Posterior polymorphous dystrophy: a light and electron microscopic study

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SUMMARY Microscopic study of a keratoplasty specimen in a case of posterior polymorphous dystrophy demonstrated via serial sections a multilaminar Descemet's membrane with focal fusiform nodular protrusions of connective tissue. The latter are thought to represent the polymorphous lesions of the posterior limiting layers of the cornea seen clinically. Ultrastructurally, fibroblast-like cells lined the posterior surface of the cornea. It is postulated that those reported cases of PPD in which epithelial-like transformation of the endothelial layer has been described may represent more advanced cases, in which corneal oedema is likely to be a prominent feature clinically. An evolving process of metaplasia rather than a static one might explain the variety of altered endothelial cells, fibroblasts, and epithelial cells which have been reported on the posterior cornea in the few PPD keratoplasty specimens studied to date.

Posterior polymorphous dystrophy (PPD) is a bilateral, congenital, usually dominantly inherited disorder of the posterior limiting layers of the cornea which is characterised clinically by discrete geographic nodular or vesicular lesions at the level of Descemet's membrane that protrude towards the anterior chamber. As the condition is rare, usually non-progressive, and commonly causes minimal visual impairment, few cases have necessitated keratoplasty. Three light microscopic studies (Morgan and Patterson, 1967; Hanselmayer, 1972a; Malbran, 1972) and 6 ultrastructural studies (Hogan and Bietti, 1969; Boruchoff and Kuwabara, 1971; Hanselmayer, 1972b; Grayson, 1974; Bron and Tripathi, 1974; Rodrigues *et al.*, 1975) of these specimens have resulted in a variety of findings, and the term 'polymorphous' seems as applicable microscopically as it is clinically. A recent study (Rodrigues *et al.*, 1975) suggested that the characteristic ultrastructural finding in PPD is multilayers of epithelial cells on the back of the cornea. We wish to report the morphological findings in a case of PPD that lacked epithelial cells on the posterior cornea, and compare the pathology in this case with that in previously reported cases.

Case Report

The patient was a 16 year-old White male whose visual acuity could not be improved beyond 20/70 in both eyes with either pinhole or refraction. The only positive finding was a diffuse opacification at the level of Descemet's membrane in both corneas, with focal translucent nodules characteristic of posterior polymorphous dystrophy (Fig. 1). It was the opinion of the examiner that the Descemet's corneal opacification was compatible with the patient's corrected visual acuity. This patient was the only child of unrelated parents. The mother also had typical posterior polymorphous dystrophy in both eyes. In December 1974 the patient underwent a penetrating keratoplasty in his right eye. Postoperatively the transplant remained clear until the fifth month, when a severe graft rejection resulted in opacification.

Material and methods

The corneal button obtained by penetrating keratoplasty was fixed in cold 4% paraformaldehyde and divided for processing by light and electron microscopy. One half of the button was embedded in paraffin and serially sectioned at 6 μ m, providing approximately 500 sections for examination. Alternate slides were stained by the haematoxylin-eosin and PAS methods and every tenth section with the

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Fig. 1 Slit-lamp photograph of the patient's cornea with Descemet's membrane changes typical of posterior polymorphous degeneration. In addition, Descemet's membrane was diffusely opacified round the clear plaque-like zones

Masson trichrome stain. The portion for electron microscopy was divided into smaller blocks, post-fixed with osmium tetroxide, and embedded in Epon. Sections $1\text{ }\mu\text{m}$ thick were stained with toluidine blue, and ultrathin sections were cut on an LKB Ultratome III, and stained with uranyl acetate and lead citrate for viewing and photography with a Philips EM-300 electron microscope.

Histopathological findings

LIGHT MICROSCOPY

The corneal epithelium was of normal thickness and showed no evidence of intracellular oedema. Bowman's layer varied in thickness, and multiple small defects were present centrally and peripherally. The stroma was unremarkable. Descemet's membrane had a multilaminated appearance (Fig. 2). The anterior lamina consisted of a thin (3 to $4\text{ }\mu\text{m}$) PAS-positive discontinuous membrane. Connective tissue separated this membrane from a posterior, thicker (up to $12\text{ }\mu\text{m}$) slightly less PAS-positive membrane. The latter in many areas was split into 2 or 3 thin components. Connective tissue, which

varied considerably in thickness, filled the zone between the laminae. Multiple fusiform protrusions into the anterior chamber were present which resulted from plaques of connective tissue interposed between the thin anterior and thicker posterior laminated portions of Descemet's membrane (Fig. 3). Most of these plaques measured 25 to $30\text{ }\mu\text{m}$ in thickness and contained rare fibroblasts. Serial sections failed to demonstrate wart-like excrescences on Descemet's membrane. In all sections the endothelial cells were flattened, elongated, and widely spaced in an irregular fashion.

ELECTRON MICROSCOPY

The significant pathological abnormalities were limited to the posterior cornea. The thin anterior lamina of Descemet's membrane seen by light microscopy consisted of only the normally 110 nm banded portion of Descemet's membrane, and the non-banded portion was not represented (Fig. 4). More posteriorly a zone of connective tissue was present which varied considerably in thickness.

Fig. 2 Descemet's membrane is multilaminated, with connective tissue interposed between a thin anterior and thicker posterior portion. Periodic acid-Schiff and haematoxylin ($\times 200$)

Fig. 3 Connective tissue plaque (arrow) forming a fusiform protrusion between the two laminae of Descemet's membrane. Periodic acid-Schiff and haematoxylin ($\times 200$)

The predominant form consisted of loosely arranged bundles of 25 nm in diameter, collagen fibrils having a periodicity of 55 to 60 nm. There were also bands and fusiform bundles of 110 nm banded material similar to that present in the most anteriorly

located portion of Descemet's membrane as well as numerous individual fibres of long-spacing collagen (Fig. 5). Small collagen filaments, 10 to 15 nm in diameter, were present in all areas but were more numerous posteriorly (Fig. 6). Here abundant base-

Fig. 4 The anterior lamina of Descemet's membrane (A) consists of only the normally 110 nm banded portion, and the non-banded portion is not present. Loose connective tissue (B) separates this band from a thick posterior layer of collagen containing abundant basement membrane material (C). (Original magnification $\times 7400$)

ment membrane material, often in lamellae, surrounded the collagen fibres and formed a separate zone corresponding to the thick posterior laminated portion of Descemet's membrane seen by light microscopy. The endothelial layer was composed of

a single layer of flattened cells more suggestive of fibroblasts than endothelial cells (Fig. 7). Mitochondria were relatively sparse and most lacked the longitudinally disposed cristae of endothelial cells. Free ribosomes were also few in number. Rough-

Fig. 5 Higher power view of the thick laminated posterior portion of Descemet's membrane. There is 110 nm banded material and numerous long-spacing collagen fibres intermixed with skeins of basement membrane material. (Original magnification $\times 18\,400$)

surfaced endoplasmic reticulum, abundant fine intracytoplasmic filaments, and subcortical densities were present. There were rare apical tight junctions; desmosomes and tonofilaments were lacking. Few microvilli were present on the cell surface facing the anterior chamber.

Discussion

The variety of morphological findings previously reported in PPD suggests either that a spectrum of pathological changes occurs in this disorder or that various entities are being classified in a single broad

Fig. 6 *In this portion of the abnormal posterior lamina of Descemet's membrane, abundant basement membrane material separates 25 nm in diameter collagen fibrils as well as small (10 nm) fibrils (arrows) sectioned obliquely and in cross-section. (Original magnification $\times 32\,800$)*

category. For example, the report by Hogan and Bietti (1969) showing warts characteristic of cornea guttata and calcium nodules in the deep stroma differs so strikingly from the other reported cases of PPD that it may represent an unrelated endothelial dystrophy. The remaining cases reporting the ultrastructural findings (Boruchoff and Kuwabara, 1971;

Hanselmayer, 1972; Grayson, 1974; Bron and Tripathi, 1974; Rodrigues *et al.*, 1975), including the present study, show similar changes in regard to Descemet's membrane but vary in the findings involving the endothelial layer.

Normally at about 4 months of foetal development evidence of Descemet's membrane first appears.

Fig. 7 The endothelial layer shows a fibroblast-like cell containing subcortical densities, rough endoplasmic reticulum, sparse free ribosomes and mitochondria, and abundant fine cytoplasmic filaments. (Original magnification $\times 43\,100$)

Multiple lamellae of the basement membrane progressively accumulate, which by the eighth month consists entirely of 110 nm banded material and measures 3 to 4 μm in thickness at birth. The postnatal zone, which is secreted by the endothelial cells, thickens progressively throughout life and consists of a granular, non-banded posterior layer (Waring *et al.*, 1974). In PPD the thin anterior banded zone is present, representing that portion normally formed *in utero*. In the cases of PPD where measurements are given the remarkably similar thickness of this banded anterior portion of Descemet's membrane (approximately 3 μm) localises the onset of endothelial dysfunction to a relatively constant time period developmentally, namely, late *in utero* or possibly in the neonatal period. In PPD the posterior granular non-banded portion of Descemet's membrane is replaced by two broad zones of collagen (zones B and C in Fig. 4). In the present study a variety of types of collagen were present in both of these zones, including layered sheets of 110 nm banded material as well as individual fibrils with 55 to 60 nm periodicity, and small (10 to 15 nm) collagen fibrils. The most posterior zone (zone C) contained in addition abundant basement-membrane-like material between the various forms of collagen, which correlates with the thick PAS-positive band seen by light microscopy (Figs. 2 and 3). Variation in thickness of the more anterior zone (B in Fig. 4) was responsible for forming the nodular or fusiform protrusions which account for the localised plaques of the posterior limiting layers of the cornea seen clinically.

Descriptions and interpretations of the endothelial layer in PPD have varied considerably. Flattened cells, often multilayered with multilocular cystic cavities, numerous microvilli, increased cytoplasmic filaments, desmosomes, and decreased cytoplasmic organelles are some of the changes observed in the endothelial layer. Some authors have interpreted these as squamous epithelial cells (Boruchoff and Kuwabara, 1971; Rodrigues *et al.*, 1975) and others as multilayers of fibroblasts (Grayson, 1974) or undifferentiated mesothelial cells (Bron and Tripathi, 1974). It is clear that corneal endothelial cells are neither morphologically nor developmentally related to endothelial cells lining vascular lumens but are more akin to the mesothelial cells lining serous cavities. Alteration of the endothelial cell as a result of a wide variety of diverse stimuli such as degeneration, dystrophy, inflammation, chemical or thermal injury, toxins, trauma, vitreous touch, and homograft reaction results in fibrous metaplasia in many instances (Waring *et al.*, 1974). The laminated zonal pattern of the posterior limiting layers, absence of the granular non-banded portion

Descemet's membrane ultrastructurally, and the fusiform connective tissue plaques seen by light microscopy allow separation of PPD as a distinct pathological entity from the above conditions in most cases.

Rodrigues *et al.* (1975) and Johnson and Brown (1976) have pointed out that the corneal endothelium can also respond by conversion or metaplasia to an epithelial-like cell. Epithelial metaplasia of the corneal endothelium appears to be rare compared to the more common pathway of fibroblastic metaplasia. In two reported cases of PPD (Boruchoff and Kuwabara, 1971; Rodrigues *et al.*, 1975) definite epithelial cells lined the posterior cornea, and illustrations in Grayson's study (1974) show cells having similar epithelial characteristics. While Rodrigues *et al.* (1975) suggest that epithelial-like conversion of the endothelial layer may be specific for PPD, this type of alteration has been found in at least one other unrelated, unilateral, congenital corneal condition (Johnson and Brown, 1976).

Problems related to sampling are an inherent part of any ultrastructural investigation. It seems likely, however, that the variety of reported changes affecting the endothelial layer in PPD reflects the fact that abnormal endothelium, fibroblast-like cells, or those showing epithelial-like transformation may occur. A normal banded anterior portion of Descemet's membrane in PPD supports the presence of endothelial cells at one point in foetal development. Subsequent metaplasia to a fibroblast-type cell with the production of a variety of forms of collagen and basement membrane material would account for the more posterior zonal alterations of the Descemet's membrane area. Finally, epithelial-like transformation may, but does not necessarily, occur in some cases. We believe that all such cell types are non-specific for this condition and reflect a spectrum of morphological change which may relate to the severity of change seen clinically. The usual clinical appearance of cases of PPD having good visual acuity is discrete posterior opacifications surrounding the plaques. The decreased visual acuity in the present case was due to the diffuse corneal opacification at the level of Descemet's membrane seen clinically and manifested morphologically by the connective tissue and basement alterations of this region. Corneal oedema was not present at the time of keratoplasty in this case, and cells having ultrastructural characteristics suggestive of epithelial transformation were not seen. In contrast, the cases of Boruchoff and Kuwabara (1971), Rodrigues *et al.* (1975), and Grayson (1974) had corneal oedema clinically and epithelial-like cells morphologically on the posterior surface of their keratoplasty specimens. The epithelial cells,

while acting as a posterior corneal anatomical barrier, lack physiological pump capabilities, and corneal oedema is possibly more likely to be seen only in those cases of PPD with this metaplastic end result.

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