COMMUNICATIONS

PUNCTATE KERATOPATHY OF WEST INDIANS*†

BY

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The purpose of this paper is to report a characteristic punctate keratopathy which affects West Indians. The clinical features will be described together with the histopathology of the lesions studied by light and electron microscopy.

Clinical Features (Fig. 1, overleaf)

The condition appears to be asymptomatic and presents as a chance clinical finding. The corneal lesions are round, discrete dense opacities 0·5 mm. or less in diameter. They lie at the level of Bowman's membrane and usually extend just into the superficial stroma. The typical lesion has a striking white or creamy, rather porous-looking centre, and this is surrounded by a pale halo which merges with the adjacent cornea. The centres have a hard, almost chalk-like quality. The overlying epithelium appears normal clinically and does not stain with fluorescein or Bengal rose. While most of the opacities conform to this description a few have a less well-defined centre while in others the surrounding halo is not so obvious. The lesions do not bear any fixed relationship to corneal nerves.

The condition may affect one or both eyes and the lesions may be single or multiple; one patient had thirteen on one cornea. The opacities may occur on all parts of the cornea but are rather more common on the lower half. Corneal sensation is normal. The lids, conjunctiva, limbus, anterior uvea, media, and fundus show no consistent abnormality.

This condition has been studied in 26 patients, 20 men and six women; their ages were between 21 and 56 years (mean 37). All are Caribbean immigrants, originating from all parts of the former British West Indies. They attended hospital for a wide variety of complaints, including conjunctivitis, uveitis, glaucoma, trauma, pterygium, megalocornea, chalazion, and refractive errors. It has not been possible to associate the keratopathy with any specific ocular or systemic disease. The lesions do not appear to cause symptoms and in no case have they been responsible for visual disturbance. Two patients gave a history of trauma to the affected eye in childhood, one by a thorn, the other by a piece of wood. One patient was aware of the condition and he knew the opacities had been present for 20 years; his opacities resembled others of uncertain duration. Some patients had been followed for up to 18 months during which time the opacities remained unchanged. The serum cholesterol is within normal limits.

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We have not seen this keratopathy in children born in the United Kingdom of West Indian parents, nor have we seen it in other races.

**Histopathological Findings**

The microscopical findings were derived from the study of corneal biopsies obtained by means of superficial keratectomy, using a 1·5 mm. Elliott trephine, from six typical cases. Three were examined in serial paraffin sections by light microscopy (17165/64; 42132/64; 2844/65); in one of these (2844/65) the corneal disc was stained in bulk with Sudan III and showed the lesion to stain intensely for fat (Fig. 2). This disappeared in chloroform and in the subsequent sections, as well as in those of the other two cases, no significant pathological changes could be found. This suggested that the lesion probably consisted entirely of lipid and the fourth case (38249/66) was therefore examined by serial frozen sections, which, when stained with oil red O, revealed an oval cluster of minute scarlet globules situated predominantly in Bowman’s membrane, but extending also into the epithelium and adjacent stroma. The staining was slightly less pronounced at the periphery and in the centre of the lesion than elsewhere (Fig. 3). Stains for mucopolysaccharide (Alcian blue; periodic acid-Schiff) and for calcium (von Kossa) were negative.

The fifth and sixth cases (EM 107 and EM 159) were examined electron microscopically.

**Electron Microscopical Findings**

**Case 5 (EM 107)**

The specimen, a corneal disc 1·5 mm. in diameter, was rapidly fixed in Caulfield’s buffered osmium tetroxide, stained with phosphotungstic acid during dehydration and embedded in Araldite.

*Light Microscopy (toluidine blue)* showed normal corneal epithelium. Within Bowman’s membrane and the adjacent stroma there were numerous minute holes of varying size.
Fig. 1.—Painting of corneal appearances of West Indian punctate keratopathy (male aged 38 years).
Electron Microscopy showed many globular cavities most evident in Bowman's membrane, but present also scattered in the adjacent stroma. They varied in size and some showed no limiting membrane, whereas others showed an electron dense membrane. There was frequently a condensation of electron dense material around them, and, where the cavities were cut tangentially, the whole structure appeared electron dense. Most cavities contained a homogeneous electron lucent material in which a few electron dense granules could be seen. The electron dense finely granular material around the cavities was also seen scattered between the stromal fibres, but the collagen fibres themselves, whether in Bowman's membrane or in the immediately adjacent stroma, appeared entirely normal and barely distorted by the presence of the cavities. There was no abnormality in the overlying epithelium and the hemidesmosomes and basement membrane were intact (Figs 4 and 5, overleaf). No electron dense bodies, as described in the next case, were seen within this lesion, but it was subsequently found that, owing to kinking of the biopsy and the angle of section, the centre of the lesion was not included and had been lost in cutting.

Case 6 (EM 159)

The specimen, a corneal disc 1·5 mm. in diameter, was rapidly fixed in Zetterqvist's buffered isotonic osmium tetroxide and embedded in Araldite. The specimen was examined in bulk after fixation and was seen to contain centrally two superficial typical lesions (Fig. 6) which were both clearly ring-shaped, the osmium tetroxide having stained the periphery of the lesion intensely, but not the centre.

Light microscopy (toluidine blue) showed a densely staining elongated oval lesion confined to Bowman's membrane. It consisted of coarse irregular granules which stained intensely. In the surrounding membrane scattered minute empty vacuoles were present. The underlying stroma showed no gross abnormality, but the overlying epithelium was shallowly detached by subepithelial fluid and numerous darkly staining cells could be seen in the basal layer at this point (Fig. 7, overleaf).
Fig. 4.—Electron micrograph (EM 107), showing many globular cavities within Bowman’s membrane. They vary in size and many show a dense limiting membrane. There is some electron dense material between the collagen fibres which otherwise appear normal. In this specimen there is no abnormality of the overlying epithelium. × 17,250.

Fig. 5.—Globular cavities (EM 107) within the stroma deep to Bowman’s membrane. These show no limiting membrane and contain homogeneous electron lucent material. The surrounding collagen appears normal and barely distorted by the cavities. × 17,250.
Electron microscopy.—Immediately above the lesion in Bowman’s membrane—and only at this focus—the overlying epithelium was detached due to epitheliolysis of the basal cells, of which the plasma membranes, basement membranes and hemidesmosomes remained adherent to Bowman’s membrane. The detached and ruptured basal cells were separated from the membrane by amorphous granular material containing disintegrating vesicles of cytoplasmic origin. The remainder of the epithelium showed no significant abnormality. The lesion itself consisted of a dense aggregation of vacuoles of varying size and shape lying within Bowman’s membrane immediately beneath the basement membrane of the epithelium. In the centre of the lesion the vacuoles were larger, more closely packed, and contained extremely electron dense material, whereas at the periphery they were fewer in number and appeared empty (Figs 8, 9, and 10, overleaf).

Under high-power magnification there appeared to be a developmental relationship between the peripheral and central vacuoles, the latter being the end-products. Some of the peripheral vacuoles showed no limiting membrane, appearing as simple holes in the collagenous feltwork of Bowman’s membrane, but most showed an electron dense lining membrane, which was often convoluted and folded to form minute villi projecting into the vacuole. Towards the centre of the vacuoles the villi became larger and more electron dense. In the fully-formed structure the electron dense villi had either completely filled the vacuole or left only a small irregular central cavity (Figs 11 and 12, overleaf). At the periphery of the lesion the collagenous stroma showed little abnormality, but at the centre it was entirely replaced by electron dense vacuoles, interspersed with a spongework of irregular minute cystic spaces. The underlying corneal stroma and keratocytes appeared normal and there was no evidence of scarring.

Discussion

This punctate keratopathy does not appear to have been recognized previously as a clinical entity although it is quite common among West Indian immigrants in Great Britain. One of the authors (BRJ) saw several patients with the condition during a visit to Jamaica, but resident ophthalmologists could offer no clue to the aetiology. It may be confused with other conditions and we, therefore, propose to discuss briefly the clinical and differential diagnosis.

Since the corneal epithelium appears normal in the West Indian punctate keratopathy, the condition is readily distinguished from Thygeson’s superficial punctate keratitis and other punctate disorders of the corneal epithelium. Similarly the epithelial and combined epithelial and subepithelial stages of adenovirus, TRIC agent, and other types of virus punctate keratitis are readily differentiated.

The West Indian spots are large enough to be seen with the naked eye, but they are denser and whiter than the opacities of epidemic kerato-conjunctivitis or the punctate keratitis due to TRIC agent. They do not appear to be related to any form of conjunctivitis, but when a patient presenting with conjunctivitis is found to have the West Indian punctate keratopathy the lesions may not be easy to differentiate from the punctate keratitis due to Neisseria or other pyogenic bacteria; in these conditions the lesions tend to be larger, oval, of less discrete outline, without the dense centres and associated with diffuse corneal infiltration. Characteristically the West Indian lesions fail to show the sequence of changes typical of the various acute infective punctate keratopathies.
Fig. 7.—Araldite section (EM 159) seen by light microscopy shows a densely staining elongated oval lesion confined to Bowman's membrane. It consists of coarse irregular granules and there are scattered minute empty vacuoles in the surrounding membrane. The overlying epithelium is shallowly detached and numerous darkly staining cells are seen in the basal layer at this point. Toluidine blue. ×660.

Fig. 8.—Electron micrograph (EM 159). The lesion in Bowman's membrane consists of an aggregation of electron dense bodies (bottom left) surrounded by vacuoles. The overlying epithelium (E) is detached because of epitheliolysis of basal cells, of which the plasma membranes, basement membranes and, hemidesmosomes (arrow) remain adherent to Bowman's membrane. Amorphous granular material (AGM) containing disintegrating vesicles of cytoplasmic origin separates the basal cells from the membrane. ×2,660.
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Fig. 9.—Higher-power view of EM 159, showing subepithelial amorphous granular material (AGM) basement membrane, hemidesmosomes (arrows), and the lesion in Bowman's membrane. This consists centrally of closely packed vacuoles containing electron dense material, and peripherally of smaller vacuoles which are either empty or have a margin of electron dense material.  $\times 7,530$.

Fig. 10.—Electron micrograph (EM 159), showing lesion (left) extending into subjacent stroma where the collagen fibres (C) and a keratocyte (K) are seen to be normal.  $\times 11,300$. 
Fig. 11.—High-power view of edge of lesion (EM 159), showing the types of vacuoles present: (1) Simple vacuoles with little or no limiting membrane, (2) vacuoles with a convoluted limiting membrane forming villi, (3) vacuoles with electron dense villi extending into the vacuole, and (4) large vacuoles almost filled with electron dense villi. × 37,500.
Fig. 12.—Electron micrographs (EM 159), illustrating possible stages in the development of the electron dense body:

(a) simple vacuoles without a lining membrane. $\times 26,000$.
(b) vacuoles with membrane forming minute villi. $\times 45,000$.
(c) vacuoles in which the villi have become electron dense. $\times 45,000$.
(d) final vacuoles almost filled with electron dense villi. $\times 45,000$. 
Spots of similar density occur in leprotic keratitis but the diffuse superficial disturbance with limbitis and vascularization, and the accentuation of the corneal nerves which characterize leprotic keratitis are absent in the West Indian keratopathy.

This condition cannot readily be confused with the corneal lesions of onchocerciasis in which the opacities are larger, more diffuse, and placed at varying depths in the stroma; and in which it is usually possible to identify the remnants of filariae in the corneal opacities and intact filariae elsewhere in the cornea or in the anterior chamber. In addition, onchocerciasis is not known to occur in the West Indies. The characteristic morphology readily differentiates West Indian keratopathy from the less dense and often pigmented scars which typically follow superficial corneal foreign bodies; indeed such scars are frequently seen in corneas affected by this keratopathy.

The pathological appearances seen in the epithelium immediately overlying the lesion, namely epitheliolysis of the basal cells, epithelial detachment, and the presence of "dark cells", are probably non-specific, for they may be found in chronic epithelial oedema from any cause (Rice, Ashton, Jan, and Blach, 1968).

The histopathological findings have shown that the lesion itself consists essentially of a sharply circumscribed area of fatty degeneration in Bowman's membrane, and the ring appearances shown with fat stains, and also seen in the osmium-fixed disc examined in bulk, suggest that the fat is more concentrated in the periphery of the lesion than at its centre. This would correspond to the halo seen clinically. By correlating the staining properties of the lesion, as seen by light microscopy, with its ultrastructure, there can be little doubt that the empty vacuoles seen by electron microscopy originally contained fat which had dissolved out in processing. The electron dense bodies packed into the centre of the lesion, which presumably correspond to the "chalk-like" appearances seen clinically, are less easily identified. They seem to derive from the fat-containing vacuoles which develop a lining membrane that then elongates and folds to form villi, which become increasingly electron dense and gradually fill the vacuoles. Some stages most closely correspond to illustrations in the literature of lipid deposits (see, for instance, Freeman, 1964), and the most likely explanation of their nature is that they are all lipid deposits differing chemically in their varying degrees of unsaturation. On the other hand, dense bodies showing this villous internal structure have not been previously described in electron microscopical studies of the cornea and we have been unable to find exactly comparable structures reported in the literature. Somewhat similar electron dense rings have been illustrated in a study of the ultrastructure features of mineralization in crustacea (Travis, 1963—Fig. 46, p. 232); these were not vacuoles, however, but cross-sections of heavy mineralization in the walls of a pore canal system. Nevertheless, the picture suggests that the dense bodies seen in West Indian keratopathy may result from calcification within lipid globules. Unfortunately the appropriate histochemical tests for calcium could not be carried out on the Epon-embedded sections and the exact nature of the material in the electron dense bodies must await further studies. There was no evidence of the crystallization of apatite.

It is well known that calcification often occurs in areas where tissue injury is associated with fatty degeneration, indeed it was thought at one time that calcification might result from successive hydrolytic cleavages of neutral fat molecules (Klotz, 1905; 1906). Although there is little support for this theory today there is no doubt that fatty degeneration favours dystrophic calcification, as in atherosclerosis, for instance, and this association has been described in the cornea (Spanlang, 1927).
If the West Indian lesion is in fact a focus of fatty degeneration which progresses to calcification, it may be relevant that both fatty degeneration (Muramatsu, 1935; Uyama, 1936) and calcification (Ballantyne, 1942; Hesse, 1942; Miller and Gordon, 1950) have been held responsible for the formation of white rings in the cornea, which clinically bear certain similarities to the lesions of West Indian keratopathy.

Since it is now generally believed that white rings in the cornea are due to minute injuries resulting from hot sparks or metal foreign bodies (Gallemaerts, 1926; Vogt, 1930; MacRae, 1935; Uyama, 1936; Hesse, 1942; Purtscher, 1949; Miller and Gordon, 1950; Halmay, 1965), it would seem reasonable to suggest that the West Indian spots may also follow similar specific trauma. The nature of such an injury, however, remains unidentified.

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