Blood on the macula: diabetes or age?

Aditi Gupta, MBBS, MRCOphth
Ramesh Sivaraj, MS, DNB, FRCS Ophthalmology

Diabetes and age can affect a patient’s central vision as a result of damage to the macula. Both of these conditions can present with haemorrhage at the macula and appropriate referral and timely management is key in determining the visual potential in these cases. Diabetic retinopathy can present with haemorrhages at the macula at various stages depending on the severity of the diabetic status and other associated risk factors. On the other hand, macular haemorrhage in age-related macular degeneration (AMD) is usually a sign of the exudative or ‘wet’ form of this disease. This article describes the various conditions which can present with blood on the macula, offering guidance on differential diagnosis and optometric management.

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Learning objectives
Be able to recognise common ocular abnormalities and refer when appropriate, with emphasis on those causing macular haemorrhages (Group 6.1.5)
Understand the treatment of a range of common ocular conditions, with emphasis on those causing macular haemorrhages (6.1.11)

About the authors
Aditi Gupta is a speciality registrar in the West Midlands ophthalmology rotation. She completed her membership (MRCOphth) examination early in her training years. She has a keen interest in medical retina diseases in teaching undergraduates and other allied health professionals.

Ramesh Sivaraj is a consultant ophthalmologist and clinical director of ophthalmology at the Heart of England NHS Foundation Trust. He is also the lead for diabetic retinopathy in the Trust. After completing specialist training in Birmingham, he undertook an Advanced Medical Retinal and Uvea Fellowship at Moorfields Eye Hospital. His special interests are AMD, diabetic retinopathy, retinal vascular diseases and uveitis.
Pathophysiology
Diabetic retinopathy is the result of microvascular retinal changes. Hyperglycaemia-induced intramural pericyte death and thickening of the basement membrane lead to incompetence of the vascular walls. Capillary wall breakdown results in the formation of micro-aneurysms. Rupture of the retinal capillaries gives rise to dot and blot haemorrhages (Figure 1). As a consequence of these changes, the blood-retinal barrier is altered and the retinal blood vessels become more permeable, resulting in leakage of fluid and lipoproteins into the macula. This causes macular oedema and formation of hard (lipid) exudates (Figure 2). As the disease progresses, vasoendothelial growth factor (VEGF) released by damaged retinal capillaries causes abnormal blood vessels to grow on the surface of the retina (neovascularisation). These blood vessels are immature and weak, which increases the risk of bleeding; thereafter there is eventual risk of scarring.¹

Exudative AMD occurs as a result of calcification and breaks in Bruch's membrane.² Disruption of the elastic lamina of Bruch's membrane in the macula acts as a prerequisite for invasion of blood vessels from the deep choroidal circulation directly into the retina (Figure 3). It is now known that there is an increased response of VEGF as a result of damage to the Bruch's membrane, resulting in choroidal neovascularisation (CNV).³ CNV represents new blood vessel formation from the choroid and is a hallmark of exudative AMD (Figure 4).⁴

Clinical symptoms
Patients with diabetic maculopathy usually describe an insidious onset of painless blurring of central vision. They might also report difficulty in reading. Patients with exudative AMD typically report an acute onset of painless progressive blurring of their central vision. They might also present with relative or absolute central or paracentral scotomas, metamorphopsia, and difficulty in reading. Often patients present after having lost their vision in one eye, which is only usually discovered accidentally when they cover the unaffected eye (for example, by rubbing it).

Clinical findings
In diabetes, haemorrhage seen at the macula can present in various ways depending on the severity of diabetic retinopathy. Micro-aneurysms appear as pinpoint dots usually seen at the macula and are located at the inner nuclear layer of the retina. They are focal dilatations of the retinal capillary bed and are the first clinically detectable lesions seen in diabetic retinopathy. Micro-aneurysms often leak as the disease progresses and this gives rise to macular oedema and formation of lipid exudates, which appear as yellow clumps or spots within the retina (Figure 2). Dot and blot haemorrhages represent haemorrhagic infarcts and are a sign of advancing diabetic retinopathy. These haemorrhages have fuzzier borders and are located in the deep neurosensory retina (Figure 1). Flame-shaped haemorrhages are linearly...
shaped and are located in the superficial neurosensory retina. Intra-retinal microvascular abnormalities (IRMA) are frequently seen adjacent to areas of capillary closure. Clinically, IRMA may resemble focal areas of flat neovascularisation. The main distinguishing features of IRMA are their intra-retinal location, absence of profuse leakage on fundus fluorescein angiography (FFA) and failure to cross major retinal blood vessels.

Neovascularisation is a hallmark of proliferative diabetic retinopathy. They appear as fronds, which can be flat or seen sprouting into the vitreous. New vessels can arise anywhere on the retina, although the optic disc is a common site (Figure 5). New vessels which rupture can further result in pre-retinal haemorrhage (Figure 6) or vitreous haemorrhage, which can sometimes overlie the macula.

CNV is a typical finding, suggesting exudative AMD. The CNV itself may be seen as yellow-green sub-retinal discoloration and is sometimes surrounded by a pigment ring. Sub-retinal haemorrhage typically develops at the margins of the CNV and sometimes obscures the entire complex. Often the area appears raised suggesting underlying sub-retinal pigment epithelial (sub-RPE) or sub-retinal fluid. The overlying retina may have cystic changes and may show signs of cystoid macular oedema. Adjacent hard exudates or drusen are other features to help distinguish exudative AMD from diabetic retinopathy; in particular the location of these can provide clues to the diagnosis, since exudates arising from diabetes tend to be more circinate in nature, located in the peripheral macula. Occasionally CNVs can bleed spontaneously and can result in sub-macular haemorrhage or vitreous haemorrhage.⁵

**Investigations**

All patients with diagnosed diabetes will receive annual screening for retinopathy. Details of such a scheme have been covered elsewhere in OT and are beyond the scope of this article. The purpose of these screenings is to detect changes relating to diabetes and to determine the risk to sight, particularly where there is macular involvement.

Where haemorrhage on the macula is suspected in patients outside of the diabetic retinopathy scheme, careful examination using binocular indirect methods (such as Volk lens) through a dilated pupil is warranted. In particular it is important to ascertain the presence of macular thickening and exudation, which can suggest macular oedema, and CNVs, which can point towards exudative AMD. Performing an Amsler chart test is also useful in order to help diagnose the presence of macular distortion from macular oedema or exudative AMD. Remember, however, that even dry AMD can induce distortion of the Amsler chart due to disruption of the surface regularity of the macula by drusen, and so the results need to be considered in the context of other clinical findings too, including VA.

Optical coherence tomography (OCT) uses light to generate a cross-sectional image of the retina. OCT plays an important role in the measurement of retinal thickness and detection of intra-retinal cystic changes, sub-retinal or sub-RPE fluid and helps in the diagnosis and management of exudative AMD and diabetic macular oedema (Figure 7). It helps in monitoring CNV activity and is used as a guide for treatment.⁶ FFA is a well-established modality for assessment of neovascular AMD. FFA is used to characterise the location of CNV (extrafoveal, juxtafoveal, subfoveal) and type of CNV (classic or occult) in exudative AMD. Quantitative FFA can also provide similar benefits as OCT in the management and treatment of AMD. In diabetic retinopathy, FFA is useful in identifying the extent of ischaemia, the location of micro-aneurysms, the presence of IRMA, neovascularisation and the extent of macular edema.⁷

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Differential diagnosis

In addition to macular haemorrhage arising from diabetes and exudative AMD, it can also occur secondary to vascular diseases such as arteriosclerosis, hypertension, retinal artery or retinal vein occlusion, retinal macroaneurysm, chorioretinitis, blood disorders as well as shaken baby syndrome, and can also occur spontaneously or as a result of trauma. Other causes are Valsalva retinopathy and Terson syndrome (intraocular, usually vitreal, haemorrhage secondary to subarachnoid haemorrhage).

Hypertension

Arteriosclerotic changes (described as silver or copper wiring of arterioles) result in a breakdown of the blood-retinal barrier, resulting in exudation of blood (haemorrhages), lipids (hard exudates), and subsequent ischaemia of nerve-fibre layers (cotton-wool spots). The haemorrhages can be seen as flame-shaped or blot-shaped and usually represent a sign of progressing hypertensive retinopathy. Hypertension has also been implicated in the pathogenesis of AMD.

Retinal vein occlusion

Hypertension and diabetes are two major risk factors for retinal vein occlusions. Obstruction of the retinal vein at the optic nerve is referred to as central retinal vein occlusion (CRVO), and obstruction at a branch of the retinal vein is referred to as branch retinal vein occlusion (BRVO). CRVO presents as variable dot and flame-shaped haemorrhages in all four quadrants of the retina, along with dilated and tortuous vessels (Figure 8). In BRVO, superficial flame-shaped haemorrhages are seen along the sector of retina drained by the affected vein; only the obstructed vein is dilated and tortuous (Figure 9). In both of these conditions, the presence of cotton wool spots indicates signs of ischaemia. As a result of ischaemic damage to the retina, increased production of VEGF causes capillary leakage giving rise to macular oedema and neovascularisation.

Macular telangiectasia

This is usually an idiopathic condition where blood vessels around the macula become dilated and incompetent. They appear as haemorrhagic spots at the macula along with lipid deposition and macula oedema (Figure 10). OCT and FFA are beneficial in identifying this anomalous vasculature and help to differentially diagnose this condition from AMD.

Retinal macro-aneurysms

These are associated with hypertension and are aneurysmal dilatations of the retinal arterioles. Clinically they present as intra-retinal haemorrhages along with exudates. Macular oedema can result due to chronic exudation (Figure 11).
have designated fast-track referral pathways for patients to be seen within two weeks, and these should be utilised.

Haemorrhage on the macula due to other causes will also warrant urgent referral, since there is a threat to sight. Formal diagnosis and management will often require techniques which are not widely used currently in optometric practice, but owing to new treatment techniques which can preserve vision, there is an increased need to be vigilant.

**Anti-VEGFs**

Intravitreal injections of Ranibizumab (Lucentis) and Bevacizumab (Avastin) are the main treatments of choice for exudative AMD. These are humanised monoclonal antibodies directed against VEGF and thus aim to prevent neovascularisation. Intravitreal Pegaptanib, an aptamer (short oligonucleotide) which specifically binds and inhibits VEGF isoforms, has also shown to be effective in the treatment of exudative AMD. Anti-VEGFs are also now being used for the treatment of diabetic macular oedema. Intravitreal injections carry a small risk of endophthalmitis, with reported risk of 0.009-0.541%. Intravitreal steroids (triamcinolone) are also being used in the treatment of diabetic macular oedema involving the fovea. Intravitreal anti-VEGF injections required. Intravitreal steroids (triamcinolone) are also being used in the treatment of diabetic macular oedema and advanced diabetic retinopathy. Focal laser is applied directly to specific leaking microaneurysms involving the macula. In cases where the foci of leakage are non-specific, a grid pattern of laser burns is applied. In the presence of advancing diabetic retinopathy and neovascularisation, pan-retinal photocoagulation (PRP) is carried out.

**Lasers**

Laser therapy is no longer used for the treatment of CNV secondary to AMD. Argon laser photocoagulation is useful in the treatment of diabetic macular oedema and advanced diabetic retinopathy. Focal laser is applied directly to specific leaking microaneurysms involving the macula. In cases where the foci of leakage are non-specific, a grid pattern of laser burns is applied. In the presence of advancing diabetic retinopathy and neovascularisation, pan-retinal photocoagulation (PRP) is carried out.

**Other treatment options**

Alternative treatment options available include Verteporfin photodynamic therapy (PDT), which has shown to be useful in the treatment of sub-foveal CNV. A highly targeted, low voltage X-ray treatment has also been developed recently. It offers a one-time treatment for certain types of wet AMD and clinical studies have shown a reduction in the number of intravitreal anti-VEGF injections required. Intravitreal steroids (triamcinolone) are also being used in the treatment of diabetic macular oedema due to proliferative diabetic retinopathy and secondary to CNV. In cases of sub-macular haemorrhage secondary to CNV, injection of tissue plasminogen activator followed by gas tamponade has been shown to be beneficial.

**Conclusion**

Diabetes and AMD are the leading causes of haemorrhages at the macula. It is useful to remember that these conditions can often co-exist too (Figure 13). Furthermore, there are other vascular conditions which can cause haemorrhages at the macula and these should be considered as differentials. Optometric vigilance is required in all cases of macular haemorrhage so that patients can be managed effectively in order to preserve their vision.