Diagnosis and management of multiple white lesions at the posterior pole

In Part 1 of a two-part series, **Christina A Rennie**, **Sam Khandhadia** and **Richard Newsom** look at the differential diagnosis of white lesions seen within the eye

Yellow-white flecks or deposits at the macula are caused by a wide range of conditions and can lead to vision loss. There is often confusion about how to differentiate the various types of lesions and how quickly they need referral. This article looks at the yellow-white flecks and deposits that predominantly affect the macular region. These include drusen and drusen-like conditions, exudates, hereditary flecked conditions, crystalline deposits, and inflammatory conditions. The aim is to highlight the important features in the patient history and fundal examination that help to categorise the lesion, its underlying condition, and guide the urgency of referral to the hospital eye service.

Fundus examination

Macular lesions are best examined using stereo-biomicroscopy through a dilated pupil using a non-contact lens. The authors use a high magnification lens, such as the Volk super 66 lens. Use of biomicroscopy gives a stereoscopic 3-D view, essential to gauge the depth of the lesion within the retina. A reasonable level of illumination is required to enhance the detection of any associated thickening or thinning of the retina. Many patients find the full beam uncomfortable, so a smaller slit 3mm in height and 1mm in width can be used. A relatively short macular examination is recommended to avoid any photopic damage.

When assessing white flecks and deposits at the macula a number of factors should be considered to aid categorisation of the condition. Is it single or multiple, unilateral or bilateral? Is there a particular pattern to the deposits? What depth is the lesion at? Do the deposits have well-defined edges? Are they shiny (for example due to a crystalline deposit) or are they more indistinct? This article will use these questions to help guide differentiation of these conditions. A number of standard textbooks have been referenced for further information.[1-4]

Drusen

Drusen types

Drusen are the commonest cause of deposits seen at the macula. They consist of yellow excrescences beneath the retinal pigment epithelium (RPE) that may vary in number, size, shape, degree of elevation, and RPE changes. These discrete deposits of abnormal material accumulate within the inner portion of Bruch's membrane. They are rarely seen before the age of 45 years, and increase between the ages of 45 and 60 by which time they are almost universal. There are five main types, with hard and soft drusen being the commonest.

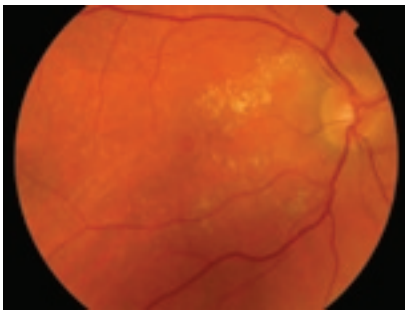

Figure 1 Hard drusen

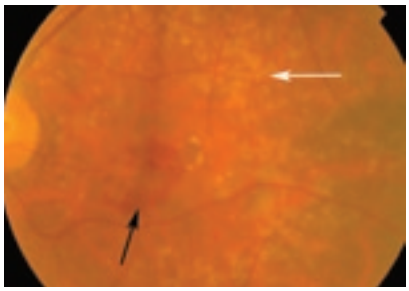

Figure 2 Soft drusen (white arrow) and intraretinal haemorrhage (black arrow)

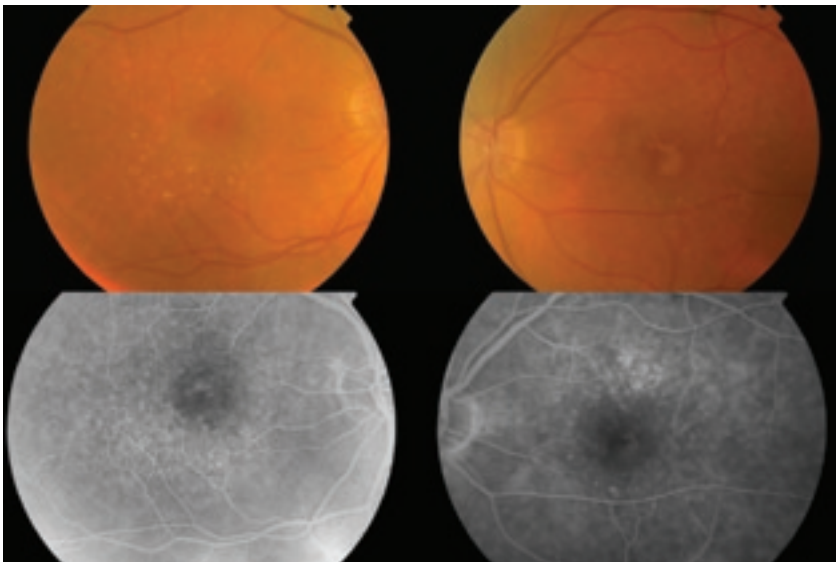

Figure 3 Basal laminar drusen

- **Hard drusen** (Figure 1) – are small and discrete. These patients are at increased risk of subsequent visual loss from geographical atrophy
- **Soft drusen** (Figure 2) – these are larger and paler than hard drusen and are associated with an increased risk of exudative age-related macular degeneration (AMD) – see below
- **Basal laminar drusen** (Figure 3) – a myriad of small, round, uniformly sized, slightly raised yellow subretinal lesions. Fluorescein angiography enhances their appearance so that hundreds of bright spots appear, giving a 'starry-sky' appearance. They occur in middle-aged individuals who are usually asymptomatic until they develop pseudovitelliform lesions, the accumulation of yellow material at the fovea that can simulate a choroidal neovascular membrane. This resolves without a scar, producing less visual loss than a true subfoveal choroidal neovascular membrane (CNV).
- **Calcified drusen** (Figure 4) – drusen may acquire a glistening appearance due to calcification which can occur in any type of drusen. These are often seen adjacent to areas of RPE atrophy.
- **Drusenoid RPE detachment** – caused by coalescence of large areas of soft drusen, this is a precursor of AMD.

Drusen and AMD

Many eyes with drusen maintain normal vision, but 10 per cent of individuals aged between 65 and 75 years will have some central visual impairment due to AMD. This is defined as some degree of visual loss associated with drusen and geographical atrophy of the RPE, or changes from subretinal neovascularisation, in individuals over 50 years old.[2] Drusen alone in the presence of normal visual acuity is considered a normal ageing process and does not require referral. When examining patients with drusen it is important to look for features of AMD. There are two main types of AMD – dry (non-exudative) and wet (exudative). The dry form is characterised by geographical atrophy, which starts as defined areas of RPE loss. These are often parafoveal with hyperpigmented edges, and coalesce to form large atrophic patches (Figure 4). The exudative form is characterised by the development of choroidal neovascularisation that leads to destruction of photoreceptors and RPE by fibrovascular tissue. Patients may describe blurred vision and distortion, especially for near vision, or a scotoma.

Clinical features that are associated with an increased risk of visual loss from AMD include large soft drusen, confluent drusen and focal hyperpigmentation of the RPE (Figure 5). These patients can be given advice on risk factor modification and antioxidant/mineral supplements to reduce the risk of developing wet AMD. They should be encouraged to self-monitor with an Amsler chart for the development of wet AMD. Subtle clinical findings can be easily missed so stereoscopic slit-lamp biomicroscopic examination is important. The presence of haemorrhages, localised retinal thickening or elevation, and distortion of central vision should alert the observer to the possibility of wet AMD (Figure 2). These individuals need urgent referral for assessment and treatment. Anti-VEGF treatments are increasingly available, and studies of ranibizumab show that 90 per cent stabilise and the vision of up to 40 per cent will improve with treatment.[5]

Familial dominant drusen

These are rare dominantly inherited conditions where the patients develop drusen at a younger age, often in early adulthood and consequently may develop exudative maculopathy and visual loss at a younger age than in AMD. The drusen are usually multiple, large and nodular, at the posterior pole and also occur nasal to the optic disc. They may have a particular pattern such as the confluent honeycomb pattern of Doyne's dystrophy (Figure 6) and the radial arrangement in Malattia Leventinese. A genetic test is available and these patients should be referred routinely for diagnosis and advice. Any patients with signs suggestive of exudative maculopathy need urgent referral.

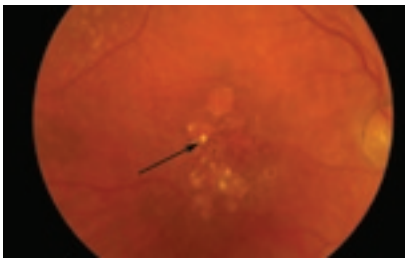

Figure 4 Atrophic patches in dry AMD with crystalline drusen arrowed

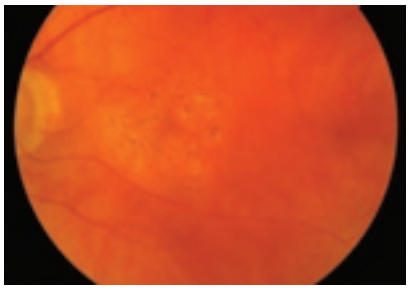

Figure 5 Hyperpigmentation of the RPE

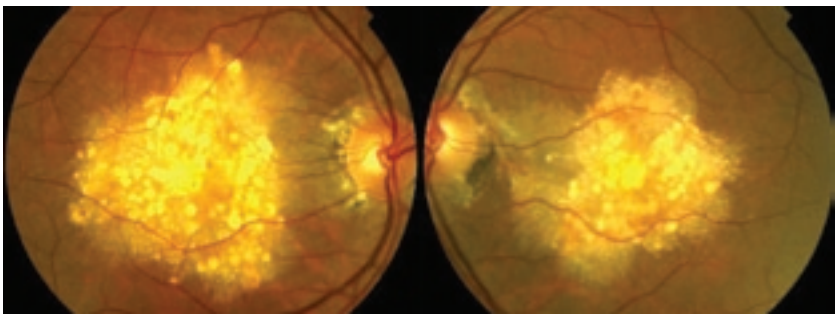

Figure 6 Doyne's dystrophy

Pattern dystrophy

Adult-onset vitelliform dystrophy (a type of pattern dystrophy commonly known as Best's disease) may be mistaken for a large drusen or small RPE detachment in AMD but has a better prognosis. It is characterised by bilateral symmetrical raised yellow-orange deposits at the fovea (Figure 7).

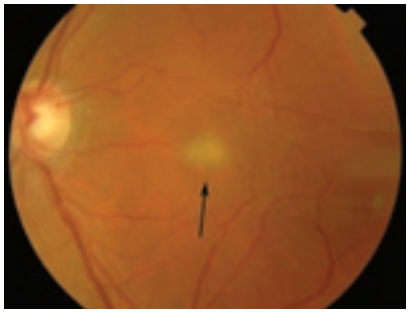

Figure 7 Vitelliform dystrophy

Rare drusen conditions

There are other rare causes of drusen where the family history and systemic disorders will aid diagnosis, such as type II mesangiocapillary membranoproliferative glomerulonephritis, and North Carolina macular dystrophy.

Hard exudates

Hard exudates are lipid deposits that are produced by lipoprotein leakage from blood vessels. The novice is often concerned about how to distinguish them from drusen but careful biomicroscopy will show that hard exudates are located more anteriorly in the retina than drusen, occurring between the inner plexiform and inner nuclear layers. They have a yellow waxy appearance with well-defined margins. They may take on a number of patterns, such as circinate (ring), clumps, or stellate configuration (Figures 8-10), depending on the underlying cause, whereas drusen tend to be more randomly spread. Signs of underlying conditions that may cause leakage and formation of hard exudates may be present, such as microaneurysms in diabetic retinopathy, or vessel dilatations in Coats' disease.

Circinate or clump pattern of hard exudates

These are the result of chronic leakage from capillaries in the macula. Common causes are diabetic maculopathy, branch retinal vein occlusion (Figure 8), and retinal artery macroaneurysm. Other rarer causes include radiation retinopathy, and retinal telangiectasia. The cause may be obvious, with multiple microaneuryms in diabetic retinopathy, and the sectoral distribution of a branch vein occlusion. These patients require referral to the GP for investigation and management of cardiovascular risk factors, and 1-2 week referral for ophthalmological management of the retinal disease.

Stellate maculopathy

This occurs when hard exudates form a star pattern at the macula which may be complete or incomplete (Figure 9). Bilateral features with disc swelling may be caused by severe hypertension or papilloedema and require emergency referral. ▶

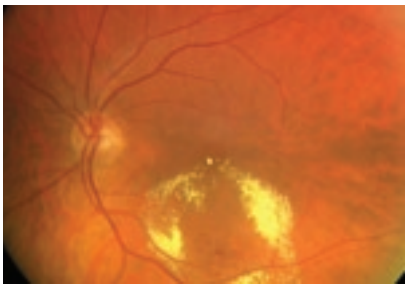

Figure 8 Branch retinal vein occlusion

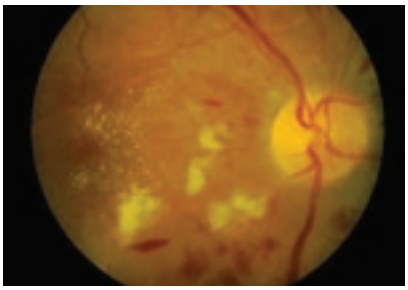

Figure 9 Stellate maculopathy

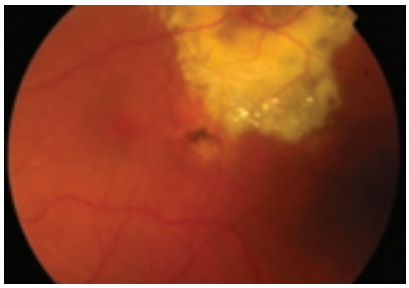

Figure 10 Coats' disease

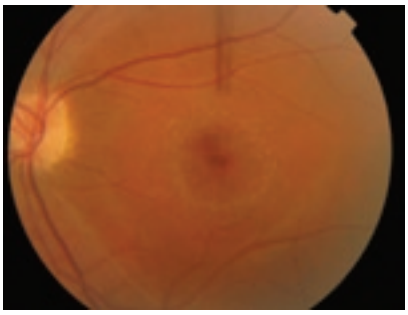

Figure 11 Fundus flavimaculatus

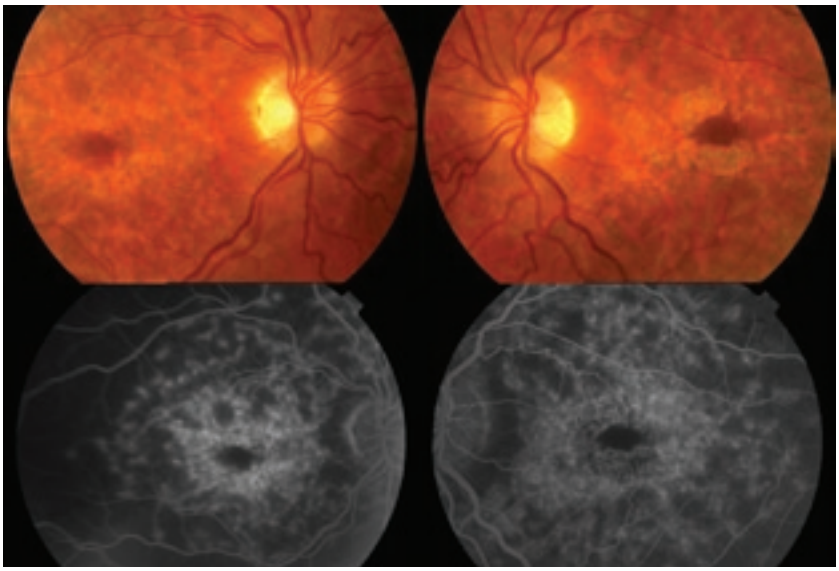

Figure 12 Stargardt's disease

Neuroretinitis (inflammation of the optic nerve and retina from various causes) and capillary angioma (on the disc or in the periphery) are rarer causes that need urgent referral.

Subretinal exudates

These are exudates deep to the retina that are associated with serous elevation of the overlying retina. These tend to be distinct from the other forms producing a large exudate rather than a pattern of small exudates. They may be seen with chronic leakage from a choroidal neovascular membrane, Coats' disease and *Toxocara canis*. Coats' disease (Figure 10) typically occurs in children and is characterised by telangiectatic and aneurysmal retinal vessel changes. These lead to intra- and subretinal exudates that progress to massive subretinal exudate and exudative detachment. This can present as leukocoria, a white reflex, and these patients require urgent referral for diagnosis, in particular to exclude other causes of leukocoria.

Crystalline maculopathies

Multiple yellow crystalline deposits at the macula can be caused by drugs, and much more rarely by hereditary or metabolic disorders.

Tamoxifen, a specific anti-oestrogen used in the treatment of breast cancer, can cause retinotoxicity at high doses and more rarely after long-term use at low doses. Bilateral multiple superficial, crystalline deposits are seen at the macula with retinal toxicity consisting of decreased visual acuity and colour vision. Discontinuation of treatment prevents further progression but there may not be full recovery of visual function. Other drugs that can induce a crystalline maculopathy include canthaxanthin, an oral tanning agent, and talc, associated with cocaine and heroin use. All patients with crystalline maculopathy require referral for diagnosis and management.

Flecked retinal syndromes

There are a group of rare predominantly recessively inherited disorders characterised by yellow flecks deep in the retina.

- **Fundus flavimaculatus** – This occurs in adults, and is characterised by ill-defined, yellowish flecks that are often of a fishtail or crescentic shape. They are present deep in the retina, below the level of the retinal vessels, and are symmetrically distributed (Figure 11). The visual prognosis is good unless there is macular involvement.
- **Stargardt's disease** – This presents in childhood with a similar appearance to fundus flavimaculatus. However, there is early foveal involvement with an oval lesion that has a 'beaten-bronze' appearance and leads to atrophy with loss of vision (Figure 12).
- **Fundus albipunctatus** (a form of congenital stationary night blindness) also features multiple yellow spots deep in the retina, which tend to spare the macula. These flecks need to be distinguished from drusen, but the shape, depth and symmetrical distribution of the lesions should aid this. Drusen are more sharply delineated, rounder, and whiter. All these patients should be referred for diagnosis and genetic counselling.

References

1 Kanski JJ, Nischal KK, Milewski SA. *Ophthalmology: Clinical Signs and differential Diagnosis*, Philadelphia: Mosby, 1999.
2 Kanski JJ. *Clinical Ophthalmology: A Systematic Approach*, 6th ed, Edinburgh: Butterworth-Heinemann Elsevier, 2007.
3 Ryan SJ. *Retina*. 4th ed, Philadelphia, Pa: Elsevier/Mosby, 2006.
4 Nussenblatt RB, Whitcup SM. *Uveitis: Fundamentals and clinical practice*, 3rd ed, Philadelphia: Mosby 2004.
5 Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S, for the ANCHOR Study Group. Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneratio. *NEJM*, 2006;355:1432-1444.

This is a sister paper to the red eye differential diagnosis paper published in *Optician*, February 29 2008. **Christina A Rennie** is a specialist registrar, **Sam Khandhadia** is research registrar and **Richard Newsom** consultant ophthalmologist, all at the Southampton Eye Unit