Corneal and conjunctival changes in dysproteinemia

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A case of dysproteinemia with corneal and conjunctival crystalline changes is described. These crystalline changes were found to be caused by stromal infiltration of the cornea and conjunctiva by cells containing numerous crystallike deposits in their cytoplasm. Morphologically identical crystals were found in abundance in plasma cells of the bone marrow.

Key words: multiple myeloma, corneal infiltrate, corneal stroma, conjunctiva, crystalline deposits, bone marrow cells, corneal birefringence, histopathology, electron microscopy, light microscopy.

The clinical features of corneal and conjunctival changes in multiple myeloma and other dysproteinemias have been described by Duke-Elder,1 Aronson and Shaw,2 and Francois and Rabaey.3 These changes are seen infrequently, and many review articles on the ocular complications of multiple myeloma do not mention them. Aronson and Shaw, in an attempt to assess the incidence of the findings, reviewed 13 patients with myeloma, none of whom had corneal and conjunctival changes.

We report herein a case in which the light and electron microscopic appearance of refractile deposits in the cornea and conjunctiva were studied.

Review of a case

History. A. R., a 50-year-old man, was hospitalized because of anemia and renal failure. Investigation revealed the following findings: (1) The erythrocyte sedimentation rate (ESR) was 115 mm. in the first hour. (2) Plasma electrophoresis showed a sharp peak of gamma globulin. Six grams of immunoglobulin G were found in the urine per day (Fig. 1). (3) Seven per cent plasma cells appeared in the bone marrow with rather immature nuclei. (4) Bones were shown to be radiologically normal. The diagnosis was dysproteinemia, probably of the multiple myeloma type.

Ophthalmological history. Two years ago the patient had a sudden loss of visual acuity in the left eye which was thought to be caused by anterior uveitis. This had disappeared almost completely after 2 weeks of treatment with atropine and topical steroids. In the intervening 2 years he had 3 to 4 similar episodes. The right eye had never been affected. On examination there were diffuse deposits of fine iridescent crystalline bodies in the cornea and conjunctiva of both eyes. These were seen most easily in the corneal stroma and were fairly evenly distributed throughout it (Fig.
2). They appeared as glistening specks on the bulbar conjunctiva. On the left there were some old keratic precipitates on the back of the cornea; the anterior chamber had no cells or flare, and the anterior segment was otherwise unremarkable. The vitreous on the left was hazy, more marked inferiorly. This haze was due to innumerable yellowish-white, dustlike opacities. The fundus could be seen past these, and no abnormality of the retina could be detected. Those areas of the peripheral retina and pars plana which could be visualized did not show any abnormality, but the area behind the vitreous opacity inferiorly could not be visualized. There was no abnormality of the posterior segment on the right.

A keratoconjunctival biopsy was taken from the left eye in an effort to elucidate the histology of the corneoconjunctival deposits. This consisted of a thin lamellar fragment of the peripheral cornea with its adjacent conjunctiva.

**Methods**

Portions of excised conjunctiva and cornea were placed immediately in phosphate-buffered 3 per cent glutaraldehyde. After fixation for 3 hours, small blocks were cut, washed in phosphate buffer, postfixed in 1 per cent osmium tetroxide for one hour, dehydrated, and embedded in epon. The remainder of the tissue was dehydrated and embedded in paraffin following a brief phosphate wash.

For light microscopy paraffin sections were stained with hematoxylin-phloxine-saffron and periodic acid-Schiff (PAS)-hematoxylin; epon sections were stained with alkaline toluidine blue. Thin sections for electron microscopy were doubly stained with uranyl acetate and lead citrate.

**Light microscopy.** The conjunctiva appeared mildly edematous. Scattered among the collagen fibers in the subepithelial tissues were small numbers of cells, either singly or in small clusters, with irregular outlines, abundant pale-staining, eosinophilic cytoplasm and small dense-staining, frequently eccentric, nuclei (Fig. 3). Within their cytoplasm were numerous poorly defined needle-like unstained clefts, several microns long and about 0.5 μ in width; the clefts were weakly bi-refrangent and PAS-negative (Fig. 4).

The conjunctival epithelium and the portion of superficial cornea which were studied were essentially unremarkable.

Half-micron sections of glutaraldehyde-fixed, osmium tetroxide-stabilized, epon-embedded tissue stained with toluidine blue showed the intra-cellular deposits more clearly as dense blue-black, sharply defined "needles" often arranged in parallel aggregates within individual cells (Fig. 5).
Fig. 2. Slit-lamp photograph of typical corneal findings.
Fig. 3. Conjunctiva. Epithelium is essentially intact; in the stroma are small clusters (arrows) of cells with abundant cytoplasm and small dense nuclei. (Paraffin; hematoxylin-phloxine-saffron (HPS); x150.)

Fig. 4. Higher magnification of Fig. 3. Within the cytoplasm of the abnormal cells are numerous small randomly arranged needlelike clefts. (Paraffin; HPS; x475.)

Very occasional deposits appeared to be extracellular. None were found in the corneal fragments.

Electron microscopy. Electron microscopic study of this tissue was limited by the poor quality of tissue preservation. The subconjunctival cells containing the deposits were characterized by dense cytoplasm which contained numerous free ribosomes (Fig. 6) and occasionally by a rich array of granular endoplasmic reticulum reminiscent of that seen in plasma cells. Most of the inclusion-bearing cells did not, however, have the morphological features characteristic of mature plasma cells, and their identity remains in question. Deposits ranged in size from 0.05 to 0.4 μ in width, and, in the plane of section, from 0.5 to 7 μ in length. The largest crystals appeared to be free in the cytoplasm, but smaller ones were often surrounded by a membrane apparently derived from the endoplasmic reticulum (Fig. 7). In the cornea a very few crystals were found, again in cells with abundant ribosomes and distinct from...
Fig. 5. In osmium-stained material, the deposits are well preserved and appear as closely packed crystallike densities filling the cytoplasm of the involved cells. (Epon; toluidine blue; ×1,550.)

Fig. 6. Conjunctival cell with deposits. The cell exhibits numerous fine pseudopodia and has dense cytoplasm containing numerous ribosomes, several poorly preserved profiles of endoplasmic reticulum, and scant mitochondria. The deposits appear as long narrow relatively homogenous masses with angular or blunt ends and parallel sides. They vary greatly in size and shape.
Fig. 7. Conjunctival deposits. Several of the smaller deposits are enclosed in a rather poorly defined, interrupted (artifactually) membrane which loosely follows their contours. No internal structure is seen.

Fig. 8. Bone marrow. A cell with prominent highly organized granular endoplasmic reticulum like that of plasma cells contains deposits like those in the cornea.
the corneal stromal cells which appeared normal. A true crystalline substructure was not demonstrated. The crystals had blunt, angular ends and straight parallel sides with occasional deformities suggestive of "fracture."

In the bone marrow, numerous cells contained apparently identical deposits. The majority of these cells had morphological features indicative of their being plasma cells. (Fig. 8).

Discussion

Multiple myeloma is one of the clinical forms of the plasma cell dyscrasias. This group is characterized by: (1) proliferation of plasma cells in the absence of identifiable antigenic stimulation, (2) the elaboration of electrophoretically and structurally homogenous M type gamma globulin or subunits of this, and (3) associated deficiency in synthesis of normal immunoglobulins.5

Several morphological types of inclusions, both in cytoplasm and nucleus, have been found in marrow and lymph node cells in multiple myeloma and the other forms of dysproteinemia. Their appearances were briefly reviewed by Maldonado and associates4 in 1966. The cytoplasmic deposits have been either amorphous or crystalline and located both within and outside the cisterns of endoplasmic reticulum. Their varied morphology and staining reactions in different cases probably reflects the biochemical variability of the abnormal circulating proteins in this group of conditions.

Two types of changes have been described in the cornea in multiple myeloma: (1) the crystalline form, and (2) the deep dystrophic form (François and Rabaey).3 Pathological studies of the crystalline form have been undertaken by Aronson and Shaw.2 They describe finding many crystalloid structures in the cytoplasm in 10 per cent of the myeloma cells of the bone marrow. These were best visualized with phase microscopy. An attempt was made to find these in a bulbar conjunctival biopsy, but no birefringent element could be detected in this specimen. However, further sections were thought to reveal the presence of lipoids in the conjunctiva. In the deep dystrophic type the posterior one third of the corneal stroma was replaced by a hyaline mass with almost complete loss of the normal collagen structure in this area except for a narrow strip posteriorly. The nature of this hyaline mass was not established, but it was proposed that it was globulin in nature.

Our case shows typical crystalline corneal and conjunctival change in dysproteinemia. This is seen to be due to the stromal infiltration by cells which contain crystals. This gives rise to the birefringence and clinical iridescence. Similar cells were identified in the bone marrow by both light and electron microscopy.

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REFERENCES