Title: Ocular Toxoplasmosis Associated Dark Without Pressure

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Letter to the Editor

Introduction

Ocular toxoplasmosis occurs secondary to a retinal infection by *Toxoplasma gondii,* an obligate intracellular protozoan parasite.[1] Typical ocular toxoplasmosis lesions are characterised by a unilateral, focal retinal lesion, which is usually described as necrotising retinitis[2,3] and account for over 90% of presentations.[4] The term dark without pressure (DWP) was originally coined by Nagpal et al to describe homogeneous, geographical, flat, brown areas on the fundus[5] and correspond to a thinned, hyporeflective ellipsoid zone band on optical coherence tomography (OCT).[6–8] While most commonly seen in isolation[5–7] and of unknown aetiology, their perilesional association with infective aetiology has been reported in recent studies of Ebola virus disease (EVD) retinal lesions.[8,9] In EVD survivors, areas of DWP were also observed adjacent to lesions typical of ocular toxoplasmosis and in one patient observed to slowly expand over a 12-month observation (Figure 1).[8] Here we report a case further highlighting fluctuations of DWP associated when ocular toxoplasmosis reactivated.

Case Report

A 23-year-old male of Brazilian origin presented with reduced vision and floaters in his left eye. Examination revealed an active lesion at the margin of an existing hyperpigmented retinal scar lesion in keeping with typical ocular toxoplasmosis (Figure 2A). In addition to the active lesion, a flat, delineated area of retinal darkening consistent with the clinical appearance of DWP could be seen on ultra-widefield retinal imaging. At subsequent widefield imaging 8 months later, hyperpigmentation of the previous active lesion was observed alongside regression

of the area of DWP to the marginal region of the hyperpigmented scar (Figure 2B). 39 months later, the patient represented to our emergency department with recurrent floaters and reduced vision in the same eye. Examination revealed a new active lesion with overlying vitritis adjacent to, but with an area of unaffected retina between the new and old lesions (Figure 3A). Several areas of perivascular infiltrates were visible on surrounding retinal veins but no clear area of DWP was visible. The patient was treated with a course of oral Azithromycin 500mg once daily for 5 weeks and a tapering course of oral prednisolone commencing at 40mg once daily together with topical Pred Forte® (Allergan).

On ultra-widefield retinal imaging conducted 56 days later, a well-defined area of retinal darkening extending inferiorly and nasally beyond the margins of the lesions could be seen (Figure 3B). OCT through the area demonstrated a characteristic thinned, hyporeflective ellipsoid zone band in keeping with DWP (Figure 3C).

Discussion

In this case report, we highlight fluctuations in the appearance of areas of DWP corresponding to delineated areas of ellipsoid zone hyporeflectivity juxtaposed with ocular toxoplasmosis lesions. The normal hyperreflectivity of the ellipsoid zone band on OCT is attributed to the high density of mitochondria within the ellipsoid portion of the photoreceptors.[10,11] Steptoe *et al*[8] proposed the reduced reflectivity of the ellipsoid zone in DWP may be secondary to a cellular bioenergetic switch and metabolic change within these organelles given that mitochondrial optical parameters are dependent on their energy state.[12]

The majority of DWP areas published to date have been observed in isolation (and therefore of unknown aetiology), commonly in the mid-peripheral fundus[5–7,13] and

regarded as benign entities.[14] However, cases of perilesional DWP enable an insight into their underlying aetiology, where the cause is known. While perilesional areas of DWP have been reported adjacent to non-infectious lesions such as congenital hypertrophy of the retinal pigment epithelium[15], and choroidal osteomas[16], they have also been associated with infectious aetiologies such as Ebola retinal lesions.[8] Over a 12-month observational period, 1 year following Ebola virus disease (EVD) infection, areas of DWP were observed to retract back towards EVD lesions in some cases, while in other examples were observed to both simultaneously expand and contract at opposing DWP margins suggesting the presence of an unknown prolonged intraretinal stimulus post-infection.[8]

While the clinical utility and pathogenesis of areas of DWP adjacent to ocular toxoplasmosis are currently unknown, given the expansion of DWP in apparently inactive toxoplasmosis (Figure 1), and regression following recovery (Figure 2), they may provide an opportunity to forecast potential episodes of re-activation before they occur, providing an opportunistic therapeutic window to initiate pharmacological prophylaxis. While the cause for DWP surrounding toxoplasmosis lesions in the absence of histological evidence is speculative, toxoplasmosis bradyzoites have the capacity to invade neighbouring cells[17] and an increasing number of pathogens have been shown to manipulate host mitochondria and their contribution to apoptosis, energy production, and immune function.[18] These may account for the change in ellipsoid zone reflectivity seen within DWP areas.

Conclusion

Fluctuations in areas of DWP occur around lesions in keeping with ocular toxoplasmosis. Further periodic observational studies of these areas may be useful

clinically to determine if expanding areas of DWP can forecast recurrent toxoplasmosis reactivations.

Figure 1. Right eye, sequential fundus imaging demonstrating an expanding area of dark without pressure (*white arrows*) adjacent to an ocular toxoplasmosis lesion over 12 months observations. A) Baseline appearance. B) Appearance at 8 months. C) Appearance at 12 months. Source: Steptoe et al.[8] (CC-BY License).

Figure 2. Left eye inferior fundus. A) Appearance of a typical ocular toxoplasmosis lesion with reactivation at the margin of the pre-existing hyperpigmented scar. Area of dark without pressure seen extending inferiorly and nasally (*white arrows*). B) Appearance 8 months later with hyperpigmentation of the previous area of activity and regression of the area of dark without pressure within close proximity of the lesion border.

Figure 3. Left eye inferior fundus appearance 39 months later. A) Active ocular toxoplasmosis satellite lesion adjacent to previous foci of activation. B) Appearance 8 weeks later with visible area of dark without pressure (*white arrows*). Green line indicates orientation of corresponding optical coherence tomography shown in segment C. Red arrow marks the point of transition between ellipsoid zone hyporeflectivity and its normal hyperreflectivity.

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