Letter to the Editor

Exudative cotton-wool spots: an under-recognised variant of a common lesion

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Cotton wool spots (CWS) are polymorphous pale lesions of the inner retina, found in a variety of systemic and retinal diseases. Typical CWS are round or oval in shape and yellow-white or grayish-white in colour, with poorly defined or feathery edges, often with striations parallel to the retinal nerve fiber layer (RNFL). They frequently accompany other retinopathic features such as exudates, oedema and haemorrhages, but can occur as an isolated finding. On imaging with fundus fluorescein angiography (FFA), CWS can correspond to areas of hyperfluorescence (from increased retinal capillary permeability), as well as patches of hypofluorescence (from masking of deeper tissues, and localized capillary non-perfusion) in some cases. Histologically, CWS are characterized by cytooid bodies, which are bulb-like accumulations of axoplasmic debris within adjacent bundles of unmyelinated ganglion cell axons(1).

As yet unreported but visually significant variant of CWS are those that are associated with substantial fluid exudation. These 'exudative CWS' can cause sub-retinal and intra-retinal fluid (SRF and IRF, respectively) accumulation, the extent of which is often disproportionate to the area and intensity of leakage evident on FFA. The SRF and IRF can cause visual deterioration that is additional to that caused by the underlying systemic and retinal pathologies. As such, leaky CWS merit diagnosis and management in their own right as a potentially sight-threatening condition. We propose adding this distinct subtype of CWS, which has not previously been described, to the peer reviewed literature. Herein we describe three clinical cases that illustrate these findings.

The first case is a 51 year-old male taking warfarin 3mg daily for a prosthetic aortic valve, with best-corrected visual acuity (BCVA) of 6/36 OD and 6/5-4 OS. There was a right inferior exudative CWS that responded to focal laser treatment (Figures 1[a-d]). The second case is a 78 year-old female taking aspirin 100mg and clopidogrel 75mg daily, with a left superior exudative CWS, longstanding poor vision OD, and

BCVA of 6/60 OU (Figure 2[a,b]). Macular thickening worsened despite focal laser treatment (Figure 2[c,d]). The third case is an 85 year-old female with bilateral moderate non-proliferative diabetic retinopathy (NPDR), a left supero-temporal exudative CWS, left choroidal neovascular membrane (CNVM), and BCVA of 6/6 OU (Figure 3[a,b]). The features in the left eye improved with intra-vitreous aflibercept treatment (Figure 3[c,d]).

Cotton wool spots are a sentinel of retinal ischaemia, and may represent oncotic inner retinal infarction due to disordered local blood flow (1). This can occur after occlusion of terminal arterioles and/or venules, in the context of restricted collateral microcirculation. CWS can be important harbingers of systemic diseases, including hypertension, diabetes mellitus, collagen vascular disorders and HIV infection, and can accompany retinal vasculopathies such as vein and arterial occlusions(2). Another postulated mechanism for CWS formation is mechanical obstruction of axoplasmic transport, as in epiretinal membrane contraction, where compression damage to axon bundles overwhelms their innate deformability(3). Typical CWSs disappear in 4 to 12 weeks and can leave a patch of atrophy, discernible on OCT as localized loss of the RNFL, ganglion cell, inner plexiform, and inner portion of the inner nuclear layers. Subsequent glial cell proliferation may lead to scar formation.

The pathophysiology of exudative CWS has not been studied in histology or animal models. An experimental model of ischaemia using microsphere embolisation of small retinal arterioles showed fluid exudation in areas where vessel walls were damaged directly by the glass microsphere(4). The distribution of CWS along the specialized radial peri-papillary capillaries, in the configuration of a double Bjerrum arc surrounding the macula, may underpin the trajectory of fluid from exudative CWS towards the fovea (5). We propose that the mechanism of substantial exudation from CWS is likely to be multifactorial, incorporating endothelial damage, a compromised blood-retina barrier and vascular endothelial growth factor (VEGF)

mediation. The resulting increased vascular permeability occurs most commonly in vasculopathic patients and may be exacerbated by systemic anti-platelet and/or anticoagulant medications.

To the authors' knowledge, this is the first description of exudative CWS in the literature. We recommend case-by-case management with judicious choice of conservative monitoring, FFA-guided focal laser and off-label use of intra-vitreous anti-VEGF agents. Multi-modal imaging can help to exclude differential diagnoses including macroaneurysms and retinal neovascularization.

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FIGURE LEGENDS

Figure 1: (clockwise from top left): (a) Colour fundus photograph OD. Inferior macular CWS with intra-retinal and RNFL haemorrhage, parafoveal hard exudate and widespread hypertensive vascular changes, (b) FFA OD at 3:50min showing localized

leakage and blockage from the CWS, and parafoveal micro aneurysms, (c) OCT OD showing inner retinal thickening from the CWS, with IRF and SRF tracking superiorly to the fovea, (d) Reduction in IRF and SRF following FFA-guided focal laser treatment to the CWS.

Figure 2: (clockwise from top left): (a) Colour fundus photograph OS showing superior macular CWS with intra-retinal haemorrhage, inferior hemi-retinal artery occlusion, abnormal foveal reflex, (b) FFA OS at 4:53min showing localized leakage and blockage from the CWS, inferior hemi-retinal arterial occlusion and petalloid leakage at the fovea, (c) OCT OS showing CMO extending inferiorly from the CWS with sub-foveal SRF, (d) Persistence and worsening of macular oedema despite focal laser treatment.

Figure 3: (clockwise from top left): (a) Infra-red reflectance OS showing CWS super-temporal to the disc, as well as macular drusen and reticular pseudodrusen, (b) FFA OS showing localized blockage and small focal spots of leakage from the CWS, as well as features of moderate NDPR and age-related macular degeneration, (c) OCT OS showing inner retinal thickening, IRF and intra-retinal exudate associated with the CWS and extending inferiorly to the fovea; temporal SRF from the CNVM, (d) Improvement in retinal thickness and IRF following intra-vitreous aflibercept treatment, increased intra-retinal lipid, resolution of SRF and localized temporal RPE loss.

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