

Corneal subepithelial monoclonal kappa IgG deposits in essential cryoglobulinaemia

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SUMMARY A 60-year-old man suffering from photophobia and visual disturbances was found to have bilateral superficial corneal grey-white gelatinous deposits. An abnormal cold-precipitable serum component was found and characterised as homogeneous IgG-kappa immunoglobulin. Corneal immunohistochemical examination revealed subepithelial IgG-kappa deposits, focally replacing Bowman's layer. The patient underwent superficial keratectomy in both eyes with satisfactory visual results.

Bilateral corneal deposits have been described in association with dysproteinaemia since 1934.¹⁻⁸ To our knowledge there is only one report⁹ describing corneal subepithelial immunoglobulin deposits in benign monoclonal gammopathy, simulating the clinical non-crystalline appearance and distribution of the corneal deposits found in our patient. Such deposits have never been described in essential cryoglobulinaemia. We present the results of bilateral superficial keratectomy performed on a patient with essential IgG-kappa cryoglobulinaemia, the only manifestation of which was the superficial corneal immunoglobulin deposits.

Case report

A 60-year-old man presented with photophobia, tearing, and gradually decreasing vision. On examination his best corrected visual acuity (VA) was 6/12 in both eyes. Slit-lamp examination of both corneas showed raised gelatinous grey-white subepithelial avascular nodules, in the corneal periphery but sparing the limbus (Fig. 1). These confluent non-crystalline nodular masses extended towards the visual axis by finger-like projections. The corneal stroma, Descemet's membrane, and endothelium appeared normal. The anterior and posterior seg-

ments were completely normal, as were the eyelids and conjunctiva.

The physical examination and bone x-rays showed nothing abnormal.

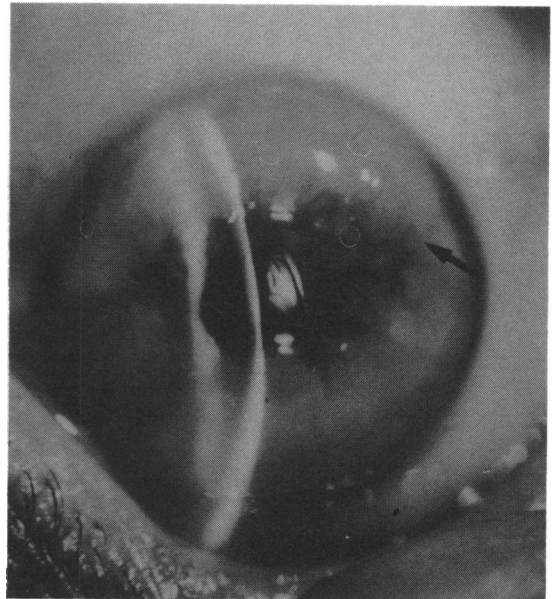
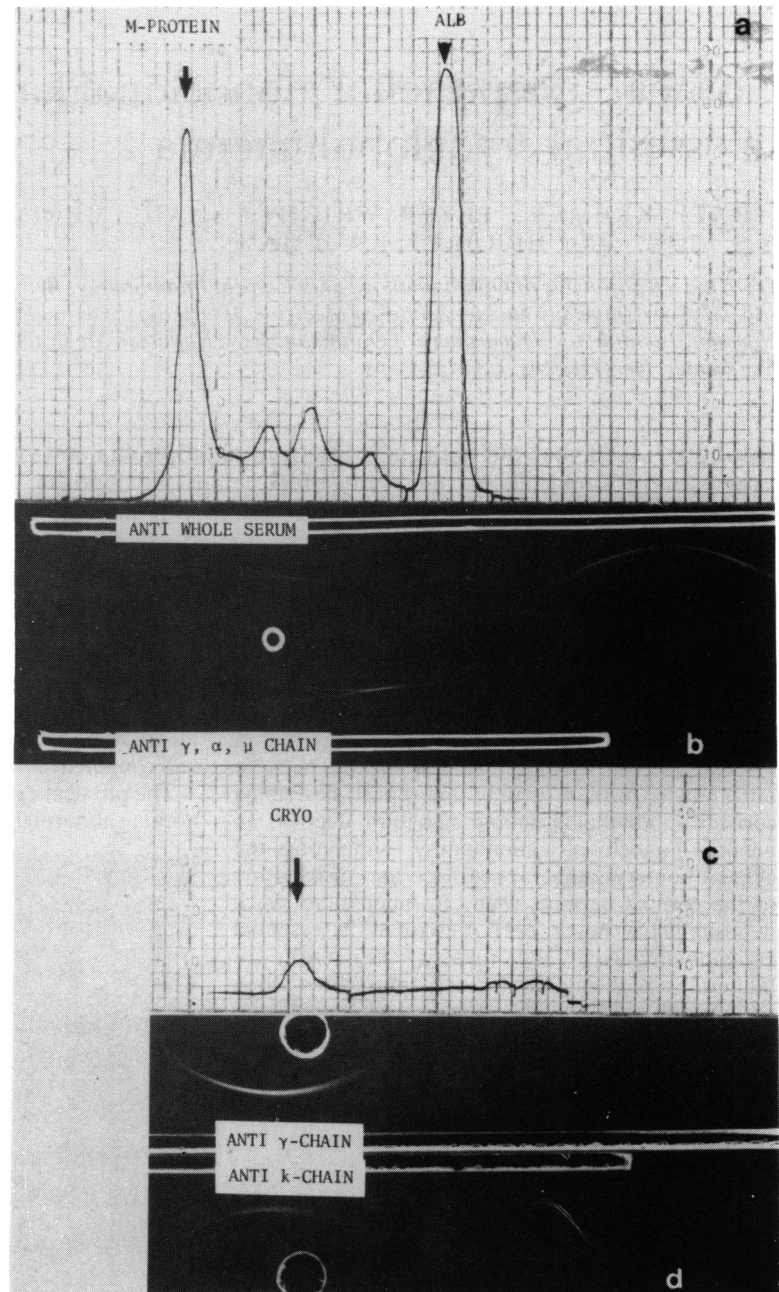


Fig. 1 Slit-lamp photograph showing the confluent nodular gelatinous-like superficial corneal deposits, extending towards the corneal centre by finger-like projections (arrow).

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Fig. 2 (a-d) Electrophoresis and immunoelectrophoresis of the patient's serum (a, b) and cryoprecipitate (c, d), revealing the presence of homogeneous IgG-kappa immunoglobulin.



Subsequently the patient's serum was examined. A cryoprecipitate was discovered and was characterised by immunoelectrophoresis as a homogeneous IgG-kappa immunoglobulin (Fig. 2). Serum immunoglobulins were quantitated by nephelometry (Table 1).

Table 1 Results of serum cellulose acetate electrophoresis

Protein	g/l	Normal range g/l
IgG	30	2.0-10.5
IgA	1.86	0.8-2.7
IgM	1.24	0.4-1.1

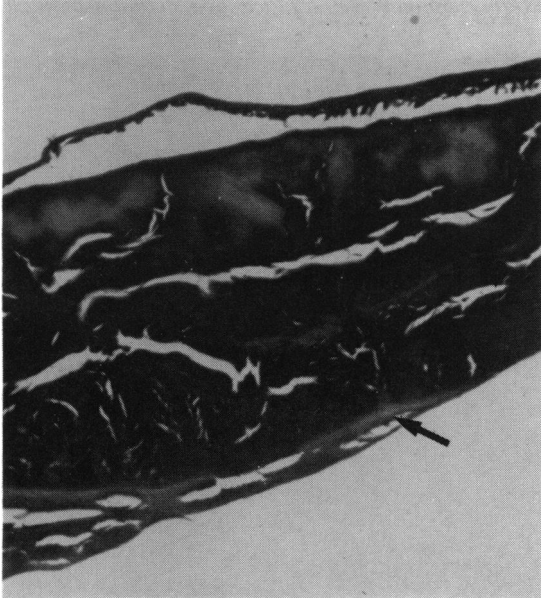


Fig. 3 Massive accumulation of red coloured subepithelial deposits located between the atrophic epithelium and Bowman's zone (arrow), which is focally disrupted. (Masson-trichrome stain, original magnification $\times 250$).

As a bone marrow biopsy showed normal appearances, the diagnosis of essential IgG-kappa cryoglobulinaemia was established.

A small lamellar biopsy was performed in the right cornea. The histopathological examination with haematoxylin-eosin showed eosinophilic subepithelial deposits, located between Bowman's layer or superficial stroma and basal epithelial layer. Bowman's layer was focally disrupted and replaced by the eosinophilic periodic acid Schiff positive material. With Masson trichrome staining red-coloured aggregates were seen beneath the elevated atrophic epithelium (Fig. 3). Stains for amyloid were negative. Electron microscopy revealed that the deposits were composed of numerous rod-shaped bodies (Fig. 4). Each rod was composed of parallel fine filaments with a 9.5–10 nm periodicity (Fig. 5). A conjunctival biopsy revealed the presence of conjunctival subepithelial aggregates of homogeneous kappa-IgG (Fig. 6).

During the following years the VA decreased gradually to 6/40, with J-7 in both eyes. It was not possible to perform skiascopy or keratometry, as the corneal surface was irregular.

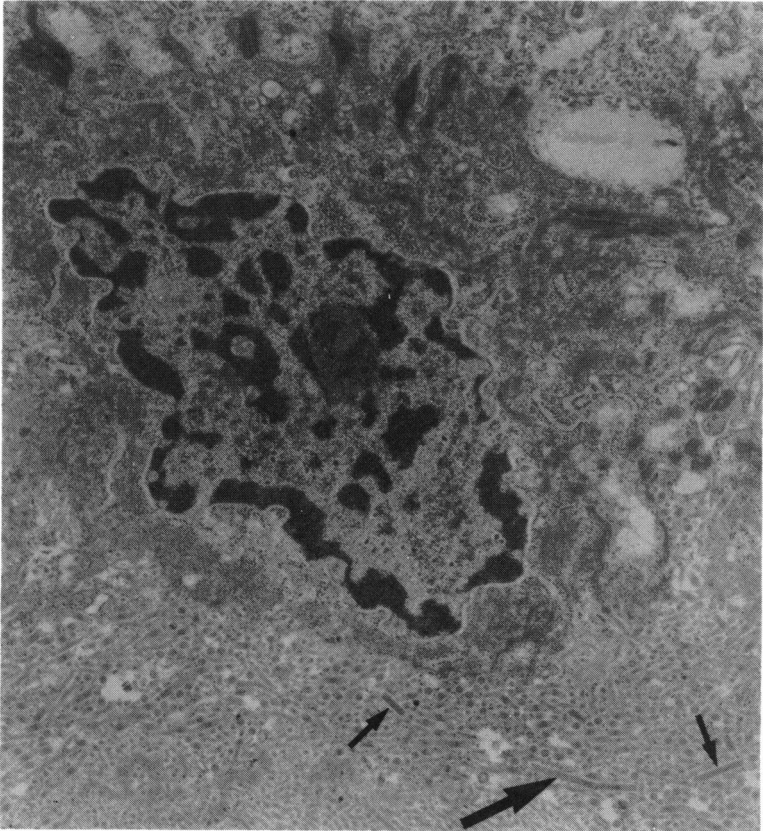


Fig. 4 Electron microscopy of the corneal biopsy specimen showing numerous subepithelial rod-shaped bodies (arrows). (Original magnification $\times 8200$.)

Fig. 5 At higher magnification (EM) the rod-shaped bodies are seen to be composed of parallel fine filaments (arrow) with a periodicity of approximately 10 nm. (Original magnification $\times 42\,000$).



Owing to the subepithelial location of the corneal deposits, approaching the corneal centre, it was decided to perform superficial keratectomy by shaving the cornea with a scalpel blade. After this procedure, the VA improved to 6/7.5 in the right eye and 6/7 in the left, with J-1 in both eyes. The keratometry revealed bilateral regular astigmatism of 0.5 D.

Immunohistochemical examination of the keratectomised material showed that the corneal immunoglobulin deposits were antigenically identical to the homogeneous IgG-kappa (cryoglobulin) serum component.

Fourteen months after the operation the corneal surface was completely smooth, and a peripheral

band of superficial stromal scarring was noted bilaterally (Fig. 7).

Discussion

Corneal immunoglobulin deposits in association with hypergammaglobulinaemia have been described mainly as crystals.^{4-8, 10-14} The definitive evidence that the latter corneal crystals are immunoglobulins was provided by Klintworth *et al.*⁶ using immunofluorescent and immunoperoxidase techniques. Garner

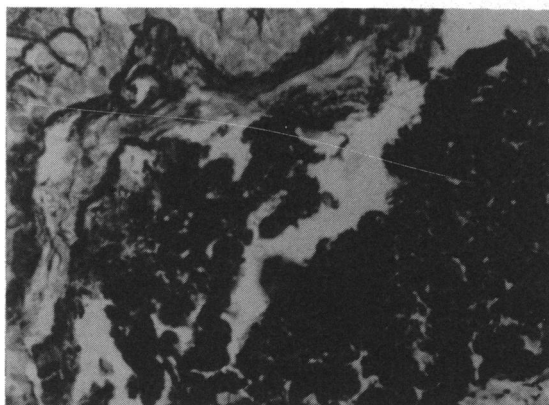


Fig. 6 Massive accumulation of conjunctival subepithelial immunoglobulin G deposits (anti-IgG positive). (Immunoperoxidase stain, original magnification $\times 400$.)

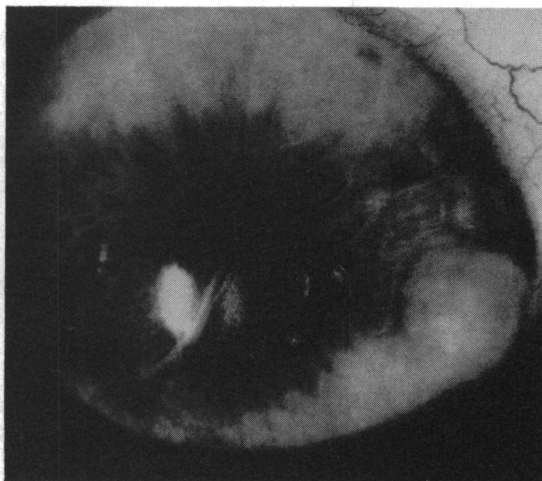


Fig. 7 Patient's right cornea six months after superficial keratectomy, showing confluent superficial stromal opacification covered by a completely smooth epithelium in those areas where the deposits have been removed.

and Kirkness¹⁴ maintain that the unifying characteristic of these crystals is the 10 nm periodicity of their banded infrastructure.

The clinical appearance and anatomical location of these corneal deposits may be quite variable.^{13,14} In most cases they are found in the stroma^{2-5,7-13} and only rarely in the corneal epithelium proper⁶ or immediately beneath it.⁹ Paraproteinaemic keratopathy in association with true monoclonal gammopathy of unknown significance (MGUS) is very rare and has been reported in only four cases.^{4,9,13,15} Our patient is the fifth recorded case with MGUS. However, as the monoclonal paraprotein found in his serum had the characteristics of cryoglobulin his disease may be defined also as essential cryoglobulinaemia.

As regards cryoglobulinaemia, Palm¹⁵ was the first author to report on superficial corneal deposits in a case of crystal cryoglobulinaemia. The nature of these corneal deposits differed from that of our patient in that they had a crystalline appearance. Oglesby¹⁶ is the only author to report on corneal non-crystalline deposits in a patient with cryoglobulinaemia, which was associated with reticulohistiocytosis. The corneal stromal involvement in this patient was predominantly posterior. However, Oglesby¹⁶ presented no histological or immunohistochemical proof for the presence of corneal immunoglobulin deposits. No surgical or medical treatment was mentioned in these two reports.^{15,16}

Allansmith and colleagues^{17,18} reported that almost all immunoglobulins can be found in normal corneas and that their concentration correlates with the serum level. They maintain that corneal immunoglobulins are derived mainly from the serum by diffusion from perilimbal vessels.

The presence of a cold precipitable immunoglobulin in the serum of our patient may explain its massive preferential accumulation in the corneal subepithelial region, as it is probably one of the coldest areas in the human body.¹⁹ According to Waltman and Hart¹⁹ the difference in temperature between the rabbit cornea and the iris amounts to 5°C. As the cryoglobulin precipitates in a temperature below 34°C, it may undergo crystalloid changes following precipitation under the corneal epithelium, the temperature of which is probably around 32°C.

These corneal cryoglobulin precipitates found in our patient were removed by superficial keratectomy, after which a smooth corneal resurfacing was achieved. For the time being invasive surgical techniques, such as perforating or lamellar keratoplasty, have been postponed. Whenever the above-described corneal deposits recur outside the corneal

centre, superficial keratectomy can be repeated. However, if they appear in the central zone, keratoplasty is indicated. It is our opinion that this procedure should probably be supplemented in future either by plasmapheresis or by low dosage chemotherapy²⁰ in order to keep the corneal graft clear.

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