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Clinical pathologic review

Ocular manifestations of monoclonal copper-binding immunoglobulin

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ABSTRACT

The dense accumulation of copper in Descemet membrane and lens capsule is the characteristic manifestation of a circulating monoclonal antibody with strong affinity for copper. The overproduction of this monoclonal immunoglobulin may be associated with either multiple myeloma or a benign monoclonal gammopathy. Despite prolonged exposure to elevated serum copper, no other tissues in the body are adversely affected by this redox metal. We describe the clinical and pathological findings in a 46-year-old woman with this disorder.

Hypercupremia associated with certain monoclonal immunoglobulins results in progressive, bilateral discoloration of Descemet membrane and lens capsule. Over time, this characteristic pattern of copper deposition will eventually impair vision. Although elevated serum copper should be injurious to many cells, the eye is the only organ adversely affected by these abnormal levels of copper. The monoclonal immunoglobulins, or M-proteins, that give rise to this condition are attributed to either multiple myeloma or a benign monoclonal gammopathy—also referred to as monoclonal gammopathy of undetermined significance (MGUS). Myeloma and MGUS have been linked to other antibody-binding syndromes, because M-proteins are known occasionally to display unusual binding properties.[20] We report the ocular manifestations of one such syndrome in a patient with hypercupremia and benign monoclonal gammopathy.

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1. Case report

A 46-year-old black woman complained of visual difficulties related to bright lights and the gradual discoloration of her eye over 1.5 years. Her past medical history consisted of an overactive bladder, obesity, and osteoarthritis. Her medications included tolterodine tartrate and acetaminophen. Her eye examination showed brown corneas and visual acuity correctable to 20/20 in each eye (Fig. 1). Systemic evaluation revealed elevated serum copper and a monoclonal gammopathy of undetermined significance. She was then lost to follow-up.

Five years later she returned with worsening visual symptoms and a new diagnosis of hypertension. Examination revealed best-corrected visual acuity of 20/30 in each eye, with substantial deterioration of vision with glare tests (below 20/400). Pupils reacted normally to light and ductions were full. Though pachymetry was not performed, the corneas appeared to have normal thicknesses. The epithelium and stroma were normal but the posterior layer of each cornea had a near confluent tan color with only a narrow rim of clear cornea peripherally (Fig. 2). Visibility was poor, but the anterior lens capsules were discolored. Intraocular pressures were normal, as was B-scan ultrasonography of the posterior segment.

General systemic and neurological examinations were non-contributory, but laboratory studies revealed an elevated total serum protein (7.8 g/dL), and an elevated serum copper of 1,473 μg/dl (normal, 70–175 μg/dL). Serum ceruloplasmin was normal (37 mg/dL). Serum protein electrophoresis showed a monoclonal peak with elevated gamma globulin of 2.6 g/dL (normal, 0.6–1.6 g/dL). Serum immunoelectrophoresis disclosed high IgG λ of 3,232 mg/dL (normal, 694–1,618 mg/dL); there were increased free λ light chains at 253.3 mg/dL (normal, 5.7–26.3 mg/dL). Urine protein studies were negative. A 24-hour urine specimen for copper was normal (<100 μg/day). Bone marrow biopsy showed a plasma cell infiltration of less than 5%. There were no lytic lesions detected on bone survey, and liver function tests were normal.

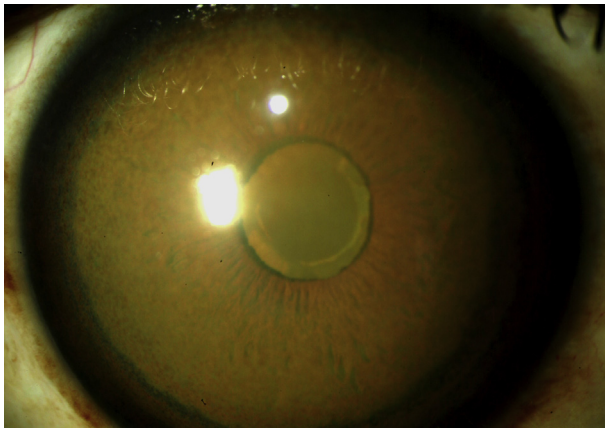

Fig. 1 – Left cornea showing brown-green discoloration at the level of Descemet membrane and sparing of the outer 1–2 mm. The discoloration is stippled and most noticeable pericentrally. The anterior lens capsule is discolored, but poorly visible. This photograph shows light reflection off the anterior lens capsule.

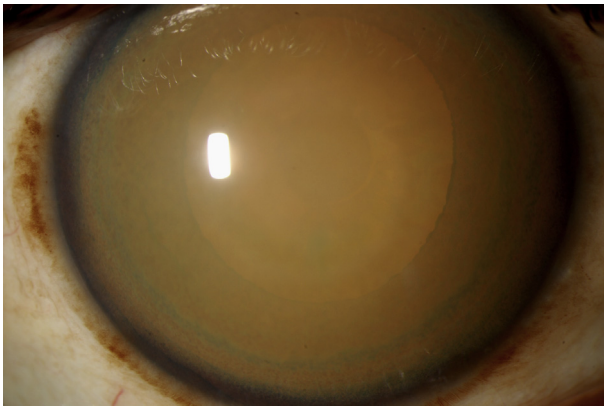

Fig. 2 – Left cornea 6 years after photograph in Figure 1 was taken. The corneal discoloration is now confluent brown. The anterior lens capsule is more pigmented but now difficult to visualize.

She underwent Descemet-stripping endothelial keratoplasty and cataract extraction with intraocular lens implant of the left eye. Descemet membrane and lens capsules were submitted for microscopic examination fixed in formalin. Two months following surgery her acuity corrected to 20/20 in dark and bright room illumination.

1.1. *Pathological findings*

The appearances of Descemet membrane and anterior lens capsule were remarkably similar. Both measured between 9 and 14 μm and contained a band of granular deposits that was densest adjacent to the epithelial surface or endothelium (Fig. 3). On hematoxylin and eosin stain, the deposits were yellow-gold in color. Corneal endothelial cells and lens epithelium were normal by light microscopy. The deposits stained positive for copper with Rhodanine (Fig. 4).

The paraffin blocks containing Descemet membrane and lens capsule were retrieved and tissue submitted for energy-dispersive X-ray microanalysis, using lens capsule from an eye with melanoma as a control. Spectral analysis showed peaks corresponding to copper (Fig. 5). The control tissue displayed no copper peak.

Immunoperoxidase stains for IgG λ showed linear uptake along the anterior surface of the lens capsule, with negative reaction on the control slide (Fig. 6). Sections of Descemet membrane did not survive processing.

2. Discussion

2.1. *Differential diagnosis*

The clinical differential diagnosis of corneal pigmentation in this setting is limited. Few conditions can be mistaken for the diffuse cocoa color of Descemet membrane other than copper. Unlike the Kayser-Fleischer ring in Wilson, peripheral Descemet membrane was spared (Fig. 7). Copper deposition in