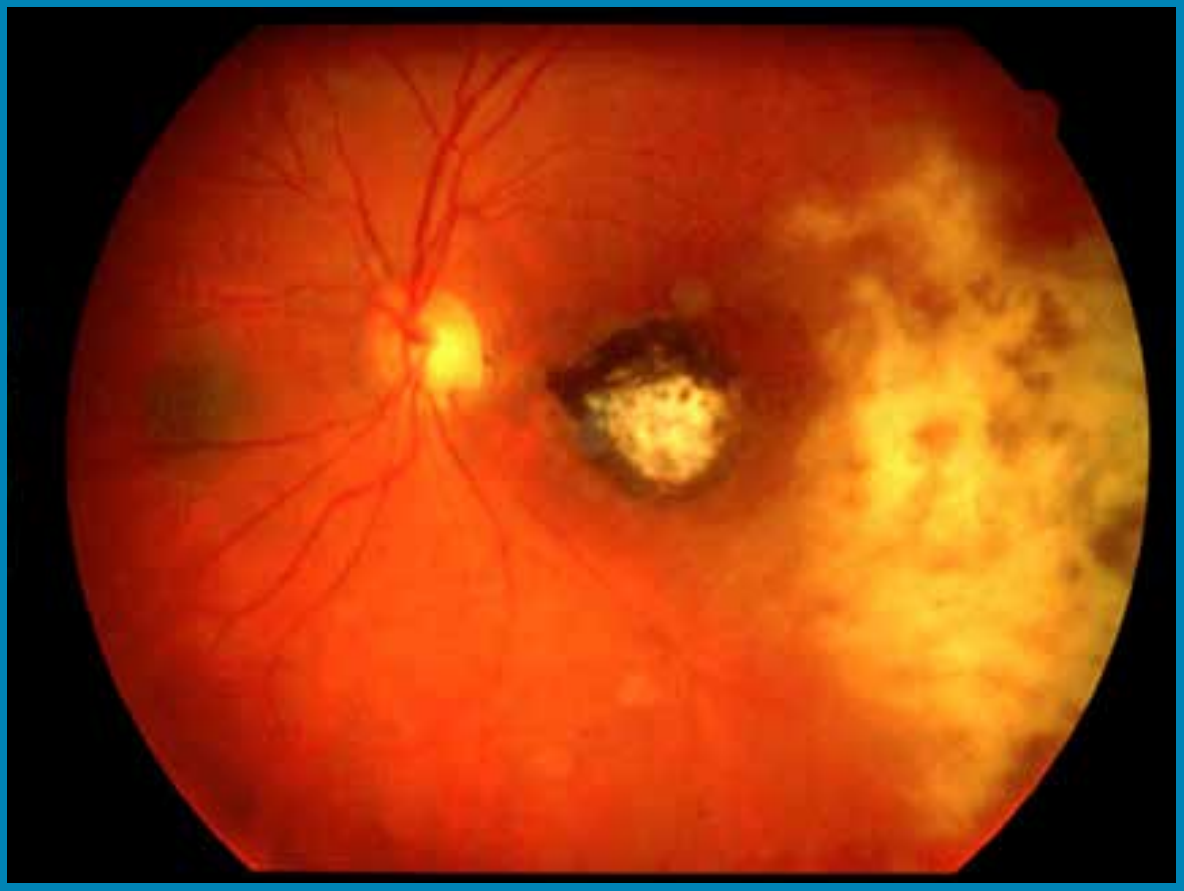


Case 1: An 11 year-old female was referred for the management. Past medical history and review of systems revealed nothing unusual. She reported contact with a cat. Visual acuity was 20/100 (0.2), OD, and 20/200 (0.1), OS.

Differential diagnosis?
Further diagnostic investigations?
Therapeutic options?
Prognosis?

RT2

Round table 2: How do you treat these cases?
Case 2 – BODAGHI B



Case 2: A 35-year-old Caucasian woman was referred for discomfort of her left eye. Past medical history included a kidney transplantation; she received conventional immunosuppressors to avoid graft rejection. Her visual acuity was 20/20 (1.0), OD, and counting fingers, OS. Anterior segments were normal. No vitreous haze.

Differential diagnosis?
Diagnostic investigations?
Treatment?

19 Inherited disease: from diagnosis to treatment

AUDO I, France

MCQ's

1. In Best Disease

a. Vitelliform deposits are hyper autofluorescent
b. Fluorescein angiography should always be performed
c. Only the electro-oculogram is necessary
d. Full field electroretinogram is severally abnormal
e. There is 1/4 chance of recurrence to the brothers/sisters of an affected child

2. Stargardt disease

a. Is the most common form of macular dystrophy
b. Full field electroretinogram is not necessary
c. A peripapillary sparing on fundus autofluorescence is typical of the diagnosis
d. Fluorescein angiography is not necessary for the diagnosis
e. There is 1/4 chance of recurrence to the brothers/sisters of an affected child

Inherited retinal diseases (IRD) are a heterogeneous group of disorders both clinically and genetically. The diagnosis process lies on a precise process including:

Personal (specifically ophthalmic history with nystagmus, high myopia, cataract, symptoms at onset, hearing difficulties, extra-digits, renal abnormalities, etc.) and familial history (family tree+++, history of high myopia in mother if it is a male patients, nystagmus, etc). The family tree will help determine a potential mode of inheritance which, for IRD can follow Mendelian inheritance (e.g. Best disease is dominantly inherited whereas Stargardt disease is autosomal recessive and choroideremia is X-linked inherited) or can be maternally inherited through mitochondrial DNA (e.g. rare mitochondriopathy including Kearns Sayre, MELAS, MIDD)

Standard ophthalmic examination, with a precise documentation of refractive error, visual acuity, lens opacities, vitreous and retinal changes

Psychophysical tests, more specifically kinetic visual fields which will also have a legal value (driving, social impact and support), as well as static perimetry

Electrophysiology which should be performed according to the ISCEV standard (https://iscev.org). **Full field (or Ganzfeld) electroretinogram (ffERG)** is the key examination while suspecting an IRD. It will mainly document peripheral retinal function and has limited macular contribution. It will distinguish between photoreceptor diseases (rod cone dysfunction, cone or cone rod dysfunction, respectively in retinitis pigmentosa/rod-cone dystrophy, cone dystrophy, achromatopsia, cone-rod dystrophy) and inner retinal diseases (such as in X-linked retinoschisis or congenital stationary night blindness- complete-ON-defect, and incomplete- both ON- and OFF-bipolar defect). FFERG is critical for the diagnosis but also has prognosis value (degree of retinal dysfunction, or abnormal ERG in Stargardt disease, in these cases FFERG should always be tested). **Multifocal ERG** will document macular function and may also have some prognostic value for instance in rod-cone dystrophy to evaluate macular preservation. **Electro-oculogram (EOG)** is only indicated in case of vitelliform deposits while suspecting Best disease or its allied disorders. It tests the function of both photoreceptor and retinal pigment epithelium (RPE). Therefore, to conclude on RPE dysfunction in case of an abnormal EOG, it is necessary to document normal photoreceptor function on the FFERG. **Visual Evoked Potentials (VEP)**, which are testing the entire visual pathway from the macula, the optic nerve to the visual cortex, would be only interesting for a differential diagnosis with an optic neuropathy (usually in case of a normal fundus to distinguish between genuine or non organic visual loss and macular or cone dystrophy versus optic neuropathy). Macular function should always be tested in case of abnormal VEPs (with pattern or multifocal ERG) to distinguish between macular dysfunction and optic neuropathy.

Retinal imaging

Aside colour fundus photographs, the past decades have seen significant progress in refining the resolution of retinal imaging with a certain functional value. These new retinal imaging are non invasive and have led to the development of a new semiology. It is now illegitimate

to perform angiography (fluorescein or indocyanin green) since they don't add any diagnostic value, are invasive and, especially for fluorescein angiography, deliver a significant amount of potential 'toxic' light in comparison with non invasive retinal imaging. They should only be performed in case of rare suspicion of neovascular complications or in atypical cases to distinguish with posterior uveitis. **Fundus autofluorescence imaging (FAI)**, most commonly performed in short wave length, give dynamic information of photoreceptor/RPE interaction while visualizing the lipofuscin, by product of photoreceptor outer segment renewal and phagocytosis by the RPE. Spectral domain optical coherence tomography (SD-OCT) documents the precise architecture of the retina. In the context of IRDs, it will document the preservation of the outer retinal bands, the thickness of the outer nuclear layer and the present of subretinal deposits. It will also be critical detect complications such as intraretinal cysts, epiretinal membranes or neovascular membrane. OCT-A can be useful for the later complication.

After this diagnostic pipeline the type of IRD can be precisely documented. A molecular diagnosis can subsequently be available and, due to the genetic heterogeneity of the disorders, is now most commonly based on next generation sequencing targeting a panel of genes that are implicated in IRDs which will also help genetic counselling.

IRDs can be subdivided into congenital but **stationary disorders** (including congenital stationary night blindness and achromatopsia) or **progressive and degenerative** with a variable age of onset. This later group can be further subdivided into the **initially/predominantly rod photoreceptor** alteration (e.g. rod-cone dystrophy or retinitis pigmentosa and its allied disorders) versus **initially/predominantly cone photoreceptor** alteration (e.g. maculopathy such as Stargardt, pattern dystrophies, Best diseases or more sever cone and cone-rod dystrophy). Leber congenital amaurosis is a severe, often congenital, form of IRD that can manifest either with rod-cone or cone-rod profound dysfunction. These IRDs can be restricted to the retina or part of syndromes such as Usher syndrome, Bardet-Biedl syndrome or spinocerebellar ataxia.

There is currently no curative treatment but patients should be supported as best as possible. They should be advised to wear sun protections, avoid tobacco and retinotoxic medications (essentially chloroquine and hydroxychloroquine). They should be referred to a low vision aid clinic and children should have an appropriate school support. Specific complications should be managed accordingly (e.g. macular cysts with carbonic anhydrase inhibitor, cataract surgery, etc.).

Promising therapeutic trials are ongoing including gene replacement therapy, neuroprotection, artificial retina and cell therapy. In December 2017, the first gene therapy product was approved by the FDA as a treatment and should pave the way for other therapies.

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20

Macular oedema

AUDO I, France

MCQ's

1. In Rod-cone dystrophy

a. intra retinal cysts can occur in up to 50% of the cases
b. it is less common with CRB1 mutations
c. full field ERG is not necessary for the differential diagnosis in this context
d. Carbonic anhydrase inhibitors remain the first line of treatment
e. Carbonic anhydrase inhibitors should be discontinued if there is no effect after one month of treatment

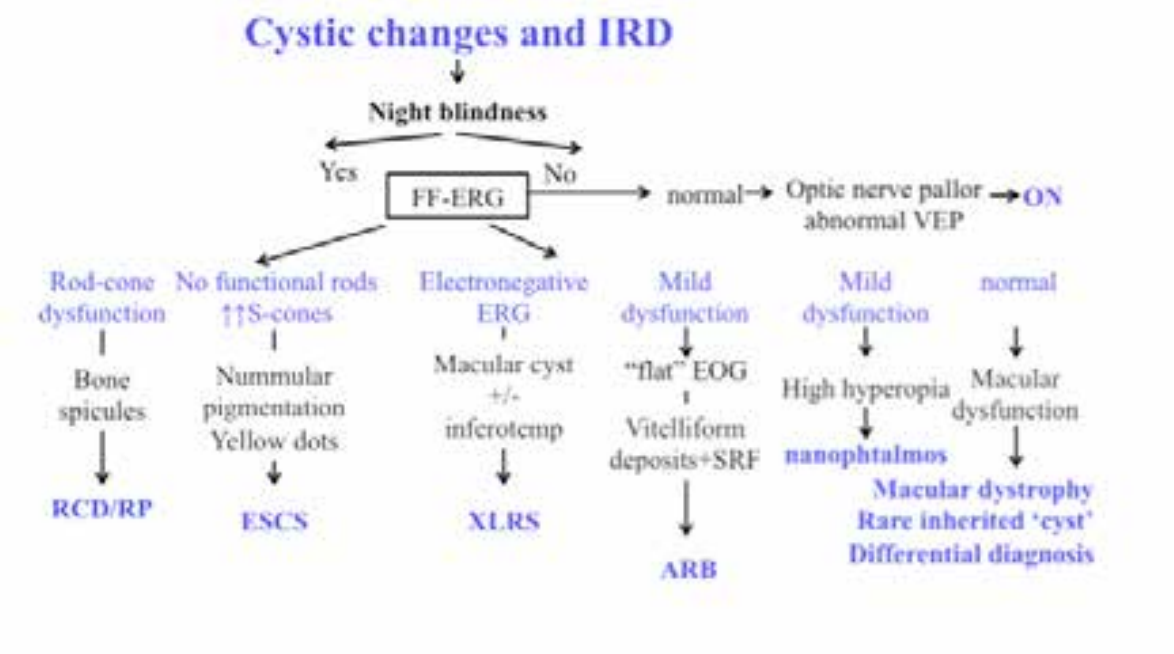
2. in Enhanced S-cone syndrome

a. patients usually don't complain of night blindness
b. full field ERG shows typical changes with no rod responses and increased S-cone response
c. patients have typical bone spicules pigmentation
d. patients may display yellow dots on fundus examination
e. it is an autosomal dominant disorder

Macular edema should be differentiated from **intraretinal cysts** as the first one is associated with blood-retinal barrier (BRB) rupture whereas the second is mainly due to an altered retinal structure with little if any BRB rupture. Intra retinal cysts tend to be symmetrically centered on the fovea and show no correlation between macular thickness and visual acuity. Major causes of macular edema and intraretinal cysts are the following with bold items being in fact more cystic than edematous

- Diabetic retinopathy
- Retinal vein occlusion (RVO)
- Vitreomacular tractions
- Ocular surgery/Irving-Gass syndrome
- Injuries/ocular trauma
- Uveitis
- Medications (e.g. prostaglandin, epinephrin, nicotinic acid and niacin, etc)
- **Inherited retinal diseases**
- **Optic neuropathies**
- **Optic nerve pit**
- Etc…

The course will discuss intraretinal cysts associated with inherited retinal diseases and emphasize the importance of symptoms (night blindness or not) as well as electrophysiology for a proper differential diagnosis. This is summarized in the following schematic.



Regarding treatment, there are no specific guidelines for the management of intra retinal cyst. Anhydrase carbonic inhibitors remain the first line standard treatment in RP/RCD with less or little effects in other IRDs. It usually consists of either oral treatment (eg Diamox 250mgx2/j + K+) or topical Azopt/trusopt 1gtteX3/day, and the patient should be informed on the necessity of prolonged treatment (at least 6 months) with possible delayed effect, in absence of contra-indication.

In case of failure, there may be indication for intravitreal steroids but the risk/ benefice ratio should be weighted carefully.

A better knowledge of the underlying pathogenic mechanisms of cystic changes in IRD is needed with natural history study to improve treatments.

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21

Toxoplasmosis

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MCQ's

1. Toxoplasma gondii is:

a. a protozoan
b. an opportunistic parasite
c. potentially responsible for congenital fetal damage
d. a nematode
e. a trematode

2. It is possible to be infected with T. gondii by:

a. Eating uncooked contaminated meat
b. Eating contaminated vegetables
c. Being stung by a mosquito
d. Walking in the mud
e. Bathing in a river

3. Congenital toxoplasmosis:

a. Is secondary to transplacental transmission of the parasite
b. Never gives serious clinical lesions to the fetus
c. Causes clinical lesions of the fetus, never the newborn or the child
d. Perhaps causing ocular lesions revealed in childhood
e. Is absent from the industrialized countries

4. Screening for toxoplasmic infection in a pregnant woman is based on:

a. The clinic
b. Demonstration of the parasite in peripheral blood
c. Serology
d. Brain Imaging
e. The interrogation of the patient

Ocular toxoplasmosis represents the most frequent form of posterior uveitis in the world (20-60% of cases).[1] It can lead to irreversible visual loss if the macula and/or optic nerve is involved, or when complicated by vitreal opacities, epiretinal membrane or retinal detachment. The real impact of treatments on the natural history of the active disease or its recurrence remain obscure.

1. Pathogenesis

Toxoplasmosis is due to an ubiquitous parasite, *Toxoplasma gondii.* It is a single-celled, obligate intracellular protozoan parasite that infects many different species worldwide. Cats are the definitive host as the parasite reproduces sexually in their small intestine producing highly resistant oocysts, which after excretion in feces remain infective for more than 1 year. Infected animals (pig, chicken, mouse, sheep, *etc*.) and humans serve as intermediate hosts. Transmission routes are variously: (1) ingestion of water, fruit or vegetables contaminated with oocysts, and cat feces in soil or sand boxes; (2) ingestion or manipulation of raw or undercooked meat, and meat containing tissue cysts (bradyzoïtes); (3) ingestion of eggs and milk contaminated by tachyzoïtes; (4) inhalation of oocysts (e.g., from cat litter or bedding); and between humans ***via*** (5) blood transfusion; (6) organ transplantation; and (7) transplacental transmission of tachyzoïtes (*i.e.* congenital toxoplasmosis). Prevention should be aimed at avoiding these risks, *e.g.*, meat cooked to an internal temperature of 67°C, or frozen to below -12°C, kills bradyzoïtes and prevents such infection.[2]

Parasites initially cross the intestinal wall and cause an acute parasitemia. They actively penetrate cells and start replicating. During the chronic phase in human tissues, they lie quiescent (bradyzoïtes), especially in muscle, eye (internal retina, mostly) and brain. *Toxoplasma gondii* may reach the eye from blood.

2. Ocular manifestations

Acquired post-natal infection is distinguished from congenital pre-natal infection. Post-natal infection may represent two-thirds of ocular toxoplasmosis cases and pre-natal infection one-third.[3] However, the classical distinction between the two etiologies is not always evident clinically, as the ocular manifestations and serological tests that characterize the chronic stage do not discriminate between them. Exceptions occur if there is evidence of organ damage *in utero* or in early infancy (microphthalmia, cerebral calcifications, hydrocephalus, *etc.*), when the pre-natal infection is almost certain, and in adolescents or adults (retinitis in the absence of a retinochoroidal scar), when post-natal infection is probable. Otherwise, in the current absence of other pathognomonic features, it is not possible to differentiate clinically between pre-natal and post-natal toxoplasmosis.[3]

The most common ocular manifestation of congenital toxoplasmosis is retinochoroiditis, but associated ophthalmologic manifestations may occur.[4,5] Few reports deal with this topic, but associated ocular pathologies have been reported in at least 34% of patients.[4, 6-9] The most frequent conditions leading to visual impairment are, as follows: strabismus, microphthalmia,

cataract, retinal detachment, optic nerve atrophy, iridocyclitis, nystagmus, glaucoma, choroidal neovascularization, and phthisis. We published a cross-sectional study of 430 consecutive children, born between March 1975 and October 2001 with proven congenital toxoplasmosis who were monitored since birth at the Croix-Rousse Hospital, Lyon, France.[4] After a median follow-up of 12 years [range 0.6 to 26], almost one-third of children (N=130: 30.2%) presented with retinochoroiditis. We detected 22 retinochoroiditis foci at birth and a further 264 during follow-up, of which 48 (17%) were active at first diagnosis. During follow-up, an initial peak of retinochoroiditis was observed before 1 year and a second peak between 7 and 8 years, with a hypothetical third peak during puberty.[5] Twenty-five patients (N=130: 19%) had associated ocular lesions, namely, strabismus due to macular lesions (N=21: 86%), unilateral microphthalmia (N=7: 5.4%), and cataract (N=4: 3%). Most conditions were detected after the onset of retinochoroiditis. In the absence of chorioretinal lesions no child presented with further ocular abnormalities. Macular lesions were most frequent in patients with other ocular lesions ($p<0.0001$) which represented a significant risk factor for macular lesions ($p=0.0003$). Visual impairment in 31/130 cases was related to macular retinochoroiditis in all but three eyes, but was unrelated to associated lesions which were less frequent than expected in this cohort. Perhaps additional ocular lesions occur later in life and become an indirect severity marker of congenital toxoplasmosis. As such pathologies may arise later in life and remain unpredictable, assessment of the ocular impact of congenital toxoplasmosis requires long-term ophthalmic follow-up, especially in children with retinochoroiditis and macular lesions. Parents should be informed not only about the risk of retinochoroiditis, but of its associated lesions and possible consequences.[4] Clinicians, parents, and older children with congenital infection, should be told that late-onset retinal lesions and relapse can occur many years after birth, that long-term follow-up is essential, but that the overall ocular prognosis of congenital toxoplasmosis is satisfactory.

The main symptoms of ocular toxoplasmosis in adult life are floaters (spots in front of the eyes), visual impairment when either the macular or optic disk is involved, severe anterior or vitreous inflammation, and scotoma (Jensen's scotoma if at the juxta-papillary focus). With granulomatous acute anterior uveitis and posterior synechias, clinical examination may show anterior chamber involvement.

Posterior segment inflammation is almost always present. In France, toxoplasmosis was the primary etiology of posterior uveitis in a series of 927 cases. The parasite infects primarily the retina with secondary involvement of the choroid and vitreous. The typical pattern in 80% of patients, as recently described by Bosch-Driessen *et al.* was a focal necrotizing retinochoroiditis frequently at the edge of a pigmented retinal scar.[10] It appeared as a grey-white focus of retinal necrosis exudation with undefined margins. This focal retinitis was often associated with choroiditis, local or diffuse vitreous reaction, retinal vasculitis and hemorrhage. Vitritis could be severe and dense thereby hiding details of the fundus. Sometimes the retinitis focus could barely be seen, resembling a 'headlight in the fog'. A retinochoroidal scar with very well defined margins appeared, 6 to 8 weeks later and was sometimes pigmented.

Atypical manifestations of ocular toxoplasmosis can also occur. These may involve the anterior segment, posterior segment, or both. Ocular toxoplasmosis manifests itself in many forms, *i.e.*: punctate outer retinitis, neuroretinitis, papillitis, pseudo-multiple retinochoroiditis, multifocal or diffuse necrotizing retinitis, serous macula detachment without retinochoroiditis, intermediate uveitis, vitritis without retinochoroiditis, vasculitis without retinochoroiditis, unilateral pigmentary retinopathy, or scleritis. Anterior manifestations may resemble granulomatous iridocyclitis without retinochoroiditis, or a Fuch's anterior uveitis.

Several posterior manifestations of toxoplasmosis can threaten visual function, especially when the macula or optic disk are involved, will be considered next. All require emergency management and close follow-up.[11] First, in young adults, active neuroretinitis lesions may occur adjacent to the optic disk which becomes edematous and hyperemic. This condition is often associated with neuroepithelial serous detachment (leading to macular scar during resorption), venous dilatation, peripapillar hemorrhage and severe vitritis. Treatment must be aggressive and initiated rapidly in order to prevent loss of visual acuity. Second, an isolated papillitis without retinochoroidal lesion can present with sudden visual impairment due to an afferent pupillary defect secondary to optic disk involvement. The absence of a retinochoroiditis focus is misleading and often makes diagnosis difficult. Optic nerve atrophy can cause permanent loss of vision. Differential diagnoses, according to context, are Cytomegalovirus papillitis, optic disk fungal abscess, sarcoidosis and ischemic optic neuropathy. Third, multifocal or diffuse necrotizing retinitis mimics viral acute retinal necrosis. With ocular toxoplasmosis necrotizing progression is slower with a gap separating necrosis and the pars plana. It affects mostly immunocompromized and elderly patients (aged >50 years).[12] Fourth, a peripheral extensive necrotizing retinitis with severe vitritis can often delay diagnosis. Without specific treatment it may be associated with retinal detachment and a severe outcome. All the foregoing posterior ocular manifestations of toxoplasmosis may lead to a variety of complications that can impair vision, *e.g.*, retinal detachment, epiretinal membrane, choroidal neovascularization, vascular occlusion, cystoid macular edema, vitreous opacification, cataract, glaucoma. Optimal and specific antiparasite treatment can prevent some of these conditions.

3. Laboratory Diagnosis

Laboratory tests should not delay the start of treatment when visual outcome is threatened. Diagnosis is entirely clinical with help from angiography, visual field assessments and OCT. In most cases serology does not help as immunoglobulin (Ig)G antibody levels are typically low in ocular toxoplasmosis patients. Serology cannot confirm, but traditionally excludes ocular toxoplasmosis. However, caution is needed because false negative cases, though very rare, do exist. In France, a mandatory national pre-natal screening program for congenital toxoplasmosis has existed since 1978 when toxoplasmosis serology was included in premarital examinations. Subsequently, in 1985, obligatory toxoplasmosis serology was added to pregnancy declarations and, in 1992, mandatory monthly toxoplasmosis monitoring of pregnant seronegative women, repeated at childbirth. Hence, between 2012 and 2032 information will become available on the precise proportions of acquired and congenital toxoplasmosis in France, simply by knowing a patient's maternal serological status.

Specific toxoplasmosis antibodies in aqueous humor can be detected by anterior chamber puncture. Two differing analytic procedures are used, *i.e.* calculation of the Goldmann-Witmer coefficient (GWC), comparing the total IgG / anti-toxo ratios of aqueous humor and serum; (positive if >3); or the Western Blot analysis, providing an immunoblot comparison of aqueous humor and serum antigens. In the latter case, a single band x3 more intense (or at least three bands less intense) in aqueous humor than in serum, is taken as evidence of local antibody production. It must be emphasised that either of these tests may be negative in the first 3 to 4 weeks prior to significant local antibody production. Polymerase Chain Reaction (PCR) analysis is applicable only to immuno-compromised patients (positive in about 75%) and the elderly, as false negative results are frequent in young immuno-competent patients.[12]

We recently published a comparison of immunoblotting (IB) (IgA and IgG) and the Goldmann-Witmer coefficient for diagnosis of ocular toxoplasmosis in immunocompetent patient.[13] We found that the GWC was significant in 48% of patients presenting suspected ocular toxoplasmosis. The intraocular production of specific antibody *anti-T.gondii* IgG and IgA was revealed by IB in 71% of samples. The combination of these two methods increased the sensitivity to 76%. Based upon the interval between symptom onset and paracentesis, IB had a greater sensitivity than GWC when sample of AH was taken in the first three weeks (65% versus 24%, p=0.039), while the difference between the sensitivity of IB and GWC was less important in cases with an interval greater than 3 weeks (76% versus 64% p=0.625). Therefore, we should remember that IB seems to be more useful than the GWC if only one of these methods can be performed, especially during the first three weeks after symptom onset.

4. Curative Treatment

Many drugs are used curatively, *i.e.* pyrimethamine, sulfadiazine, combined pyrimethamine and sulfadoxine, cotrimoxazole (trimethoprime-sulfamethoxazol), clindamycin, azithromycin, and atovaquone. Classic treatments include pyrimethamine and sulfadiazine, both of which inhibit folic acid metabolism essential to the parasite. The aim is to stop their multiplication and limit the inflammatory reaction. Treatment is short-term, for 4 to 6 weeks, depending upon disease severity and lesion diameter. Either of the latter drugs may cause bone marrow depression, hence folinic acid is used to counteract this effect, because humans can use preformed folinic acid whereas *T. gondii* cannot.

Antibiotics are expected. In theory they would reduce the duration and severity of ocular inflammatory activity, the risk of definitive visual loss (reducing scar size), and that of ocular recurrence, and minimize severe adverse effects. Corticosteroids are added to antiparasitic drugs to reduce the duration and severity of ocular inflammation, and diminish tissue damage (experimental data in rabbits). However, they must never be given alone, without antiparasitic drugs as they can provoke a fulminant ocular toxoplasmosis. However, clinical studies have revealed both the advantages and disadvantages of such treatments. A recent evidence-based systematic review by Stanford et al. found that only 3 of 173 trials were randomized and controlled.[14] These studies showed no evidence of beneficial antibiotic effects on the

duration or severity of inflammation, and only weak evidence for a long-term treatment effect of cotrimoxazole on lesion recurrence in chronic recurrent toxoplasmic retinochoroiditis. The latter, however, was consistently associated with adverse effects. No study has investigated effects on permanent visual acuity and no randomized study has compared treatment with the natural course of ocular toxoplasmosis.

A prospective, non-randomized, multicenter study of 149 patients compared 4 treatment groups (all given concomitant corticosteroids), namely: (1) pyrimethamine + sulfadiazine + corticosteroids; (2) clindamycin + sulfadiazine + corticosteroids; (3) cotrimoxazole + corticosteroids; and (4) a control group. No treatment effect on the duration of inflammatory activity has been demonstrated[6]. However, treatments reduced the diameter of the retinal inflammatory lesion by more than one-half the papillary diameter (49% *versus* 20% in control group). One can notice that corticosteroids were always present in the treatment groups! They had no effect on the recurrence rate during 3 years of follow-up (mean 49%). Moreover, cotrimoxazole (960 mg x2 daily for 2 weeks, followed by 480 mg x2 daily) was less effective than standard pyrimethamine treatment (100 mg on Day 1, followed by 50 mg daily; plus sulfadiazine 4 g/day) during 4 weeks of treatment. Adverse events were reported in 4% of patients given cotrimoxazole, as compared to 26% given pyrimethamine + sulfadiazine. A prospective randomized study[15] in ocular toxoplasmosis compared standard treatment (pyrimethamine 100 mg daily x2, followed by 25 mg daily; plus sulfadiazine 2 g daily and prednisolone) with cotrimoxazole (960 mg x2 daily; plus prednisolone) and found similar efficacy with respect to scar size, visual acuity and recurrence rates. Treatment continued for the standard 6 weeks duration, compared to 4 weeks for the preceding study, but the daily pyrimethamine dosage was halved, making it difficult to compare with usual clinical practice. Many clinicians have started to use cotrimoxazole + corticosteroid on the assumption that it has a better safety profile than classical therapy, but the foregoing study was unable to address the issue adequately. However, cotrimoxazole + corticosteroid has the advantage of less total medication, less hematological toxicity, no necessity for a folinic acid supplement, low cost, better compliance, and an oral liquid form for children.

A prospective, randomized, multicenter study of azithromycin in 46 patients compared it to sulfadiazine plus pyrimethamine and corticosteroids.[10] The frequency of adverse effects following azithromycin (33%) was significantly lower than with sulfadiazine (64%), as was the severity. However, measurements of time to inflammatory resolution, decreased retinochoroiditis size, and best visual acuity did not differ between treatments. Also, recurrence rates after 1 year of follow-up were similar for both treatment groups (azithromycin 56%; sulfadiazine 33%). Previously, the cited authors investigated the efficacy of azithromycin monotherapy in patients with ocular toxoplasmosis[10]. Eleven immunocompetent patients with ocular toxoplasmosis were given azithromycin (500 mg on Day 1, followed by 250 mg daily for 5 weeks). Intraocular inflammation resolved within 4 weeks for 7 patients, including 2 cases with progressive retinitis previously treated with pyrimethamine plus sulfadiazine and folinic acid. No systemic adverse effects of azithromycin were encountered which is encouraging since adverse effects with conventional therapy constitute a major problem, leading to treatment discontinuation in 40% of immunocompromized and 26% of immunocompetent patients[16].

Azithromycin achieved high intracellular and tissue concentrations. *In vivo* and *in vitro* efficacy was reported and an effect on the cystic form, when administered for longer than 4 weeks. Thus, the two preceding clinical studies suggest that azithromycin, alone or combined with pyrimethamine, may offer an effective alternative treatment for ocular toxoplasmosis. Its apparent lack of toxicity represents a key advantage. Moreover, it is the sole toxoplasmosis drug not to be contraindicated in pregnancy.

Three combination regimens compete as the first choice for ocular toxoplasmosis treatment: (1) pyrimethamine + sulfadiazine + folinic acid; (2) pyrimethamine + clindamycin + folinic acid; and (3) pyrimethamine + azithromycin + folinic acid. Alternative regimens have also been tried: (4) cotrimoxazole; (5) clindamycin + sulfadiazine; (6) pyrimethamine + atovaquone + folinic acid; and (7) pyrimethamine + sulfadoxine + folinic acid. On taking into account the apparently few adverse effects of azithromycin, we strongly believe that it should now become the first choice for treating ocular toxoplasmosis, when combined with pyrimethamine and folinic acid, especially in patients with a sulfamid allergy precluding sulfadiazine, cotrimoxazole, and pyrimethamine + sulfadoxine combinations.

Clindamycin must also used in other ways of administration. Subconjunctival injection seem to be as effective as conventional therapy[17-19]. Nevertheless, conjunctival necrosis has been described[20]. Even if it seems rare, this is a disastrous complication. Two recent randomized, single-blind, prospective studies have demonstrated the equivalence of intravitreal injection therapy of 1 mg clindamycin (0.1 ml) and 400 µg dexamethasone to standard treatment with pyrimethamine, sulfadiazine, and prednisolone [21,22]. However, for an identical efficacy of the 2 protocols (same reduction of size, same gain of visual acuity, same reduction of the hyalitis, same rate of recurrence at 2 years), the side effects were notably less in the intravitreal injection group. The effectiveness and safety of this modern treatment remains to be confirmed by using it on a larger scale with greater hindsight. Nevertheless, this route of administration seems to be an interesting option for pregnant women or in case of intolerance or allergy to systemic antibiotic treatment.

The foregoing therapies are usually continued for 4 to 6 weeks and may be extended if necessary. When vision is threatened, oral corticosteroids should be initiated within the first 48 hours of antiparasitic treatment, and then be stopped at least 7 days before withdrawing specific drugs. The usual corticosteroid dose is 60 mg per day, followed by dose tapering according to the clinical response. We would recommend that oral corticosteroids should always be used, as most studies that have shown potential antibiotic efficacy have used corticosteroids concomitantly. In emergencies (previous lesions cited or a focus near to foveola) intravenous corticosteroids may be used.

Absolute indications for treatment are, as follows: (1) an inflammatory focus, or focus resembling inflammation, threatening the macula and/or optic nerve localized in Area 1 (Figure 7), toxoplasmic neuroretinitis and toxoplasmic papillitis; (2) severe hyalites; (3) multifocal or diffuse necrotizing retinitis; (4) complications such as vascular occlusion, retinal detachment, epiretinal membrane, choroidal neovascularization and cystoid macular edema;

and (5) immunocompromised patients. Indications, according to circumstances, are: (1) visual acuity impairment <20/40; (2) a large retinochoroiditis focus (>papillary diameter x2-3), even when in the peripheral retina, because of the risk of a large visual field defect, and secondary complications from prolonged inflammatory activity; and (3) associated severe acute anterior uveitis, because of complications that can impair visual function. At present, when the retinochoroiditis focus is peripheral, with no complications, and affects an immunocompetent patient, *i.e.* in the absence of an evident need to treat, ocular toxoplasmosis treatment remains controversal given the risk of adverse effects. However, we are confident that the azithromycin + pyrimethamine + folinic acid regimen will overcome such cautiousness in the near future.

5. Preventive Treatment

One clinical trial has shown that treatment can reduce the toxoplasmic retinochoroiditis recurrence rate.[22] This was a long-term prospective, randomized, open-label study administered intermittent cotrimoxazole (one tablet of trimethoprim 160 mg / sulfamethoxazole 800 mg, every 3 days) to 124 patients and monitored them monthly for up to 20 consecutive months. Clinical signs of recurrence developed in 7% of cotrimoxazole patients and 24% of control (p=0.01). So far, no follow-up data are available on long-term protection after treatment discontinuation. Thus the overall duration of treatment to ensure long-term efficacy remains unknown. Unfortunately, this is not nor a placebo-controlled prospective study neither a blinded randomized one. Clinical indications for preventive treatment are usually macular and/or optic nerve vulnerability (Area 1) denoted by 2 recurrences, or more, per year, a known reason for recurrence (e.g., seasonal), or planned intraocular surgery. Other studies presented similar results [24-25]. A recent one demonstrated long-term benefits, with no recurrence with a 3-year follow-up period after a one-year treatment.[25]

Apart from preventive treatment we would point out the need to prevent toxoplasmosis infection by hand hygiene, deworming cats, enclosing kitchen gardens, washing fruit and vegetables, clean drinking water, cooking meat to a safe temperature, child education, and avoidance of geophagia.

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Answers to MCQ's on page 130

1.
a. True
b. True
c. True
d. False

2.
a. True
b. True
c. False
d. False

3.
a. True
b. False
c. False
d. True
e. False

4.
a. False
b. False
c. True
d. False
e. False

22

Exudative diseases

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Retinal attachment is an active process. Retinal exudation is the result of a disbalance arising in the flow of fluid through the subretinal space. It may arise as an excess inflow of fluid into the subretinal space, or due to a disfunction in retinal and RPE pumps used to push this fluid out to the choroid and retinal vasculature. Metabolic factors, inflammatory mediators, oncotic pressure and oxidative/toxic by-products impact on water transport through the RPE to the choroid, and even across the sclera. The clinical manifestations may be localized to a small area of the retina or can be generalized. They may manifest themselves with only exudation or be associated to other signs such as hard exudates, choroidal folds or elevation or vascular alterations within the retina. There may also be systemic signs and symptoms that can orient you to the cause, and thus to the most appropriate therapeutic strategy.
As a clinician it is your role to recognize as best you can the clinical picture in front of you, ask the appropriate questions that can orient you to the most appropriate set of diagnostic tests, and hence the treatment.

1. Pathophysiology

The attachement between the retina and retinal pigment epithelium (RPE) is based on an active metabolic process as well as key physiologic and anatomic features. Anatomically fluid and proteins have limited access into the retina due to the blood retinal barrier and Bruch's membrane. Active water channels in Mueller cells and the RPE (aquaporins II and IV) and potassium channels (kir) insure that excess fluid is pumped out of the retina and subrretinal space. Fluid flow through the RPE is aided by the osmotic gradient across Bruch's membrane. Within the choroid, the fenestrations in the choroidal arterioles insure that the intercellular space has a high protein content. This oncotic pressure draws out fluid from the retinal tissue and directs it to the choroidal venous circulation. Excess extravascular colloidal protein is eliminated by bulk flow across the suprachoroidal space and sclera thanks to the intraocular pressure that maintains a constant outward flow.
A serous retinal detachment develop when the RPE pump is overwhelmed. The RPE may itself be damaged, allowing a flow of fluid and colloidal proteins into the subretinal space, but in addition, compensatory mechanisms in surrounding RPE cells must be deficient to allow the fluid to accumulate. If allowed to persist for any length of time, the subretinal fluid will increase in protein content leading to a more persistent detachment as the restoration of a normal oncotic pressure takes time.
While several factors are often present in causing the appearance of serous retinal detachments (SRD), it is possible to stratify the etiologies according to major underlying mechanisms: (1) conditions causing an increase in oncotic pressure; (2) increase in fluid flow; (3) RPE pump disregulation; (4) tractional components (vitreous, anterior PVR).

Table 1: Etiologies of serous retinal detachment regrouped based on main underlying mechanism

Increased Oncotic Pressure	Increased fluid flow	RPE pump disregulation	Tractional component
Immunogammo-pathies e.g. leukemia, multiple myeloma, Waldenström	Vascular malformations (hemangiomas, phacomatosis)	Hypertensive choroïdopathy Toxemia of pregnancy	Long standing Pars plana inflammation
Choroidal (uveal) effusion syndrome	CNV (AMD, polypoïdal)	Inflammation (VKH, SO, scleritis, collagen vascular diseases)	Long standing scleritis
Persistent subretinal fluid e.g. post retinal de-tachment surgery	Tumors (metastatic)	Infections: Syphilis, Lyme, Brucellosis, Chikungunya….	Anterior PVR
Hypotony		Central serous chorioretinopathy (CSR)	
		Steroids	
		Toxicity: cefuroxime methanol, check point antibodies, anti-MEK1	
		Trauma	

2. Etiologies related to increased oncotic pressure:

2.1 Uveal Effusion Syndrome

Usually associated with a ciliochoroidal effusion, the SRD is a spill over from the primary process. The mechanism is related to an increase in oncotic pressure within the supraciliary space and the choroid. A classification of the various etiologies is presented in table 2.
The clinical presentation is characterized by the presence of visibly dilated episcleral vessels, a shallow anterior chamber (particularly in hypotony and uveal effusion syndromes), a myopic shift. The choroidal effusion has often a smooth brown orange contour that transilluminates

(illumination through the sclera is best). If present for a prolonged time, leopard spots are present on the surface of the detachment. They are clearly visible on angiography and by autofluorescence. The serous detachment when chronic contains a thick syrupy fluid that is heavier than water. It is present in the most dependent position of the eye and slowly shifts location if the head position is tilted.
On examination, the ultrasound can reveal the present of a suprachoroidal detachment, thickened sclera, or the presence on UBM of a ciliary body detachment, particularly important in cases of scleral thickening or hypotony. The ultrasound is useful in differentiating serous from hemorrhagic choroidal detachments often present following glaucoma surgery. In hypotony, the OCT will show folds in both the retina and choroid. This can be used to monitor response to therapy.

Table 2: Etiologic classification of ciliochoroidal effusion which can lead to a serous retinal detachment

Hydrodynamic factors	Inflammatory factors	Neoplasias	Scleral abnormalities
Malignant hypertension	Post trauma or surgery	Metastatic carcinoma	Nanophthalmos
Ocular hypotony wound leak, trauma, glaucoma filter, RRD, cyclodialysis	Post photocoagulation/ cryotherapy	Lymphoid, leukemia or melanocytic choroidal infiltrations	Mucopoly-saccharidosis
Elevated Venous Pressure AV filstula Vortex vein compression by a scleral buckle Idiopatnic prominent episcleral veins Valsalva Sturge Weber syndrome	Drug reaction	Malignant melanomas	Idiopathic uveal effusion syndrome
	Uveitis/Scleritis		
	Orbital cellulitis		

2.2 Immunogammopathies & neoplasias:

The serous detachments are often independent of retinal vascular changes. They can manifest as localized detachments in the posterior pole or large inferior peripheral detachments. Often systemic symptoms or signs can be illicit that can orient to the correct diagnosis if it is not already known. Serous detachments are quite common with lymphoblastic and myelogenous leukemias.

It is not uncommon for a translucent serous detachment to take on a more "cloudy" appearance as it starts to resorb with appropriate treatment. As the fluid resorbs, the protein concentrates leading to a "hazy" appearance of the residual subretinal fluid.

3. Increased fluid flow:

Retinal vascular malformation when large can overcome retinal compensatory mechanisms leading to the formation of a SRD. InAMD, certain disciform scars are composed of large vessels poorly responsive to anti-VEGF therapy and cause a significant subretinal accummulation of fluid.
Metastatic tumors, particularly from a glandular origin (breast) can cause large SRD. The presence of multiple lesions in the choroid, often bilateral alters to the metastatic origin. Solid tumors such as multiple myelomas can also cause a serous effusion localized at the edge of the tumor.

4. Disfunction of the RPE causing a serous retinal detachment

4.1 Hypertensive choroïdopathy:

While found in the same context as hypertensive retinopathy, there is no direct correlation. It is characterized by an occlusive disease process affecting initially the choriocapillaris, and leading to pinpoint infarcts in the RPE. The lesions present initially as pale white punctate lesions associated with small localized SRD. After about 3 weeks, they evolve to punched out lesions with a dark pigmented center: Elschnig spots. More significant alterations can occur if the deeper choroid was also affected leading the peripheral choroid to the formation of large polymorphic areas of atrophy, as well as linear bands of choroidal atrophy corresponding to vascular sclerosis: Siegrist's streaks.
In about 1/3 of cases of hypertensive choroïdopathy, a peripheral serous detachment will develop with at time a turbid appearing subretinal fluid. This picture is seen with malignant hypertension, disseminated intravascular coagulation, some cases of temporal arteritis and toxemia of pregnancy.

4.2 Toxemia of pregnancy:

Findings are similar to those in hypertensive choroïdopathy. It tends to be bilateral, bullous detachment with in most cases a good prognosis, when dealt with some haste. A low platelet count is often present as well as a low level fo fibrinogen, both of which may require compensation. Pigment alteration can be quite extensive to the point where years later, the patient is felt to have a heredodegenerative process, or macular scarring. Asking an appropriate history regarding past pregnancies is important in these situations.

4.3 Central Serous Retinopathy (CSR):

A common disease in middle aged men>women. Usually self limiting, it is associated with one or more areas of RPE disfunction visible on fluorescein. Multiple areas of leakage are better seen with ICG. Initially, a wait and see approach is adequate. With persistence or recurrence, treatment with aldosterone or an analog is quite effective. Some cases will benefit from subthreshold laser applied to the area of RPE stippling. PDT has been used in the past but does not seem to be as effective as subthreshold laser therapy.
Steroids are known to cause CSR. They tend to develop large subretinal areas of exudation, often recurrent in different locations. Reducing the steroid dose often improves the condition, though it may only resolve upon complete discontinuation of the steroids. Some cases were related to intramuscular administration. Aldosterone and its analogs are effective regulators of the effect of corticosteroids, but many cases only lead to a lessening of the lesion height and area.

4.4 Infectious Causes:

Syphilis is known to cause a serous retinal detachment present in the foveal area. It presents initially with a more classical retinochoroïditis, but the appearance evolved over a week or two to a serous detachment. There is associated leakage from the optic nerve and other subtile signs of inflammation. A high level of suspicion is needed in these cases.
Of note, localized serous detachments have been described with a number of bacterial and viral infections. There are usually accompanying systemic complaints that point in the direction of a systemic illness. The ocular manifestation may or may not involve optic nerve head or other signs of inflammation.

4.5 Inflammation:

Classically, subretinal detachments have been described in the acute phase of Vogt-Koyanagi-Harada's disease. It may precede or be concurrent (mostly) with a postural headache. The detachment is multifocal initially and may coalesce into a large bullous detachment, often bilateral. There is choroidal thickening observed on OCT and ultrasonography. The fluorescein shows typical pinpoint areas of leakage. With aggressive systemic steroids, the detachments rapidly disappear. The serous detachment often contains copious protein, visible on the OCT but also visible clinically as fibrin strands spanning the subretinal fluid.
Limited SRD are seen in collagen vasculopathies. These are usually in the posterior pole within the macular area.
Serous detachments are observed in severe, often long standing posterior scleritis and poorly controlled pars planitis. The subretinal fluid is often thick and slowly shifting. If vitreous inflammation developed, it can lead to vitreous traction bands further complicating the picture. Serous detachments in scleritis are often associated with large choroidal detachments which can be mistaken for amelanotic melanomas.

4.6 Toxicity

Several reports have indicated the development of a macular SRD, but also more extensive RD with the use of intracameral cefuroxime. Detachments have developed with standard intraocular dosing, but has also occurred when the dilution was not appropriate.
SRD are observed with the use of monoclonal antibodies used in oncology, particularly against melanomas (eg MEK1 inhibitors), but also Checkpoint inhibitors.

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23

ROP

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MCQ's

1. **Regarding retinopathy of prematurity (ROP):**
   a. It is a major cause of blindness and visual impairment in children in both developing and industrialised countries
   b. Retinal vessels have completely developed by 36 weeks of gestational age
   c. VEGF is the unique secreted factor that leads to retinal neovascularisation
   d. Intravitreal injections of anti-VEGF are used to treat ROP

2. **Regarding ROP:**
   a. Retinal zone 1 includes ora serrata
   b. First retinal signs are observed in retinal zone 3
   c. Plus disease is observed when vessels are incompetent, leaking, and tortuous
   d. Intravitreal anti-VEGF injecton is restricted to stages 4 and 5

3. **Regarding premature babies:**
   a. The most common ocular pathology in premature babies is ROP
   b. After eliminating ROP, regular ocular controls every two years are requested
   c. They are in higher risk of anisometropia
   d. They are in higher risk of strabismus and amblyopia
   e. Tropicamide is mostly used alone for dilation in ROP screening

RETINOPATHY OF PREMATURITY (ROP) is a major cause of both blindness and visual impairment in children in developing and industrialised countries. ROP was first described in the 1940's as "retrolental fibroplasia" when high saturation oxygen supplementation began to improve survival of preterm infants, but also caused blindness. Today, in addition to high oxygen saturation, very preterm infants of low gestational age and low birth weight have been identified as a group in risk of developing ROP. Neonatal care is essential in reducng hypoxia-induced retinal ischaemia and in screening ROP so as to detect its first signs and to treat it when necessary.

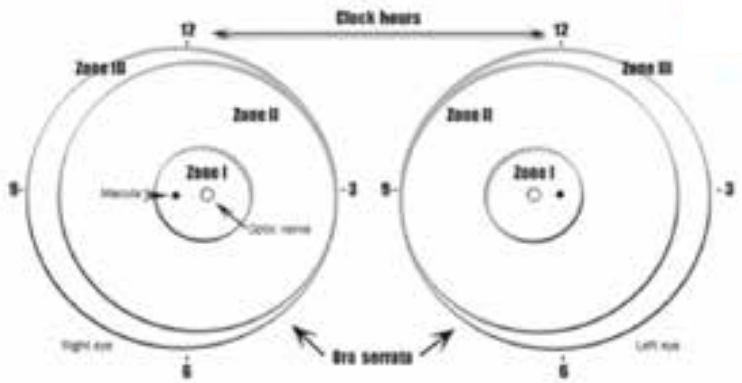
1. Pathophysiology and epidemiology

The incidence of ROP is closely related to birth weight and gestational age (GA), and is more common in developing countries. It is more severe and more frequent in extremely premature infants and in newborns with extremely low birth weights. Despite progressive improvements in neonatal care, the frequency of ROP is increasing.

Retinal vascularisation begins at 16 weeks of GA from the optic nerve and progresses toward the periphery. The vessels reach the ora serrata at 36 weeks nasally and 40 weeks in the temporal retina. Therefore, when an infant is premature retinal vascularization is incomplete. The pathogenesis of ROP is hypothesised as follows: 1) excess of oxygen (extrauterine life and oxygen therapy) creates hypoxia-induced retinal ischaemia and vasoconstriction of retinal vessels; 2) developmental angiogenic factors such as VEGF, IGF1, FGF and angiotensin-2 are secreted, leading to retinal neovascularisation.

2. Classification

The classification of ROP is based on 3 retinal locations (zone I to III), five stages (stage 1 [peripheral lesions] to stage 5 [retinal detachment]), and the presence or absence of plus disease (dilation and tortuosity of vessels). The international classification of ROP (ICROP) was revised in 2005. It establishes the location and severity of ROP. This classification analyses 4 points: retinal zone, retinal extension (in clock hours), severity/stage, and plus disease (vascularisation) of ROP.



3. Clinical examination

Clinical examination is the key in screening for ROP. According to the guidelines of the American Academy of Ophthalmology (AAO), American Academy of Pediatrics, and American Association for Pediatric Ophthalmology and Strabismus (AAPOS), infants with a birth weight <1500 g or a gestational age ≤30 weeks of GA should receive dilated ophthalmoscopic examinations for ROP screening. These exams are mostly performed at a neonatal intensive care unit (NICU) and ideally with contact wide-field imaging retinal photography system such as RetCam, Panocam or Phoenix ICON, or with binocular indirect ophthalmoscopy with scleral depression. When using the camera system, imaging of the retina can be transmitted via telemedicine from the NICU. Dilation of babies must be at least 7 or 8 mm for optimal examination. It can be obtained with combination of tropicamide and low-dose phenylephrin. The imaging system provides better documentation of disease severity and progression, thus the treatment can be optimised. Screening of premature babies should be performed 4 to 7 weeks after birth according to their GA, and then observation of peripheral retinal vasculature will be evaluated.

4. Principles of treatment

Initially the standard mode of treatment for ROP was surgery for retinal detachment in advanced stages of disease, and in the mid-1980's cryotherapy emerged. Following ETROP trial, guidelines recommended modern screening of ROP and peripheral laser treatment instead of cryotherapy. Recently, intravitreal anti-VEGF therapies have been successfully utilised in treatment of ROP. This promising therapy is performed with a single intravitreal anti-VEGF injection with adapted doses. In late stages 4 and 5, retinal surgery is useful, and lens sparing vitrectomy is recommended.

As understanding of the pathophysiology of ROP has increased, emphasis has shifted to selective therapies that target components of the angiogenesis cascade. However, further studies will be needed because many questions remain regarding the management of ROP. Better knowledge of the disease should lead to better screening methods, predictive algorithms, and innovative therapies.

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Answers to MCQ's on page 148

1.
a. True
b. False
c. False
d. True

2.
a. False
b. True
c. True
d. False

3.
a. False
b. False
c. True
d. True
e. False

24

Vitreomacular interface: new disease or new classification

van MEURS JC, The Netherlands

BETTER IMAGING TECHNIQUES allow us to notice changes in anatomy and offer opportunities to try and understand pathophysiology.

It is interesting to assess new findings such as epiretinal proliferations in lamellar macular holes and displacement of inner foveal layers in macular pucker.

New classifications would gain most if they are correlated with function and prognosis of natural history. With incomplete data on natural history of macular pucker and lamellar macular holes, combined with the unpredictability of surgical outcome, the lack of controlled studies leaves room for unsubstantiated opinions and treatment proposals.

For such elective surgery it is important also to mention the percentage of patients getting worse after surgery.

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25

Retinal detachment in myopic patients

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THE TERM RETINAL DETACHMENT is used to describe a separation of the neurosensory retina from retinal pigment epithelium (RPE). The most common form is a rhegmatogenous retinal detachment (RD) that occurs as the result of a full-thickness retinal break. More than half of nontraumatic RDs occur in myopic eyes.

Risk factors for RD include myopia, cataract or other intraocular surgery, Nd: YAG-laser treatment, injury, a history of RD in the fellow eye, and a strong family history of RD. Combination of these factors may increase the risk further.

1. Definition of myopic patient

Prevalence of myopia varies according to ethnicity and geographic region, and the prevalence of myopia has increased over the past half century. The incidence is higher in Asian countries, and myopia is a major cause of visual impairment especially in Europe and East Asia.

Myopia is generally defined as spherical equivalent of –0.50 D or more. Definition of high myopia varies slightly; it has classically been defined as spherical equivalent refractive error exceeding –6.0 D, an axial length longer than 26.5 mm, or both.

Pathological myopia is defined as high myopia with any posterior myopia-specific pathology that results from excess axial elongation (posterior staphyloma, specific macular complication such as choroidal neovascularisation, choroidal atrophy, myopic foveoschisis and macular holes with or without RD).

A novel classification of high myopia diides it into isolated anterior (peripheral) and posterior (macular) and combined pathologic subtypes.

2. Incidence of RD in myopic patients

An increasing axial length is associated with an increasing cumulative risk of RD. Of involved eyes without previous intraocular surgery, 53% are myopic with a spherical equivalent error greater than –1.0 D. The Eye Disease Case-Control Study Group found that an eye with a spherical equivalent refractive error of –1.00 to –3.00 D had a 4-fold risk of idiopathic RD as compared to a non-myopic eye; if the refractive error was greater than –3 D, the risk was 10-fold. The data of the study suggest that almost 55% of non-traumatic detachments in eyes without previous surgery are attributable to myopia.

Cataract surgery combined with high myopia may be related to the onset of RD. Cataract surgery in itself is a risk factor for RD. Lens exchange to a much thinner artificial lens enlarges the volume of the vitreous cavity and the vitreous body is shifted anteriorly. Additionally, the removal of the natural lens disturbs the barrier function of the lens between the anterior and posterior segments and induces biochemical changes in the vitreous body. These modifications seem to expedite destabilisation of the vitreous and promote posterior vitreous detachment (PVD) that may be related to the onset of pseudophakic RD. High myopia is a major risk factor for the occurrence of pseudophakic RD.

According to the results of several studies, an increasing axial length is associated with an increasing cumulative risk of RD after cataract surgery. The highest cumulative risk was observed in eyes with axial length of ≥26 mm. Males had an almost 2-fold risk of postoperative RD. The highest incidence of RD in myopic eyes occurred in patients aged 50-54 years.

The National Population Study evaluated data from over 2 million eyes that underwent cataract surgery in France. In non-myopic eyes, the estimated risk of RD is 0.99% at 4 years after surgery. Among myopic patients, the risk of RD increased 25-fold in those 40-54 years of age and 20-fold in those 55-64 years of age as compared to non-myopic patients 75 years of age and older.

2.1. Rhegmatogenous retinal detachment from peripheral breaks

A spontaneous rhegmatogenous RD is usually preceded by PVD. The development of PVD from liquefaction of the vitreous body occurs at a younger age in eyes with high myopia. The Scottish Retinal Detachment Study showed that 86% of eyes that suffered from RD had a PVD.

The frequency of retinal peripheral degeneration increases with axial length. Lattice degeneration is a risk factor for developing a RD; especially when a PVD induces a tear. Lattice degeneration is present in 6% to 8% of the population; approximately 20% to 30% of patients with RD have lattice degeneration, and 2.8% of RD is associated with atrophic round holes within lattice degeneration.

2.2. Retinal detachment of posterior pole in highly myopic eyes

Detachment of the macula is specific to highly myopic eyes and is associated with foveoschisis or macular hole. Foveoschisis was found in 9% of eyes with high myopia and posterior staphyloma. It is characterized by retinoschisis in multiple retinal layers with or without localised RD.

In addition, RDs from macular hole are typical in highly myopic eyes. Vitreous cortex adhering to the retinal surface around the hole induces tangential traction that generates an inward vector component in deep staphyloma, resulting in a RD. Furthermore, in highly myopic eyes RD can be caused by paravascular microholes. Multiple, small and round retinal holes are associated with posterior major vessels.

3. Treatment

Procedures employed for surgical management of RD in myopic eye are scleral buckling and vitrectomy. While in the past most patients used to be treated by scleral buckling, vitrectomy now predominates. Comparative studies have shown that both methods remain valid and each has clear indications, but that they can be carried out simultaneously or successively.

Indication for buckling procedure: phakic eye, no precious surgery; clear localisation of retinal breaks with no or minimal vitreous traction, and no or only slight proliferative vitreoretinopathy. The prospective randomised European trial (SPR trial) showed that in most patients with pseudophakic RD, vitrectomy was superior to scleral buckling. Furthermore, vitrectomy combined with gas or silicone oil tamponade is indicated for treatment of RD of posterior pole in highly myopic eyes.

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26

Central serous chorioretinopathy and ERD

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CENTRAL SEROUS CHORIORETINOPATHY (CSC) is an important cause of vision loss in middle-aged men with an annual incidence of approximately 1:10,000. CSC manifests by serous retinal detachment, retinal pigment epithelium (RPE) disturbance and increased choroidal thickness. It belongs to the pachychoroid disease spectrum characterized by dilated choroidal vessels of the Haller layer called pachyvessels, attenuation of an inner choroid and choroidal vascular hyperpermeability detected by indocyanine angiography (ICGA).

1. Pathophysiology: the mineralocorticoid pathway hypothesis

Although the exact pathogenesis of CSC is currently unknown, clinical and experimental studies suggest the involvement of the steroid pathway. Corticosteroid exposure following therapeutic administration or endogenous overproduction like in Cushing syndrome are associated with the disease. CSC is one of the rare ophthalmic diseases that is aggravated by glucocorticoids ,uggesting that glucocorticoids favor the accumulation of fluid under the retina in this specific condition, instead of acting on its absorption as observed in macular oedema. This paradoxical effect of glucocorticoids is also seen in other parts of the body. In internal medicine, glucocorticoids are used to reduce oedema of numerous origins such as inflammation, infection, allergy, trauma and neurotoxicity. However, their use is also associated with adverse side effects including water and sodium retention. These side effects occur because glucocorticoids bind also to the mineralocorticoid receptor (MR).

Recently, the involvement of MR has been hypothesised in the pathogenesis of CSC. Indeed, glucocorticoids could potentially regulate ion and water channels in the eye through MR activation resulting in the paradoxical pro-oedematous effects of glucocorticoids in CSC patients. In rat eyes, inappropriate MR activation by glucocorticoids regulates the vasodilator potassium channel KCa2.3 and induces smooth muscle cell relaxation in choroidal vessels, resulting in the choroidal thickening and subretinal fluid.

2. Risk factors

Several risk factors for CSC have been recognised, and the most consistent of them is steroid exposure from therapeutic administration or from endogenous overproduction as in Cushing syndrome or pregnancy. The following risk factors show association with the occurrence of CSC:

- hypertension
- shift work
- sleeping disturbance
- psychopharmacologic medications
- psychological stress
- type A personality
- narcissistic traits
- helicobacter pylori infection

The association between CSC and obstructive sleep apnea remains controversial. Recently,

several studies suggest that a genetic background may predispose to CSC. An association of chronic CSC with genetic variants in *ARMS2* and *CFH* have been found in a large cohort of patient. Lately, a variant of MR gene was associated with chronic CSC, supporting a possible role of MR in the pathogenesis of the disease.

3. Clinical presentation

Classically, the term CSC covers two distinct entities. The most common type is acute CSC mostly seen in younger patients, characterised by solitary subretinal detachment (SRD) associated with serous dome-shaped pigment epithelial detachment (PED). Fluorescein angiography (FA) shows one or multiple focal leaks with an "ink-blot" or "smokestack" patterns. Acute CSC resolves spontaneously within 3-6 months with good visual outcome. Chronic CSC (also known as diffuse retinal pigment epitheliopathy) is defined as a persistant SRD >4 to 6 months in duration that can lead to irreversible photoreceptor damage and permanent vision loss. Widespread RPE alterations are visualised in autofluorescence images showing gravitational tracks. FA demonstrates multiple leaks with non-intense dye leakage. In acute and chronic CSC, indocyanine green angiography shows dilated choroidal veins during early phase and hyperfluorescent patches that are supposed to be secondary to choroidal vein hyperpermeability during the mid-phase.

More recently, another classification has been proposed dividing the chronic CSC in two groups. Persistent CSC defined as non-resolving subretinal fluid for at least 4 months of observation with or without gravitational tracks on fundus autofluorescence imaging.

4. Updates in imaging

Advances in imaging have highlighted choroidal vascular dilation and hyperpermeability in the pathogenesis of CSC.

Optical Coherence Tomography: The emergence of OCT with deep imaging techniques such as enhanced depth imaging (EDI) or swept source OCT (SS-OCT) have allowed a better visualization of the choroid and the RPE/Bruch's membrane complex. An increased choroidal thickness has been reported in eyes with CSC as well in the fellow eyes as compared to healthy subjects. Choroidal thickening can result from focal or diffuse dilation of large choroidal vessels (Haller layer) associated with a thinning of the inner choroidal layer and choriocapillaris. RPE detachment inside or outside the neuroepithelial detachment has been described in most cases of CSC. It co-localises with the area of dilated choroidal vessels on SD-OCT and with vascular hyperpermeability on ICG angiography.

OCT angiography (OCT-A) allowed non-invasive visualisation of the retinal and choroidal vessels. A recent study shows that flow voids co-localise with choriocapillaris thinning and deep choroidal vessel dilation. OCT-A is very useful in chronic CSC with flat irregular PED, showing choroidal neovascularisation in 35% of these cases.

5. Treatment

To date, no consensus exists as regards the management of non-resolving or chronic CSC. Several treatments may be proposed. Laser photocoagulation of a focal leakage outside the fovea as detected by fluorescein angiography can accelerate subretinal fluid resolution. Half-fluence or half-dose photodynamic therapy (PDT) is effective in reducing subretinal fluid duration and in improving visual acuity, but some adverse events such as choroidal neovascularisation, RPE atrophy, or RPE tear have been reported.

Several studies have reported on mineralocorticoid receptor antagonist (MRA) therapy in CSC patients with variable results in terms of SRD resolution. Most were retrospective studies. To our knowledge, only four randomised, controlled prospective trials have been published. The first one was a prospective, randomised, placebo-controlled study with a cross-over design assessing spironolactone treatment in 16 patients with chronic CSC. A statistically significant reduction insubretinal fluid and central macular thickness (CMT) was found in the spironolactone group compared to the placebo group. Recently, two other prospective, randomised, placebo controlled trials have supported these results by showing a significant reduction in subretinal fluid and CMT, and an increase in best corrected visual acuity (BCVA) in eplerenone and spironolactone groups compared to the placebo group. However, another randomised, placebo controlled trial in 17 patients (19 eyes) showed no difference in subretinal fluid reduction between patients treated with eplerenone and placebo. This discrepancy could be due to differences in study protocols, inclusion criteria, and small sample sizes. The efficacy of the treatment thus still remains to be confirmed in further randomised controlled trials.

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27

Pars planitis

MISEROCCHI E, Italy

THE TERM "PARS PLANITIS" was first used by Welch in 1960 when he described a condition that was characterised by peripheral retinal inflammation, vitreous opacities, and cystoid macular oedema. Ten years earlier, Schepens had used the term "peripheral uveitis" to describe a clinical entity similar to pars planitis. Others have used terms like "vitritis", "chronic cyclitis", "peripheral uveoretinitis" to refer to the same condition in which inflammation is localised to the intermediate part of the eye.

1. Definition, epidemiology and pathogenesis

Pars planitis is an idiopathic chronic intermediate uveitis that predominantly affects children and adolescents. The term "intermediate uveitis" describes inflammation of the anterior vitreous, ciliary body, and peripheral retina which may or may not be associated with infection or systemic disease, whereas the term "pars planitis" has been recommended for a particular subset of intermediate uveitis associated with snowbank or snowballs in the absence of systemic disease.

Most cases (70% to 80%) of intermediate uveitis in children exist without an underlying disease, therefore they are classified as idiopathic intermediate uveitis or pars planitis. Pars planitis is the most common form of intermediate uveitis (85% to 90%) and presents with two peaks in age distribution, a younger group between 5 and 15 years of age and an older one between 20 and 40 years.

The pathogenesis is not completely understood. Although some etiopathogenetic studies have suggested an autoimmune process with a genetic prediscposition, the etiology of pars planitis remains unknown. Some studies suggest a genetic predisposition linked to HLA-DR2, HLA-DR15, and HLA-DRB1*08:02 haplotypes genes.

2. Clinical characteristics

The majority of children with pars planitis present with bilateral and symmetric disease. The most common symptoms at onset are floaters and blurred vision; however, the presenting symptoms in children with pars planitis may be extremely variable. Some children are asymptomatic and diagnosed during a routine ophthalmologic examination. Some others present an acute onset with redness, discomfort and severe anterior chamber inflammation. In teenager the onset is usually insidious with blurry vision or floaters.

Pars planitis usually (75% to 90%) affects both eyes, however, it may present with asymmetrical involvement and the less affectd eye can show only a few cells in the vitreous. The typical signs of pars planitis are vitritis, snowballs (inflammatory cell aggregates in the vitreous), snowbanks (inflammatory exudation that accumulates in the inferior pars plana), and retinal vasculitis. Mild to moderate anterior segment inflammation with small keratic precipitates and posterior synechia may occur in 25-50% of children.

Band keratopathy, peripheral corneal endotheliopathy with corneal oedema, and posterior synechiae are almost exclusively seen in children as compared to adults with the same disease. Dense vitreous opacities can cause leukokoria, often misdiagnosed as a cataract. Compared to adults, children have more severe and more chronic intraocular inflammation.

3. Complications

There is a higher rate of complications in children with pars planitis compared to adults. The diagnosis in children is often delayed and severe complications can be seen at the initial visit.

- *Cataract* develops in 60% of children and is usually a posterior subcapsular opacity, and cataract extraction with intraocular lens implantation may be complicated because of chronic inflammation.
- *Cystoid macular oedema (CME)* is the most common complication and the main cause of vision loss. Approximately 50% of children develop CME that becomes refractory and chronic in 10%.
- *Epiretinal membranes and vitreous haemorrages* secondary to vitreoretinal traction.
- *Glaucoma* can be both open-angle or angle-closure in type and occurs in 10% of patients.
- *Retinal and optic disk neovascularisation* is due to ischaemia from peripheral retinal vasculitis and high level of VEGF from intraocular inflammation. Neovascularisation may cause vitreous haemorrhage that is more common in children than in adults, or tractional/rhegmatogenous retinal detachment.
- *Inferior peripheral retinoschisis* is a complication present almost exclusively in children.

4. Diagnosis

The diagnosis of pars planitis is clinical. It can be very challenging in children for many reasons: the inability to express discomfort, the truly asymptomatic nature of the disease, and the lack of co-operation during the ophthalmological examination.

The diagnosis of idiopathic pars planitis is based solely on clinical findings. There is no specific diagnostic laboratory test. The association of intermediate uveitis with systemic disease is very rare in children. However, to rule out systemic causes of intermediate uveitis laboratory tests are indicated for sarcoidosis (angiotensin converting enzyme, ACE), Lyme disease (*Borrelia* serology), cat-scratch disease (*Bartonella* serology), tuberculosis, and syphilis. Chest radiogram is needed to rule out sarcoidosis and magnetic resonance imaging is useful to exclude multiple sclerosis in older children and teenagers. In unilateral cases, ocular toxocariasis should be considered, because a peripheral *Toxocara* granuloma may be very difficult to differentiate from snowbanks. Masquerade syndromes are important to exclude in children, in particular retinoblastoma that can present as dense whiteish vitreous opacities resembling snowbanks.

Fluorescein angiography (FA) shows perivascular, optic disk leakage, and CME. FA is beneficial in assessing the activity of retinal vascular inflammation and in showing perivasculitits and retinal or optic disk neovascularisation in children with pars planitis. FA is also a valuable tool to document the response to treatment, especially in eyes with macular oedema and peripheral vasculitis. Indocyanine green angiography (ICG) has no particular clinical benefit in pars planitis. Optical coherence tomography (OCT) is useful in detecting macular oedema and in monitoring the response to treatment during follow-up visits.

5. Treatment

The decision of treatrment in children with pars planitis is a controversial issue even today. No consensus exists, especially as regards patients with minimal intraocular inflammation and good visual acuity. According to guidelines suggested by Forrester and coworkers, a visual acuity of 20/40 was considered the threshold for treatment decision in pars planitis. However, we need to consider pars planitis in children as an aggressive disease deserving an aggressive treatment. Foster and colleagues pointed out that treating inflammation early and aggressively, rather than using a visual acuity threshold, may be more effective for long-term visual outcome.

The presence of macular oedema, vitreous haze leading to visual loss, advanced cataract, and vasculitis are currently indications for treatment irrespective of the visual acuity level. A stepladder approach is the most widely used therapeutic approach.

The first line of therapy are corticosteroids with variable administration route: periocular, intravitreal or systemic. Periocular and intravitreal injections may be a therapeutic option to control short-term intraocular inflammation, mainly CME, in particular when the disease is unilateral or asymmetric. Patients with bilateral involvement, severe ocular inflammation or unilateral disease unresponsive to periocular corticosteroids should be treated systemically with corticosteroids.

Steroid-sparing immunosuppressive agents should be considered as the second step in patients with severe, long-standing inflammation. The choice of conventional immunosuppressants may include methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil.

Biologicals such as anti-tumour necrosis factor (TNF)-alpha agents (adalimumab and infliximab) may be used successfully as the third step in patients not responding to more conventional immunosuppressive agents. However, since pars planitits is associated with an increased risk for development of multiple sclerosis, and TNF-alpha blockers may potentiate demyelinating disease, extreme caution is needed before starting such therapy in children with pars planitis. In patients with optic nerve or retinal or choroidal neovascularisation anti-VEGF injections are used in association with systemic corticosteroids to reduce retinal inflammation.

Pars plana vitrectomy with or without laser photocoagulation represents a fourth step of therapy in patients with vitreous haemorrhage, retinal detachment, epiretinal membranes. In some cases it is also useful to remove vitreous opacities.

6. Prognosis

The prognosis of pars planitis is variable and seems to be worse in younger age groups because of a higher rate of complications. The prognosis in children depends on the severity of vitreous inflammation. Usually pars planitis remains active for many years. In 10% of cases pars planitits has a self-limiting course, in 30% of cases the course may present alternating phases of remissions and exacerbations, and in about 60% of cases the disease has a continuous insidious course. The goal of treatment is to control the inflammation and CME that is the real sight-threatening complication of pars planitis. When inflammation is well controlled the long-term prognosis is good with the majority of patients maintaining a visual acuity of 20/40.

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Classic

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Lymphoma

TOUITOU V, France

MCQ's

1. **Which of the following is suggestive of primary vitreoretinal lymphoma (PVRL):**
   a. Granulomatous mutton fat keratic precipitates
   b. Painful hypertensive unilateral uveitis
   c. Posterior synechiae
   d. Peripheral vitritis
   e. Leopard skin/spot -like aspect of the fundus

2. **Which initial work up could be useful for a 72-year-old patient with chronic posterior uveitis, moderate to dense vitritis, and extensive whitish retinal lesions:**
   a. Anterior chamber tap with IL-10 analysis
   b. Anterior chamber tap with viral polymerase chain reaction
   c. Brain magnetic resonance imaging
   d. Retinal biopsy
   e. Lyme (borrelia) serology

3. **Most cases of PVRL:**
   a. Are T-cell or natural killer (NK) cell lymphoma
   b. Are classified as Hodgkin's lymphoma
   c. Are associated with systemic disease (such as athological lymph nodes)
   d. Will develop CNS involvement at some time of the disease

4. **Regarding the treatment of PVRL with concomitant Primary Central Nervous System Lymphoma (PCNSL):**
   a. Treatment is based on whole brain radiation with orbital radiation in all patients over 60 years of age
   b. Treatment is based on whole brain radiation for the PCNSL localisation and intravitreal injection of methotrexate for the PVRL localization
   c. Treatment often relies on systemic methotrexate-based polychemotherapy
   d. First-line treatment usually involves intrathecal chemotherapy with intravitreal chemotherapy

PRIMARY INTRAOCULAR LYMPHOMA or primary vitreoretinal lymphoma (PVRL) is a subset of primary central nervous system lymphoma (PCNSL). Diagnosis of PVRL is particularly difficult as it can mimic non-specific uveitis, leading to considerable and potentially fatal diagnostic delay. In spite of the recent progresses, the diagnosis of PCNSL remains a challenge and is often delayed for several months.

1. Clinical presentation

PCNSL must be suspected in any case of chronic posterior uveitis, especially in patients older than 50 years of age. Typically, the patient presents with a painless white eye and a history of uni- or bilateral floaters. Visual acuity is usually preserved or mildly reduced. On slit lamp examination, anterior segment is usually normal or discloses minimal stellar keratic precipitates and, sometimes, cell deposition on the posterior face of the lens capsule or the intraocular lens. Posterior synechiae are typically absent. Vitritis can vary from minimal to severe, being usually moderate, with cellular infiltrates organized in clumps or sheets, being possibly more dense in the periphery. Retinal or subretinal infiltration can be observed, manifesting as whitish or creamy lesions with a typical aspect of leopard skin. Rarely, optic nerve infiltration can be observed. Macular oedema is rare, and mainly observed in patients who have undergone surgery (cataract or vitrectomy). Rare manifestations of PVRL include bilateral hyphaema, severe anterior chamber reaction, and hypopyon, retinal haemorrhage, vasculitis, retinal vein occlusion, exsudative retinal detachment, extraocular spreading through the sclera, and optic neuropathy.

2. Diagnosis

Diagnosis is based on cytology and molecular analysis of lymphocyte clonality from vitreous samples. Intraocular IL-10 level has proved to be a valuable tool for screening purposes in case of suspicted PVRL. Using ELISA techniques, an IL-10 cut-off of 50 pg/ml from aqueous humour and 400 pg/ml from the vitreous, provides a sensitivity of 89% and 80%, respectively, and a specificity of 93% and 99%, respectively, in the diagnosis of PVRL. Recently, threshold values have to be reconsidered using multiplex analyses and a cut-off of 65 pg/ml in the vitreous and 30 pg/ml in the aqueous humour, associated with a sensitivity of 93% and 78% and a specificity of 100% and 97%, respectively. Whatever the technique, IL-10 measurement should always be associated with determination of the IL-10/IL-6 ratio in the aqueous humour to confirm the clinical suspicion and to determine patients requiring a cytological confirmation with vitrectomy or, rarely, retinal biopsy. New diagnostic and prognostic markers, such as MyD88 analysis, or miRNA expression, are being evaluated as ancillary tools that could improve the diagnostic yield of vitrectomies, although these analyses likely will not replace cytologic analysis.

3. Treatment

Despite definite progress in terms of reduced diagnostic delay, prognosis of PCNSL remains poor for most patients. Recommendations for treatment of PCNSL include high dose

intravenous methotrexate (MTX) -based polychemotherapy with or without whole brain radiotherapy (WBR). For patients with concomitant PVRL and CNSL (10-20% of patients) no consensus exists regarding the addition of a local treatment (ocular radiotherapy or intravitreal chemotherapy). Treatment of PVRL in the absence of associated cerebral localisation is even more controversial. The best therapeutic options, between local treatment, systemic treatment or a combination of both options, are still very much debated.

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Answers to MCQ's on page 166

1. *a. False*
   b. False
   c. False
   d. True
   e. True

2. *a. True*
   b. False
   c. True
   d. False
   e. False

3. *a. False*
   b. False
   c. False
   d. True

4. *a. False*
   b. False
   c. True
   d. False

RT3

Round table 3: My job is difficult!
Case POURNARAS C

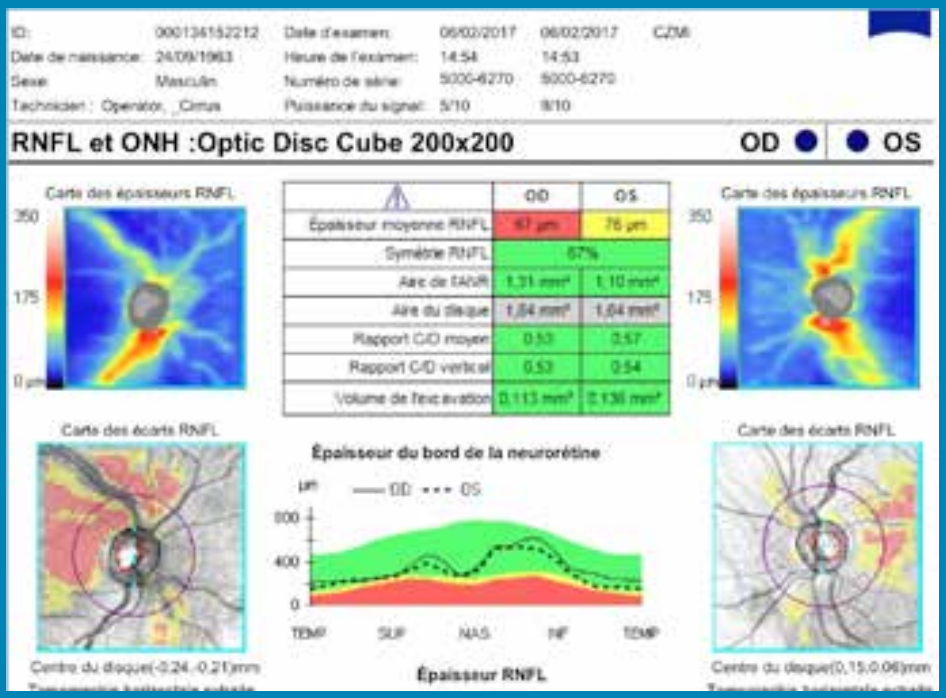
The proliferative form of diabetic retinopathy is a major cause of visual impairment in working-age adults, either because of retinal ischaemia or macular oedema related complications. The standard treatment in proliferative diabetic retinopathy is panretinal photocoagulation (PRP) that is effective but has established side effects such as peripheral visual field damage. Vascular endothelial growth factor (VEGF) is thought to drive the process of vascular proliferation and abnormal vessels barrier permeability. Anti-VEGF therapy has been studied extensively in diabetic macular oedema (DME), and results have shown it to be effective, improving vision outcomes. Limitations of anti-VEGF treatment, however, require careful patient selection.

The patient above is born in 1978, visual acuity 20/20

Propose a treatment plan.

RT3

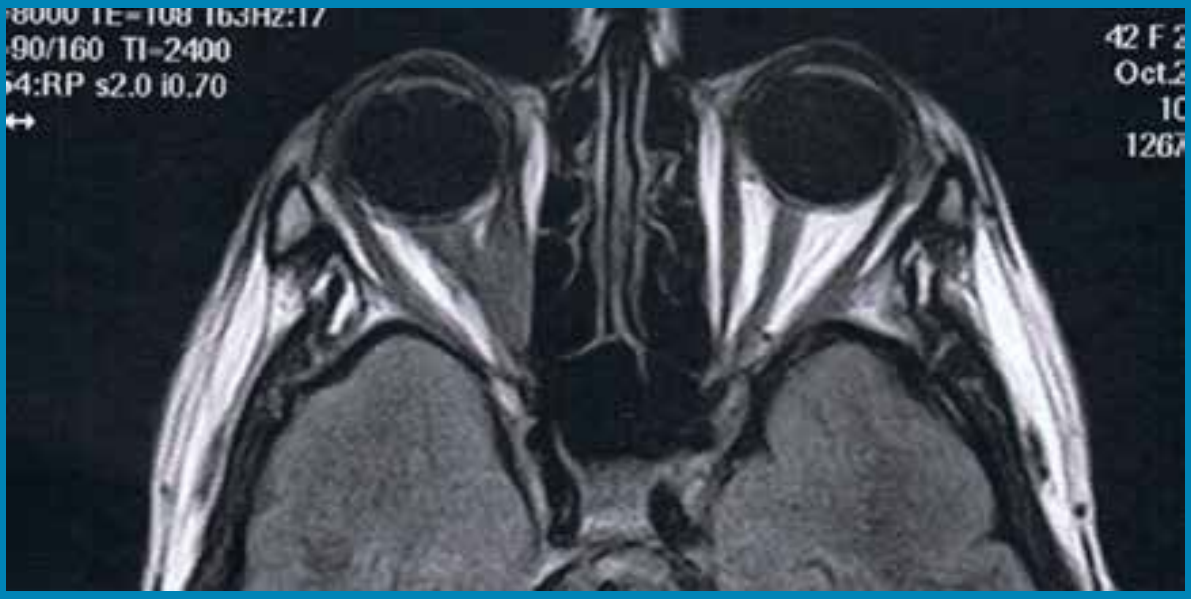
Round table 3: My job is difficult!
Case BRON A



A 55-year-old man was referred to the glaucoma service by an experienced ophthalmologist for progression of glaucoma in spite of a medical treatment and good complance. He was asking for recommendations to stop this progression.

RT3

Round table 3: My job is difficult!
Case MOURIAUX F



A 43-year-old patient was referred for diplopia that appeared a month earlier. On examination, diplopia increases in the right lateral gaze. No loss of visual acuity is observed and intraocular pressure is normal. There is no inflammatory signs including no arthralgia, no signs of either skin or gastrointestinal disorders. Hertel exophthalmometer shows a difference of 2 mm with a projection of the globe at 17 mm on the right against 19 mm on the left.

Round table 3: My job is difficult!
Case KHAIRALLAH M

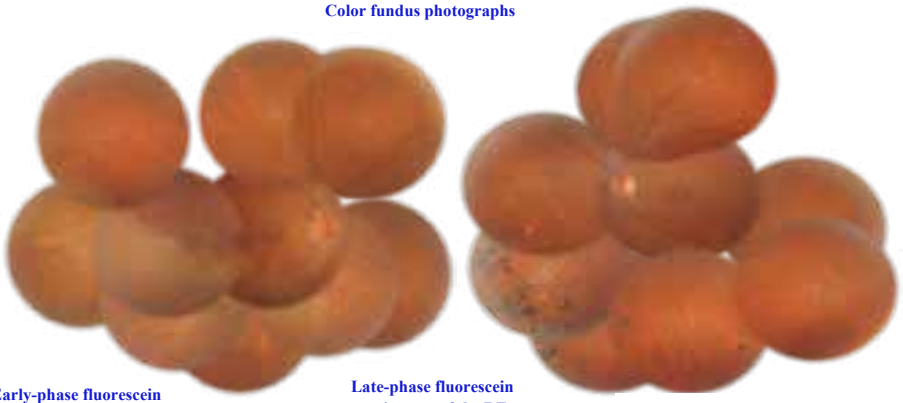
A 53-year-old woman

History: Unremarkable

Ocular pain and superior visual field defect in the RE

RE	LE
-VA=20/30 -0.5+ AC cells, fine KPs, Koeppe nodule -Flare: 25ph/ms -IOP: 13 mm Hg -1+ vitreous cells	-VA= 20/25 -No AC cells -Flare: 4ph/ms -IOP: 15mm Hg -No vitreous cells

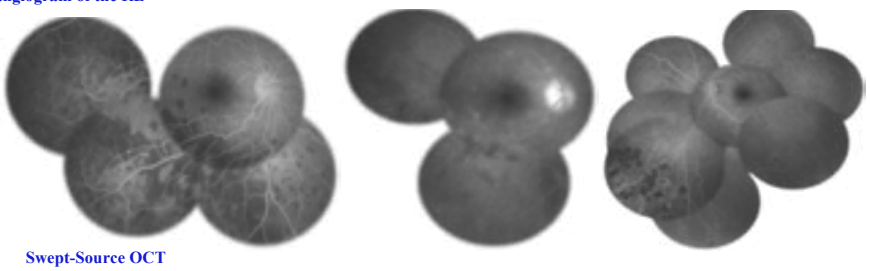
Color fundus photographs



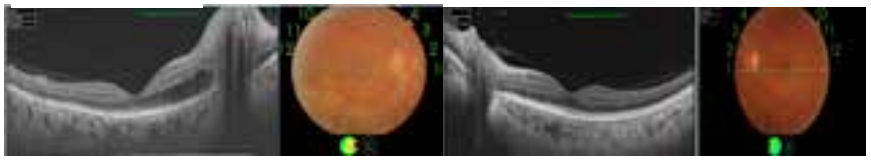
Early-phase fluorescein angiogram of the RE

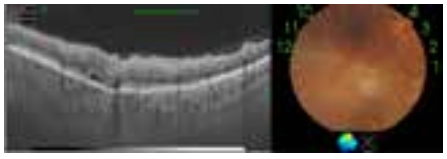
Late-phase fluorescein angiogram of the RE

Late-phase fluorescein angiogram of the LE



Swept-Source OCT

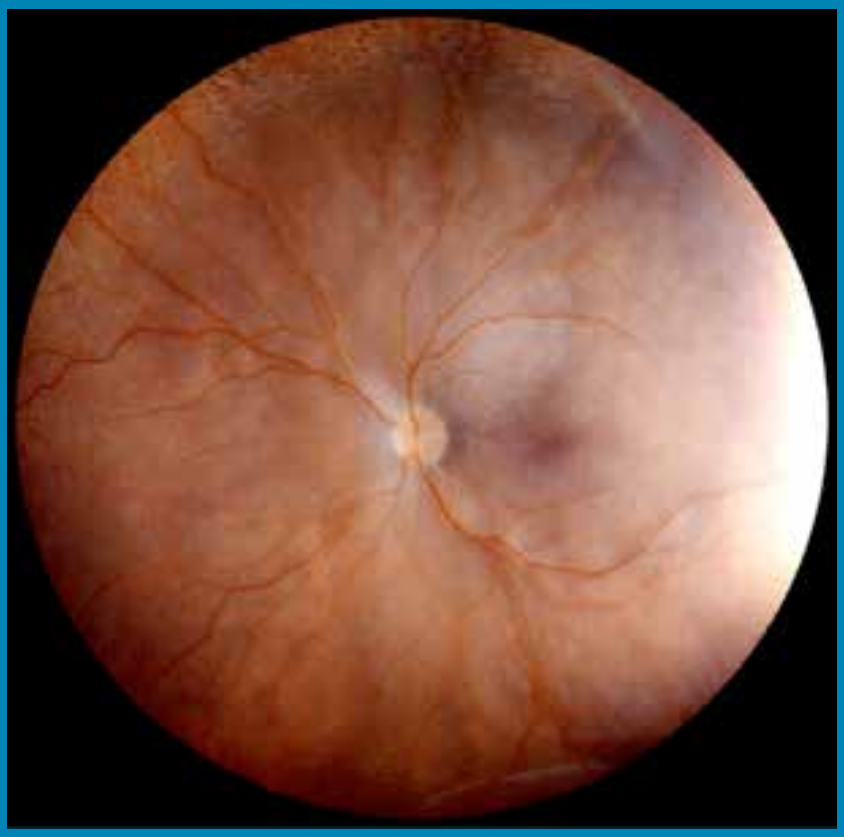


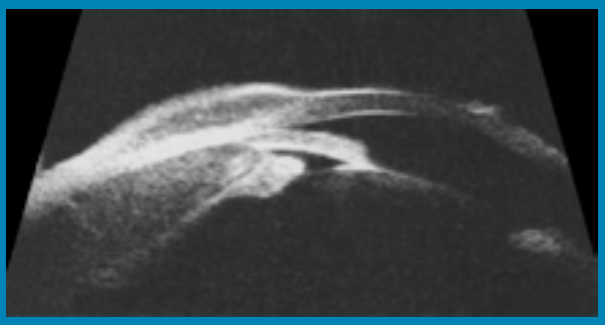


Differential diagnosis? Work-up?

RT3

Round table 3: My job is difficult!
Case ZOGRAFOS L





A 45-year-old man presented with progressive visual loss of the left eye during the last 6 months. He was referred for a presumed diffuse uveal melanoma. The best corrected visual acuity was 20/40, the conjunctiva presented a salmon coloured infiltration around the limbus, the anterior segment was unremarkable, and the intraocular pressure was 16 mmHg. The choroid presented a diffuse thickening with pepper and salt modifications of the retinal pigmented epithelium in the periphery. There was perifoveal localized retinal detachment and on ptical coherence tomography the profile of the retinal pigment epithelium was irregular. The ciliary body on the ultrasound biomicroscopy was thickened.

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