It is not known whether myelination of retinal fibers leads to myopia or myopia leads to myelination of retinal fibers. Alternatively, myopia and retinal myelination may be associated with other factors. Schmidt et al proposed that myelinated fibers could blur retinal images and induce visual deprivation. Such deprivation at a critical stage of ocular development could lead to axial elongation, akin to structural changes seen in eyes with unilateral congenital cataract or severe ptosis. However, scotomas in myelinated congenital cataract or severe ptosis are generally smaller than predicted by the extent of myelination, suggesting that light penetrates to the photoreceptor layer despite the myelin interference. Furthermore, many cases of myelinated fibers do not show visual deficits or have significant myopia.

It is also possible that the increased axial length of the eye predisposes to retinal myelination. If the process of lamina cribrosa development is prolonged, as could occur in axial myopia, myelination could continue down the optic nerve and into the retina. Although this hypothesis has some merit, it cannot explain lesions discontinuous with the optic nerve head or myelination of eyes without increased axial lengths.

It is likely that our patients were genetically predisposed to be hyperopic. During ocular development one eye became myelinated as a cause of, or resulting in, disruption of the preprogrammed growth pattern of that eye. The resultant axial elongation led to 10 D of anisometropia in the first case and more than 2 D in the second case. As a consequence, these patients developed amblyopia in their more ametropic eyes. Myelination did not cause organic loss of vision from macular dysfunction as reported in some of the patients of Hittner and Antoszyk. The question as to whether myelination causes myopia or vice versa is left unresolved, but our cases do suggest that anisometropia can be a more powerful influence on the relative visual acuity of each patient’s eyes than the presence of retinal myelin. Lempert has proposed smaller optic disc size as an organic as opposed to functional reason for decreased vision in hyperopic anisometropia. Although the optic discs of our patients appeared normal in each eye, we cannot exclude this as an alternative explanation for their decreased visual acuity.

With an estimated amblyopia prevalence of 2% to 3%, much of which is anisometropic amblyopia, and a 0.9% prevalence of unilateral nerve fiber layer myelination, one would expect that the combination of these findings would be seen more frequently. We do not know why there have been no previous published reports about this finding, but do believe that these cases are unique in the literature on myelinated retinal nerve fibers.

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Corneal Copper Deposition Secondary to a Variant of Multiple Myeloma: 30-Year Catamnesis

The historical association of defects in copper transport, increased serum copper levels, decreased ceruloplasmin levels, and copper deposition in the peripheral limbal cornea is well described in the clinical entity of Wilson (hepatolenticular) disease. However, a rarer pattern of copper deposition in the central cornea may occur with hypercupremia associated with monoclonal gammopathies. Copper deposition in the central Descemet membrane along with anterior and posterior lens capsules has been reported in individuals with multiple myeloma, benign monoclonal gammopathy, and IgG monoclonal gammopathy associated with pulmonary carcinoma. We report a 30-year catamnesis, a follow-up medical history of a patient who was first described in the Archives in 1975. She initially complained of blurred vision and a subjective change in her “iris color.” She was noted to have copper deposition in the Descemet membrane of the central cornea and in the anterior and posterior lens capsules and was subsequently diagnosed with hypercupremia secondary to a monoclonal gammopathy, an unusual variant of multiple myeloma.

Report of a Case. A 41-year-old white woman complained of slowly progressive, painless blurring of distance vision over the preceding several years. Her husband had commented on her changing “iris color” from blue to green. Her past medical history was unremarkable. She was taking no medications nor using alcohol or tobacco products. Her family history was negative for ocular disease.

Her best-corrected visual acuity was 20/20 OU at distance and Jaeger 0.5 OU at near. Intraocular pressures were normal. Biomicroscopy showed a pronounced iridescent sheen in the axial 7 to 8 mm of each cornea at the level of the Descemet membrane and a 2- to 3-mm circumferential limbal clear zone. The anterior and posterior lens capsules also had cocoa-powder staining. The anterior vitreous was clear, and the fundus examination result was normal. Goldmann and tangent screen visual fields and electrotoretinographic testing results were normal.

Color vision was evaluated with the Ishihara plates, Hardy-Rand-Rittler pseudoseichromatic plates, the Farnsworth dichotomous panel D-15 test, the Farnsworth 100 hue test, and the Nagel anomaloscope.
The mother and father of the patient had normal color vision by the last technique, but the patient responded as a deuteranomalous trichromat: ie, the patient required a higher fraction of green light to match the yellow test area. The patient’s color vision anomaly was likely acquired as a result of the filtering effect of the copper in the ocular media.9

The patient’s parents, children, and husband were examined, and the results were normal. Evaluation of her farm water wells, cows’ milk, and other possible sources of copper exposure or contamination was unrevealing.

The patient was in excellent health and without abnormal physical findings. Results of chemical, hematologic, and serologic studies were normal with the exceptions of serum copper levels and protein electrophoresis and immunodiffusion. Test results for Bence Jones proteinuria and electrophoresis of urine for κ and λ chains were negative. The patient’s serum copper concentration ranged from 1000 to 1740 µg/dL, 14 times the normal concentration (normal range, 75-145 µg/dL). However, the copper concentrations in her urine, saliva, cerebrospinal fluid, and hair were normal. Ceruloplasmin levels in the upper limits of the normal range at 36 to 45 mg/dL. Total serum protein concentration was normal, but there was a marked predominance of a monoclonal IgG, type λ, with depression of IgA and IgM.

The diagnosis of multiple myeloma was made on the basis of the bone marrow biopsy, which revealed increased atypical plasma cells (12%-15%; normal, <2%). Many of these cells were larger than normal, with increased nuclear size and nucleoli, consistent with multiple myeloma. Skin and liver biopsies were normal.

Oral and intravenous radiolabeled copper studies revealed a 4-fold decreased copper clearance in the patient compared with a healthy biologic sister as a control. With gel filtration, electrophoresis, and ultrafiltration techniques, 99% of the excess copper was shown to be bound to a γ-globulin, consistent with the elevated IgG levels found initially. This suggested that the patient had an immunoglobulin with an abnormal structure, which resulted in a high affinity for copper. Further purification of this protein demonstrated that the copper-binding protein was an IgG with A-type chains.7 A 10-week course of penicillamine chelation treatment resulted in a 20-fold increase in urinary excretion of copper and a 44% reduction in serum copper. Despite this treatment, the serum copper levels remained greater than 10 times normal without a change in the immunoglobulin level. A trial with 2 courses of the cytotoxic agent melphanal (8 mg) daily initiated with prednisone (120 mg) daily for 4 days resulted in only a moderate decrease in IgG levels.

In the subsequent years, the patient remained remarkably healthy despite high circulating levels of copper (Table 1).

We reevaluated this patient in February 2004, more than 30 years after her initial evaluation. She had noted a mild gradual decline in vision in both eyes and reported that she no longer drove at night. She was in excellent health except that, in the intervening years, she had experienced a single pathologic rib fracture that healed without incident. Apart from her eyes, the only other apparent systemic manifestation of hypercupremia was her copper-colored hair. Her family history remained unremarkable.

On ophthalmologic examination, her best-corrected distance visual acuity was 20/50 OD and 20/40 OS. Results of her intraocular pressures, motility, and external and adnexal examinations were normal. On biomicroscopy, her central corneas had dense copper deposition at the level of the Descemet membrane, still sparing the limbal 2 mm (Figure 1).

In each eye, the anterior chamber was deep and clear without cell and flare, and the iris appeared normal. The anterior and posterior lens capsules were coated with copper-colored material, and each lens had mild nuclear sclerosis (Figure 2). The anterior vitreous was poorly visualized because of the media opacities. Although the view was hazy, the fundus examination result was grossly normal.

Comment. Copper deposition in the deep central cornea in association with hypercupremia is highly suggestive of a monoclonal gammopathy. This association has been reported with multiple myeloma,1-3 monoclonal gammopathy associated with lung adenocarcinoma,4 and benign monoclonal gammopathy (Table 2). Hawkins et al5 described a patient with multiple myeloma who

Table 1. Patient’s Serial Serum Copper and Immunoglobulin Levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Copper Levels, µg/dL (Normal Range, 75-145)</th>
<th>IgG Levels, mg/dL (Normal Range, 564-1765)</th>
<th>IgA Levels, mg/dL (Normal Range, 85-385)</th>
<th>IgM Levels, mg/dL (Normal Range, 53-375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 1973</td>
<td>1000-1740</td>
<td>2350-3200</td>
<td>35-37</td>
<td>38-42</td>
</tr>
<tr>
<td>July 1996</td>
<td>840</td>
<td>1550</td>
<td>42</td>
<td>58</td>
</tr>
<tr>
<td>June 1999</td>
<td>897</td>
<td>1520</td>
<td>71</td>
<td>62</td>
</tr>
<tr>
<td>November 2002</td>
<td>832</td>
<td>1683</td>
<td>59</td>
<td>45</td>
</tr>
</tbody>
</table>

Figure 1. Slitlamp photograph, left eye. Note the marked central corneal copper deposition.

Figure 2. Slitlamp photograph, left eye. Note the marked copper deposition on the anterior lens capsule.
Table 2. Summary of Reported Cases of Hypercupremia, Corneal Copper Deposition, and Monoclonal Gammopathy

<table>
<thead>
<tr>
<th>Measure</th>
<th>Goodman et al and Ellis</th>
<th>Martin et al</th>
<th>Probst et al</th>
<th>Hawkins et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/Age, y</td>
<td>F/69</td>
<td>M/60</td>
<td>M/65</td>
<td>F/64</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Multiple myeloma</td>
<td>Lung adenocarcinoma; monoclonal gammopathy, IgG (\kappa)</td>
<td>Benign monoclonal gammopathy; IgG (\kappa)</td>
<td>Multiple myeloma; IgG (\kappa)</td>
</tr>
<tr>
<td>Serum copper levels, µg/dL</td>
<td>1800-3400</td>
<td>770</td>
<td>2030</td>
<td>2380</td>
</tr>
<tr>
<td>(normal range, 75-145)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceruloplasmin levels, mg/dL</td>
<td>19-21</td>
<td>38</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>(normal range, 18-43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h copper urine levels, nmol (normal range, 0-600)</td>
<td>NA</td>
<td>NA</td>
<td>2549</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment</td>
<td>XRT to spine; cyclophosphamide; melphalan; penicillamine; no change in serum copper levels</td>
<td>XRT to lung</td>
<td>Zinc glutonate for 2 mo; no change in serum copper levels</td>
<td>NA</td>
</tr>
<tr>
<td>Visual acuity at first evaluation</td>
<td>20/40 OD, 20/30 OS</td>
<td>20/40 OD, 20/30 OS</td>
<td>20/25 OU</td>
<td>20/20 OU</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; XRT, external beam radiation.
*The IgG contained light chains of either of 2 types: \(\kappa\) or \(\lambda\).

had corneal deposits on the central Descemet membrane, iris surface, and lens capsule. Her laboratory evaluation was significant for elevated serum copper levels (2380 µg/dL), normal serum ceruloplasmin levels, and an increased IgG \(\kappa\) γ-globulin level, and she was diagnosed subsequently with multiple myeloma (IgG \(\kappa\)), stage II. Goodman et al described similar clinical findings in a patient with multiple myeloma. Martin et al reported a case of corneal and lenticular copper deposition associated with hypercupremia and a monoclonal gammopathy that was related to a poorly differentiated adenocarcinoma of the lung. Their laboratory evaluation was significant for elevated serum copper levels (770 µg/dL), normal serum ceruloplasmin levels, and an increased IgG \(\lambda\) γ-globulin level. Bone marrow biopsy revealed no dysplastic cells, and the patient was subsequently diagnosed with adenocarcinoma of the lung. After cataract extraction, the lenticular tissue was examined by electron microscopy and revealed electron-dense round deposits containing 10 to 20 nm granules in the lens capsule.

In all these historic cases, the distribution of copper deposition in the Descemet membrane is similar: limbal-sparing central cornea in the Descemet layer. In contrast, the copper deposits of Wilson disease are in the peripheral limbal 2 to 3 mm of the Descemet membrane with a clear central corneal zone. Patients with Wilson disease may also deposit anterior lens pigment, producing the “sunflower” cataract. The reason for the differences in distribution of the corneal and lenticular copper deposits is unknown. Normally, copper does not bind to immunoglobulins. Why, in each of these reported cases, copper binds to elevated γ-globulin fractions is also not known.

Our case is unique because of this long-term catamnesis and the patient’s benign clinical course of multiple myeloma. At her first visit, the patient underwent extensive evaluation to characterize the cause of the hypercupremia. The elevated γ-globulin level appeared to be the culprit. Based on the bone marrow biopsy specimen, the patient was diagnosed with a mild variant of multiple myeloma. The patient has had more than 30 years of documented elevated serum copper levels and stable ceruloplasmin levels. The striking feature is systemic and ocular stability. Ophthalmologically, she has had some progression in the density of the copper deposition and cataract, but her acuity has remained remarkably good. Although progressive copper deposition may explain some visual decline, her age-related cataracts have progressed as well. Systemically, she has remained well, with her hair being the only other apparent site of deposition of copper.

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