Diagnosis and Detection

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Abstract
The aim of the chapter is to provide a practical but exhaustive guide in detecting macular edema and to describe its features depending on the retinal condition which cause it. The most useful imaging techniques and tools ( Biomicroscopy, retinography, Optical Coherence Tomography, Fluorescein/Indocyanine-Green Angiography) will be analysed in order to identify the best diagnostic algorithm in each pathology. At the end of the chapter a summary table synthesize what previously widely described.

Introduction
Broadly defined, macular edema is an abnormal thickening of the macula associated with the accumulation of excess fluid in the extracellular space of the neurosensory retina. Intracellular edema involving Müller cells has also been observed histopathologically. The term 'cystoid macular edema' (CME) is applied when there is evidence by biomicroscopy, fluorescein angiography (FA) and/or optical coherence tomography (OCT) of fluid accumulation into multiple cyst-like spaces within the macula. Although the classical pathology of CME consists of large cystoid spaces in the outer plexiform layer of Henle, such fluid-filled spaces can be seen in various layers of the retina depending in part on the underlying etiology (Johnson, 2009)1. The standard clinical method for determining macular edema is the subjective assessment of the presence or absence of macular thickening by slit lamp fundus stereo biomicroscopy. The traditional methods of evaluating macular thickening, including slit lamp biomicroscopy and fundus photography, are useful for visualizing signs correlated with retinal thickness such as hard and soft exudates, hemorrhages and microaneurysms, but traditional evaluating methods are relatively insensitive to small changes in retinal thickness and are unable to detect specific anatomic details especially at the vitreomacular interface.

In diabetic retinopathy, macular edema is considered to be clinically significant if the following apply; (1) presence of any retinal thickening within 500 μm of the foveal center; (2) lipid exudates within 500 μm of the foveal center with adjacent thickening, and (3) an area of thickening >1 Macular Photocoagulation Study disk area (1 disk area = 1.767 mm²) within 1 disk diameter.
(1.5 mm) of the foveal center (Early Treatment Diabetic Retinopathy Study Research Group, 1985)².

Fundus photography is used mainly for follow-up. This type of fundus photography is commonly used for clinical trials and used less in clinical practice. Stereo images, rather than a single image, are necessary to identify macular edema and retinal thickening (fig. 1).

Variations in the amount of stereopsis present in paired stereo photographs or in the threshold for thickening adopted by the observer may further complicate the accurate and reproducible detection of areas of edema. The lack of sensitivity of the clinical examination for detection of mild edema has been demonstrated for eyes with a foveal center thickness between 201 and 300 μm (200 defined as the upper limit of normal). Only 14% of eyes were noted to have foveal edema by contact lens biomicroscopy. The term ‘subclinical foveal edema’ describes such cases (Brown et al., 2004)³. Although the system proposed by Brown et al. is useful for the identification of foveal edema, it is not likely to identify cases of nonfoveal clinically significant macular edema – that is, if there was retinal thickening or hard exudates associated with adjacent retinal thickening observed within 500 ± 50 μm of the center of the foveal avascular zone or a zone or zones of retinal thickening 1 disk area or larger, any part of which was within 1 disk diameter of the center of the macula (Sadda et al., 2006)⁴.

OCT is the criterion standard in the identification of CME. OCT is a noninvasive imaging modality that can determine the presence of CME by visualizing the fluid-filled spaces in the retina. The amount of CME can be monitored over time by quantifying the area of cystoid spaces on a cross-sectional image through the macula.

Studies have reported OCT to be comparable to FA in the evaluation of CME, especially with the newer, high-resolution OCT scanners. OCT is beneficial by quantifying the thickness of the retina and by allowing quantitative measurements of macular edema over time. This noninvasive method is especially useful in monitoring the response to treatment. Newer OCT software has increased imaging resolution, which has led to the identification of specific patterns of CME (fig. 2).

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**Fig. 1.** Color pictures showing diabetic retinopathy. Macular edema and retinal thickness are better seen in a stereo image (wear red/cyan 3-dimensional goggles to visualize the stereo effect). **a** Single-frame image. **b** Stereo anaglyph image.
**Fig. 2.** OCT images of central vein occlusion with CME before (a) and after (b) treatment. The thickness map and differential thickness map (c) show resolution of the edema.
While OCT provides an objective evaluation of macular edema and is displacing conventional subjective methods, the older evaluation techniques still predominate, especially in the less developed world (Hee et al., 1998; Shahidi et al., 1994). Fundus autofluorescence (FAF) is collecting the fluorescence emitted by fluorophores of the retina. In particular, to excite lipofuscin, excitation between 470 and 550 nm can be used (Delori et al., 1995).

More than 1 instrument is able to acquire an FAF picture using different wavelengths (Table 1).

For visualization of macular edema, however, macular pigment plays a major role. In a normal blue FAF image, the dark spot visible in the central fovea is due to the macular pigment’s absorption of the blue light used to excite lipofuscin autofluorescence. In the case of CME, by using blue FAF, it is possible to visualize displacement of macular pigment and consequently the cysts (Fig. 3). This tool could be used to evaluate changes during follow-up (Fig. 4, 5).

Currently FA is the most common technique used for the diagnosis of macular edema, although it only provides a qualitative assessment of vascular leakage for this pathology. FA illustrates minute dots of fluorescence, which corresponds to leakage adjacent to the terminal macular vessels. In the case of macular edema, the fluorescence appears only in the late phase, becoming visible after 10–15 min. It appears around the fovea and extends centrally and peripherally, involving only a portion of the fovea. If the condition progresses into cyst formation at the macula, fluorescein can be seen to leak into the cysts. The edematous

![Fig. 3. CME secondary to central retinal vein occlusion visualized in FA (a) and 488-nm FAF (b).](image)

**Table 1. Excitation and barrier wavelength for acquiring with different instruments autofluorescence**

<table>
<thead>
<tr>
<th></th>
<th>Heidelberg HRA</th>
<th>Topcon 450</th>
<th>Zeiss F10</th>
<th>Nidek F10</th>
<th>Canon CX-I</th>
<th>Optos</th>
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<tr>
<td>excitation wavelength (nm)</td>
<td>488</td>
<td>550–605</td>
<td>510–580</td>
<td>490</td>
<td>≥500</td>
<td>532</td>
</tr>
<tr>
<td>barrier filter (nm)</td>
<td>500</td>
<td>670–720</td>
<td>695–755</td>
<td>510</td>
<td>&gt;600</td>
<td>&gt;600</td>
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</table>
fluid accumulates in the outer plexiform layer of Henle over an area that is seldom more than 2 disk diameters.

Associated findings on FA may help determine the etiology of CME. If leaking microaneurysms are present in the setting of diabetic retinopathy, then diabetes is likely the cause. Vascular collaterals crossing the horizontal raphe on FA can help determine if the etiology of the edema (as well as retinal hemorrhages, if present) is likely due to a vascular occlusion.

Indocyanine green angiography (ICGA) is not considered an effective tool for detecting macular edema. In some cases, however, ICGA can be useful in assisting in or confirming a differential diagnosis.

**Fig. 4.** CME secondary to Crohn disease, before (a) and after (b) treatment. The disappearance of CME restored the characteristic darker central area of the macular pigment. (c, d) Patient with diabetic retinopathy and CME. 488-nm FAF (c) and 550- to 605-nm FAF (d) show the importance of visualization of macular pigment and its displacement for indirect visualization of CME (dotted circles). The inability to visualize macular pigment with green or yellow FAF explains the nonvisualization of CME.
Considering Macular Edema Based on the Disease

Irvine-Gass Syndrome

The first identification of macular edema occurring after ocular surgery is attributed to Irvine (1953)\(^8\) while its angiographic appearance was described by Gass (1997)\(^9\) 13 years later. When CME develops following cataract surgery and its cause is thought to be directly related to the surgery, it is referred to as Irvine-Gass syndrome. Despite improvement of surgical techniques, this condition still represents one of the most frequent complications of cataract extraction.

When compared with normal postsurgical responses, the patient affected by postsurgical CME usually complains of blurred vision and reduced color perception and contrast sensibility.

The first set of images (fig. 6–13) shows a case of Irvine-Gass syndrome. At fundus examination, this condition usually appears as a blunted or irregular foveal light reflex with prominent cystic formations (fig. 6).

In autofluorescence (fig. 7), the cysts appear as hyperautofluorescent structures due to the shifting of the macular pigments that normally attenuate the autofluorescent signal in the macular region (Johnson, 2009)\(^1\). The appearance of the fundus alone is not usually enough to make an accurate diagnosis, so further examination is required.

The infrared retinography images (fig. 8) show a nonhomogeneous macular appearance while red-free images (fig. 9) often show bright irregular and almost round shapes in the macular region.

FA (fig. 10) still represents the ‘gold standard’ test to be performed in this pathology: in early and mid phases of the examination, a leakage from parafoveal retinal capillaries can be detected. In the late phases of the fluorescein angiogram, a progressive filling of the cystic spaces leads to a petaloid pattern of pooling in the macula. A leakage of the optic disk usually appears in late-phase angiography (fig. 11).

ICGA (fig. 12) does not show any alterations except for a pooling in very late phases (Ray and D’Amico, 2002)\(^10\). Sometimes the amount of fluorescein angiography leakage does not correlate well with visual acuity; as a result, an important distinction between angiographic and clinically significant CME has to be considered.

Fig. 5. Diabetic patient with diffuse macular edema and CME. As delimited by yellow dots, an area of diffuse edema is not clearly visible in 488-nm FAF (a). CME is visible in both images (red dotted circle). In contrast, diffuse edema is shown as a decrease in FAF intensity since the fluid under or inside the neurosensory retina is masking the fluorescence coming from the retinal pigment epithelium.
Time domain OCT and more recently spectral domain OCT (fig. 13) have enabled this condition to be better defined and permit more accurate follow-up examinations. In addition, the presence of retinal thickening and cystoid spaces can be detected (usually in the foveal region of the outer retina and peripherally to the fovea in the inner retina). Sometimes a detachment of the neurosensory retina occurs which is easily visualized with OCT.

Irvine-Gass syndrome is often a self-limited pathology, and it can regress spontaneously. In some cases, postsurgical CME can persist for more than 6 months in a chronic form. In the chronic syndrome, cystic spaces can coalesce to develop a foveal macrocyst characterized by photoreceptor...
disruptions or even evolve with the formation of a lamellar macular hole.

Diabetic Macular Edema
Diabetic macular edema results from the inner blood-retinal barrier being compromised, which leads to leakage of plasma constituents in the surrounding retina. This condition represents the leading cause of legal blindness in the working age population of most developed countries.

In diabetic retinopathy, at fundus examination (fig. 14), diabetic edema can appear as a localized or diffuse macular thickening depending on the severity of retinopathy. The localization of macular edema can be guided by the presence of characteristic elements such as microaneurysms and hard exudates.

Except for autofluorescence, retinography is not useful for the diagnosis of diabetic macular edema: infrared (fig. 15) and red-free (fig. 16) images can show microaneurysms, hard exudates or hemorrhages; however, CME can sometimes be detected by infrared as hyperreflectant round areas. The autofluorescence (fig. 17) of cysts looks hyperautofluorescent because of the displacement of macular pigments that naturally attenuate the autofluorescent signal.

FA (fig. 18, 19) allows areas of focal versus diffuse edema to be distinguished: a focal edema consists of a well-defined, focal area of leakage from microaneurysms or dilated capillaries, whereas diffuse edema appears as a widespread zone of leakage from altered vascular structures. Diffuse cystoid edema can be detected by the presence of...
diffuse macular leakage accompanied by pooling of dye in cystic spaces (Bhagat et al., 2009)\textsuperscript{11}.

ICGA cannot be used to detect diabetic macular edema but can reveal the presence and localization of a microaneurysm. Sometimes diabetic edema appears in ICGA, however, as diffuse hyperfluorescence due to a diabetic choroidopathy or due to a breakdown of the blood-retinal barrier (Weinberger et al., 1998)\textsuperscript{12}.

OCT represents an important tool, helpful both in the diagnosis and follow-up procedure. According to Kim et al. (2006)\textsuperscript{13}, macular edema can assume 5 different morphologic patterns at OCT evaluation:

Pattern I is a diffuse retinal thickening, which appears as increased retinal thickness with areas of reduced intraretinal reflectivity, especially in the outer retinal layers (fig. 20);
Pattern II is CME, which appears as oval, only slightly reflective intraretinal cavities, separated by highly reflective septa (fig. 21);

Pattern III shows posterior hyaloidal traction, which appears as a highly reflective band over the retinal surface (fig. 22);

Pattern IV exhibits serous retinal detachment not associated with posterior hyaloidal traction, which appears as a dark accumulation of subretinal fluid beneath a highly reflective and dome-like elevation of detached retina (fig. 23);
Pattern V shows posterior hyaloidal traction and tractional retinal detachment, which appear as a peak-shaped detachment with a highly reflective signal arising from the inner retinal surface and with an area of low signal beneath the highly reflective border of detached retina (fig. 24).

Retinal Vein Occlusions
Macular edema can also characterize retinal vein occlusions. The most important feature of CME in this condition is that its extension is related to the nonperfused area. Consequently during fundus examination an involvement of the entire posterior pole can occur during central retinal
**Fig. 23.** Diabetic macular edema. Pattern IV.

**Fig. 24.** Diabetic macular edema. Pattern V. S = Superior; N = nasal; I = inferior; T = temporal.

**Fig. 25.** Fundus CRVO. White arrow = CME; blue arrowheads = hemorrhages; white arrowhead = thrombotic vessel.

**Fig. 26.** OCT of CRVO. Arrows = CME.
vein occlusion (CRVO; fig. 25, 26), while branch retinal vein occlusion (BRVO) usually involves a limited portion of the posterior pole (fig. 27).

In the late phases of the fluorescein angiogram, the pooling of dye into the cystic spaces is clearly visible. In CRVO in the mid to late phase there is papillary and vascular leakage (Tranos et al., 2004). In the late phases of the fluorescein angiogram, the pooling of dye into the cystic spaces is clearly visible. In CRVO in the mid to late phase there is papillary and vascular leakage (Tranos et al., 2004).

OCT shows retinal thickening and/or CME involving 1 or more quadrants depending on the occlusion site and severity in BRVO (fig. 28) while it is diffuse in CRVO (fig. 26). CME consists of differently sized cysts affecting all the retinal layers and can sometimes be complicated by a neurosensory retinal detachment.

Uveitis
CME represents a common but not specific feature associated with uveitis, and it is the most frequent cause of vision loss in patients affected by this pathology. CME develops most commonly in pars planitis, birdshot retinochoroiditis, idiopathic acute iridocyclitis and retinal vasculitis.

CME also develops in anterior uveitis, HLA-B27-related uveitis and any chronic uveitis. Since CME is not specific to a typical category of uveitis, a global examination of the patient including FA and ICGA, inflammatory indexes and immunohistochemical analysis should be required (Johnson, 2009).

FA (fig. 29) and ICGA (fig. 30) are useful in order to characterize the vascular involvement and help to classify the vasculitic processes as either occlusive or nonocclusive.

OCT (fig. 31) is helpful to distinguish the retinal thickening and allows the presence of inflammatory epiretinal membranes, alterations in vitreoretinal interfaces and uveitic macular edema to be detected.

CME associated with uveitis can appear with 3 different patterns depending on its localization and extension (Roesel et al., 2009): (1) cysts involving the inner layers; (2) cysts involving the outer plexiform layer, and (3) cysts involving all the retinal thickness associated with a disruption or loss of the photoreceptors’ inner-outer segment junction. In chronic CME, fluid accumulation is associated with thinning of the retina and fibrosis.

Vitreoretinal Tractional Conditions
Vitreoretinal tractional conditions can sometimes be characterized by a particular type of CME. At biomicroscopy examination, CME is difficult to detect since the posterior pole appearance is usually subverted by the epiretinal membrane. Retinography or FA does not provide further information about CME features, but both can be useful in visualizing epiretinal membrane traction lines or pooling of dye in the cystic spaces.

OCT represents the most helpful tool for the diagnosis and follow-up of these pathologies. OCT can show perifoveal vitreous detachment, a thickened hyperreflective posterior hyaloid and epiretinal membranes. CME can appear both as multiple cystic spaces (fig. 32) or with a typical pagoda-shaped profile, especially when the edema is caused by an incomplete vitreous detachment, such as a gull-wing posterior vitreous detachment (fig. 33). Sometimes a neurosensory retinal detachment occurs. The macular traction may resolve in the formation of a lamellar-macular hole (Tranos et al., 2004).
**Fig. 28.** OCT of BRVO. Arrow = CME. *Inset* Plane of imaging.

**Fig. 29.** Uveitis. FA, wide field. Red arrowhead = Vessel abnormalities; white arrowheads = histochemical areas.

**Fig. 30.** Uveitis. ICGA, wide field. Red arrowhead = Vessel abnormalities.

**Fig. 31.** Uveitis. *a* Site of imaging. *b* OCT. White arrow = CME; red arrow = neuroretinal detachment.
Idiopathic Macular Telangiectasias

Idiopathic macular telangiectasia is a retinal disorder characterized by the presence of dilated ectasias of retinal capillaries that can lead to chronic macular edema. A recent classification includes 2 different types of idiopathic macular telangiectasias (Charbel Issa et al., 2008)16:

*Type 1* shows aneurysmal telangiectasia which is visible at fundus examination and affects men in their midlife; this variant usually has a monocular presentation;

*Type 2* exhibits perifoveal telangiectasia which is not visible at fundus examination; this category is usually bilateral, without sex preference, and affects people between 50 and 60 years of age.

Important information can be acquired from retinal imaging. Regarding retinography, in infrared imaging (fig. 34), macular cystic spaces appear as hyporeflectant, almost round zones. In red-free/confocal blue reflectance imaging (Heidelberg HRA2, 488 nm; fig. 35), a focal or oval hyperreflectance pattern is usually detectable, and it usually appears larger than the hyperfluorescent area characterized in FA images, thus suggesting that the margins of the lesion go beyond the angiographically appearing leakage. Parafoveal deposits appear as spots with increased reflectance. A circle area of hyperreflectance around the macula (due to a lack of macular pigment) can be observed. A correspondence between areas of increased confocal blue reflectance and increased autofluorescence in the perifoveal area can be seen; areas of only increased confocal blue reflectance reveal a normal outer retina in OCT. In autofluorescence (fig. 36), macular cystic spaces appear as hyperautofluorescent almost
round zones, and the highest central autofluorescence of longstanding cysts may suggest the loss of foveal macular pigments and photoreceptors. A correlation can be shown between areas of increased confocal blue reflectance and increased autofluorescence in the perifoveal region.

In FA (fig. 37, 38), parafoveal telangiectatic capillaries can be detected in the early angiographic phases (fig. 37). In the mid to late phases (fig. 38) of the examination, FA images reveal hyperfluorescent areas corresponding to zones of macular pigment loss in autofluorescence and of increased reflectance in red-free zones. The areas of late hyperfluorescence show abnormalities of the outer retina on OCT examination and do not correspond to intraretinal or subretinal fluid.

ICGA (fig. 39) usually shows no choroidal alterations (Bottoni et al., 2010)17.

OCT (fig. 40) shows the presence of intraretinal foveal cysts localized in the outer retinal layers and abnormalities of the outer plexiform layer with a ‘wrinkled’ appearance suggesting Müller cell sufferance. One of the main features of idiopathic macular telangiectasias is that strangely intraretinal cysts that can be observed in OCT scans do not appear hyperfluorescent in late phases of FA, while outer retina abnormalities correspond to the areas of late hyperfluorescence.

**Age-Related Macular Degeneration**

Macular edema represents a common finding in wet age-related macular degeneration (AMD) due to the exudation which characterizes this pathology.

In the early phases of the disease, cystic spaces usually appear small in size and are difficult to observe on biomicroscopic examination, while other features of the lesion-like drusen, such as macular hemorrhages, subretinal fluid and pigmented epithelium retinal detachments, are predominant.

FA (Macula Photocoagulation Study Group, 1991)18 is still considered the ‘gold standard’ test for the diagnosis of wet AMD, and it usually enables detection of mid- to late-phase CME due to the pooling of dye inside the cysts. However, active lesions are characterized by an increase in dye leakage during the test, which causes a masking effect on the subretina. In contrast, old lesions
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are characterized by a confluence of the cystic spaces and reduced leakage; as a consequence, CME becomes easier to observe both at fundus examination and with FA (fig. 41).

ICGA is a very useful examination to study AMD lesions, such as occult, polypoidal, chorioretinal anastomoses and choroidal neovascularization (CNV). However, ICGA is not as helpful in identifying CME.

Currently the most useful technique to detect and study CME in wet AMD is OCT. With the development of the spectral domain OCT
technology, OCTs are able to acquire high-definition images, which allow the operator to identify even extremely small cysts in the earliest phases of the disease and to describe their distribution into the different retinal layers.

Depending on lesion type and in the early phases of the disease, CME shows different patterns of localization: classical lesions usually present intraretinal fluid localized in small cystic spaces primarily disposed into the internal layers (nuclear and plexiform; fig. 42). Occult CNVs are seldom characterized by a huge macular edema: in these lesions CME, when present, is typically represented by intraretinal small cystic spaces localized to the external retinal layers (nuclear and, more rarely, plexiform; fig. 43).

Retinal angiomatous proliferation lesions represent the type of CNV characterized by the larger amount of CME and often involve both external and internal retinal layers (fig. 44). The same cyst

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**Fig. 40.** Idiopathic macular telangiectasias. OCT. Arrow = CME.

**Fig. 41.** AMD. FA, advanced CNV. White arrow = CME; red arrowhead = hard exudates; black arrow = retinal pigment epithelium detachment.
Fig. 42. AMD. OCT, classical lesion. White arrow = CME; white arrowhead = CNV complex; red arrows = neurosensory retinal detachment.

Fig. 43. AMD. OCT, occult lesion. White arrows = CME; red arrowhead = hard exudates; blue arrow = retinal pigment epithelium detachment.

Fig. 44. AMD. OCT, retinal angiomatous proliferation lesion. White arrow = CME; white arrowhead = CNV complex; red arrow = neurosensory retinal detachment; blue arrows = retinal pigment epithelium detachment.
localization can be observed in polypoidal lesions (fig. 45).

In advanced CNV, CME is characterized by large cystic round spaces surrounded by hyper-reflective boundaries; sometimes a single cyst can involve the entire neurosensory retina (fig. 41, 46). Small round/oval structures with circular midreflectant elements and a central brighter core, which can be observed surrounded by a crown of hyperreflectant spots, can be confused with CME. These formations, called a ‘rosette’ or ‘outer retinal tubulation’, represent a stability mark of the lesion (fig. 47) (Zweifel et al., 2009)19.
For these many reasons, OCT is extremely useful in both the diagnostic process and during follow-up examinations.

Table 2 resumes what previously described in the text and estimates the relevance of each diagnostic technique in defining the aetiology of cystoid macular edema.

Table 2. Summary of examination methods

<table>
<thead>
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<th>Retinography</th>
<th>FA</th>
<th>ICGA</th>
<th>OCT</th>
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<tbody>
<tr>
<td>Irvine-Gass syndrome</td>
<td>R</td>
<td>S</td>
<td>U</td>
<td>–</td>
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<td>S</td>
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<td>AMD</td>
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ICGA = Indocyanine green angiography; AMD = age-related macular degeneration; R = rarely useful; S = sometimes useful; U = usually useful; – = usually not performed.
References