Grand Rounds

A 54-year-old man with bilateral symmetrical circular corneal opacities

Colm McAlinden, MD, MB BCh, BSc (Hons), MSc, PhD, MRCOPth, and Christopher P. R. Williams, BSc (Hons), MB BCh (Hons), MRCP, FRCOphth

Author affiliations: Department of Ophthalmology, Princess of Wales Hospital, Bridgend, United Kingdom

History
A 54-year-old man was referred to the Princess of Wales Hospital, Bridgend, United Kingdom, for evaluation of corneal opacities found on routine eye examination. He was asymptomatic and had no history of contact lens wear. Past ophthalmic, medical, and drug history were unremarkable. Of note, the patient reported having taken various brands of multivitamins over the preceding 3 years. He did not smoke tobacco, but he had a history of smoking cannabis in the past. He denied alcohol excess. The patient reported that his siblings and mother all had recent eye examinations and no signs of corneal opacities. His mother denied drug use during pregnancy. The patient was observed over a period of 2 months, with no change in appearance of the stromal opacities.

Examination
On examination, unaided visual acuity was 20/20 in each eye. Slit-lamp examination revealed bilateral, symmetrical, circular, gray-white stromal opacities in the midperipheral cornea measuring 5 mm in diameter. The width of the ring was approximately 0.5 mm. Corneal sensation was normal, and there was no corneal vascularization or epithelial defects. The anterior chamber was deep and quiet, with no iris transillumination in either eye. Intraocular pressure by Goldmann applanation tonometry was 16 mm Hg in each eye. There was minimal nuclear sclerosis in each eye. Funduscopy was unremarkable apart from a small choroidal nevus in the right eye.

Ancillary Testing
Anterior segment imaging was acquired, including photography (Figure 1), optical coherence tomography (Tri-...
count, liver function, bone profile, random glucose, C-reactive protein, erythrocyte sedimentation rate, Borrelia burgdorferi antibodies, lipid panel (including apolipo-protein A-1), serum protein electrophoresis, antinuclear antibody, caeruloplasmin, angiotensin converting enzyme, ferritin, transferrin, transferrin saturation, iron, and heavy metal screen for lead and copper. Urine amino acids, glycosaminoglycan, creatinine, and glycosaminoglycan:creatinine ratio were also ordered to exclude gross amino acid disorders and mucopolysaccharidoses. Blood and urine testing revealed no significant abnormalities. Because infectious etiology was deemed unlikely, corneal cultures were not acquired.

Treatment

Because the work-up was negative and the condition was nonprogressive, the patient was observed.

Differential Diagnosis

The differential diagnosis for corneal opacities is broad (see Table 1). History, examination, and investigations should narrow this significantly; however, one should consider previous trauma, infection (acanthamoeba keratitis, herpetic keratitis, or interstitial keratitis), inflammation (Wessely immune ring) or Cogan syndrome. Cogan syndrome is a rare vasculitic condition causing intraocular inflammation and vestibuloauditory dysfunction, typically affecting young adults. Anterior and posterior embryotoxon is also on the differential list, both producing ring like corneal opacities. Coats white ring is usually associated with previous corneal foreign body. Drug deposition as well as metabolic disorders are major differential diagnoses, both of which must be carefully considered. Common drug offenders causing corneal deposition include amiodarone, chloroquine, hydroxychloroquine, tamoxifen, chlorpromazine, silver, gold, and amantadine. Metabolic disorders associated with corneal changes include Wilson’s disease and lysosomal storage disorders (eg, cystinosis, mucopolysaccharidosis, and Fabry disease). Finally, some stromal dystrophies can cause circular corneal opacification (eg, Schnyder corneal dystrophy).

Diagnosis and Discussion

This unusual presentation of circular stromal opacities was comprehensively investigated, and no identifiable cause was found. Only a small number of similar idiopathic cases have been reported in the literature, the first being described by Ascher in 1963.

One may infer deposition from a previous environmental or drug exposure or from an agent contained within the multivitamin products consumed by the patient. The multivitamins consumed were on an ad hoc basis over the previous 3 years and included various brands from various supermarkets. However, drug deposition within the stroma is unusual; noteworthy exceptions include gold and silver. Furthermore, one would expect drug depositions to involve the peripheral and central cornea, presumably because of travel from the limbus into the cornea. Copper deposition in Wilson’s disease is at the level of Descemet’s membrane (Kayser-Fleischer ring), crystals in Waldenström’s macroglobulinaemia is at the epithelial level, and diffuse stromal haze is observed in mucopolysaccharidoses. Subepithelial peripheral pigmentary globules may be seen in alkaptouria, cystine crystals in cystinosis, and numerous minute grayish dots throughout the stroma in lecithin-cholesterol-acyltransferase deficiency. Hence, none of these conditions matched the history, clinical appearance, and laboratory testing of the present case. Although arcus senilis is usually observed by a clear region between the limbus and the opacity, our case had a much larger band of clear cornea, and the appearance was more focal and discrete. Table 1 provides clinicians with the differential diagnosis along with examples, key relevant clinical features, appropriate work-up and treatment. It is also important to inquire closely regarding dietary and supplement intake in patients presenting with corneal opacities. Our patient was asymptomatic, and his vision was normal. However, we felt it was prudent to investigate for any underlying systemic malignancies or other life-threatening conditions.

The absence of corneal vascularization and symmetrical appearance may point more toward a degeneration or dystrophy, such as a phenotypic variation of a stromal dystrophy, with perhaps the most similar being Schnyder cornal dystrophy. The degenerations of crocodile shagreen and Vogt’s limbal girdle differ in appearance, as does the Hudson-Stähli line in iron deposition, Stocker’s line in keratoconus, and posterior embryotoxon.

Figure 3. Scheimpflug Pentacam HR image demonstrating the stromal opacity sparing the epithelium and endothelium.
Table 1. Differential diagnosis of circular/ring-shaped corneal opacities

<table>
<thead>
<tr>
<th>Main classification</th>
<th>Examples</th>
<th>Key relevant clinical features</th>
<th>Appropriate work-up</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Acanthamoeba keratitis</td>
<td>Usually history of contact lens wear, swimming/showering in lenses; Initially mild photophobia and pain; later, severe relative to clinical signs; Variable clinical signs, including superficial punctate staining, dendritiform lesions, edema, perineural infiltrates and stromal infiltrates; Paracentral infiltrates may coalesce to form a ring-shaped infiltrate</td>
<td>Confocal microscopy, Culture and PCR&lt;sup&gt;3-12&lt;/sup&gt;</td>
<td>G. PHMB 0.02% or G. chlorhexidine 0.025% AND G. propamidine 0.1% or G. hexamidine 0.1%&lt;sup&gt;12&lt;/sup&gt;-22</td>
</tr>
<tr>
<td>Herpetic keratitis</td>
<td>Simplex: hypoesthesia, can be epithelial, stromal or endothelial</td>
<td>PCR in epithelial disease, Can culture vesicles&lt;sup&gt;13-15&lt;/sup&gt;</td>
<td>Simplex: Oc. ganciclovir 0.15%, PO aciclovir/valaciclovir</td>
<td>Prophylactic antibiotics&lt;sup&gt;11-17&lt;/sup&gt; Zoster: PO aciclovir/valaciclovir&lt;sup&gt;11-17&lt;/sup&gt;</td>
</tr>
<tr>
<td>Interstitial keratitis</td>
<td>Corneal stromal inflammation with/without stromal vascularization; Redness, tearing, photophobia, irritation, visual loss depending on location&lt;sup&gt;11,12,13,18-20&lt;/sup&gt;</td>
<td>Syphilis serology, serum ACE (sarcoid), chest X-ray (tuberculosis, sarcoid), tuberculin skin test&lt;sup&gt;13,12,15,18-20&lt;/sup&gt;</td>
<td>Treat underlying cause; Topical steroids and cycloplegics&lt;sup&gt;11,12,13,18-20&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Immunological</td>
<td>Wessely immune ring</td>
<td>Sterile intrastromal immune reactions to foreign antigens</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Cogan syndrome</td>
<td>Systemic autoimmune vasculitis; Typically young adults; Intraocular inflammation (redness, photophobia, pain, blurred vision) and vestibulocular dysfunction (tinnitus, vertigo, hearing loss); Corneal signs: peripheral anterior stromal opacities and neovascularization; Systemic features in about 30%&lt;sup&gt;15,24-29&lt;/sup&gt;</td>
<td>Multidisciplinary involvement, ESR, CRP, FBC&lt;sup&gt;15,24-29&lt;/sup&gt;</td>
<td>PO immunosuppression, Topical steroids for keratitis&lt;sup&gt;15,24-28&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Gold (chryiasis)</td>
<td>Yellow-brown deposits in the corneal stroma (may be deposited in the corneal epithelium or lens)&lt;sup&gt;13,20,21&lt;/sup&gt;</td>
<td>Not usually required</td>
<td>Not usually required</td>
</tr>
<tr>
<td>Silver (argyrosis)</td>
<td>Pigmentation of the conjunctiva, cornea, skin, and external mucosal membranes with silver; Occupational exposure or topical silver-containing medicines&lt;sup&gt;11,22,26&lt;/sup&gt;</td>
<td>Consider biopsy&lt;sup&gt;26&lt;/sup&gt; (mucous membranes)</td>
<td>Avoid exposure&lt;sup&gt;94&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Wilson disease (hepatotenticular degeneration)</td>
<td>Rare, autosomal recessive; Deposition of copper in tissues due a deficiency of caeruloplasmin; May present with liver disease, psychiatric disorders and choreoathetosis; Corneal Kayser-Fleischer ring (brown-yellow zone of deposition in periphery at level of Descemet membrane; Sunflower cataract&lt;sup&gt;25,26,27&lt;/sup&gt;</td>
<td>Multidisciplinary involvement, Bloods including liver function tests, renal function, full blood count, clotting and serum ceruloplasmin, Other investigations guided by presentation&lt;sup&gt;15,38&lt;/sup&gt;</td>
<td>Chelation therapy&lt;sup&gt;15,39&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lysosomal storage disorders:</td>
<td>Cystinosis</td>
<td>Cystinosis: autosomal recessive, widespread tissue deposition of cysteine crystals, including cornea, causing renal impairment in childhood&lt;sup&gt;15,40,41&lt;/sup&gt;</td>
<td>All require multidisciplinary involvement; specific investigations to consider: Cystinosis – white cell cysteine&lt;sup&gt;15,40,41&lt;/sup&gt;</td>
<td>Cystinosis – cysteamine&lt;sup&gt;15,40,41&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>Mucopolysaccharidoses: mainly autosomal recessive, absence</td>
<td>Mucopolysaccharidoses: – urine GAGs pattern</td>
<td>Mucopolysaccharidoses – allogeneic hematopoietic stem cell transplantation and enzyme</td>
<td>Mucopolysaccharidoses – allogeneic hematopoietic stem cell transplantation and enzyme</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Main classification</th>
<th>Examples</th>
<th>Key relevant clinical features</th>
<th>Appropriate work-up</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemochromatosis</td>
<td>Genetic or acquired, iron deposition in the</td>
<td>Assessment of iron overload, genetics and organ damage, lipid panel including apolipoprotein A-1</td>
<td>Phlebotomy, Treatment of complications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sclera, conjunctiva and cornea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lechithin-cholesterol-acyltransferase deficiency</td>
<td>Disorder of lipoprotein metabolism – either complete (Norum disease) or partial (fish eye disease); Norum disease presents with systemic involvement; fish eye disease presents with corneal opacification only (numerous small gray intrastromal dots, usually more prominent peripherally)</td>
<td>Lipid panel including apolipoprotein A-1, Genetic testing</td>
<td>Treatment of complications</td>
<td></td>
</tr>
<tr>
<td>Hematological disorders</td>
<td>Copper deposition in the central Descemet membrane along with anterior and posterior lens capsule</td>
<td>Copper deposition in the central Descemet membrane along with anterior and posterior lens capsule</td>
<td>Referral to hematology; specific investigations to consider: Serum protein electrophoresis ESR</td>
<td>Various treatment options depending on underlying cause</td>
</tr>
<tr>
<td>Stromal dystrophies</td>
<td>Macular corneal dystrophy</td>
<td>Schnyder corneal dystrophy is the only one that may produce ring-shaped stromal opacification</td>
<td>Nil</td>
<td>Consider penetrating keratoplasty</td>
</tr>
<tr>
<td></td>
<td>Congenital stromal corneal dystrophy</td>
<td>Onset childhood, midperipheral panstromal haze also develops, causing the entire cornea to appear hazy</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fleck corneal dystrophy</td>
<td>About 50% patients demonstrate corneal crystals</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior amorphous corneal dystrophy</td>
<td>Reduced vision</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Central cloudy dystrophy of François</td>
<td></td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-Descemet corneal dystrophy</td>
<td></td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schnyder corneal dystrophy</td>
<td></td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Anterior embryotoxon (arcsis)</td>
<td>Stromal lipid accumulation, ring shaped, separated from the limbus by a clear zone, Common in elderly patients, occasionally associated with dyslipidemia in younger patients</td>
<td>Nil</td>
<td>Treatment of dyslipidemia in younger patients</td>
</tr>
<tr>
<td></td>
<td>Posterior embryotoxon</td>
<td>Thickened and anteriorly displaced Schwalbe line, Normal variant in about 15%, Associations include: Axenfeld-Rieger anomaly</td>
<td>Gonioscopy, Treatment of glaucoma if present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coats white ring</td>
<td>Typically small whitish stromal opacity often associated with previous corneal foreign body</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count; G, guttae; GAGs, glycosaminoglycans; IgG, Immunoglobulin G; Oc, oculemt; PCR, polymerase chain reaction; PHMB, polyhexamethylene biguanide; PO, per os.
Other alternative considerations are immunological and infective responses such as Coats white ring, Wessely immune ring, Gram-negative rods, fungi, herpes simplex/zoster, and Acanthamoeba. However, none of these fit the history and clinical features of the present case. Other differentials include immunoglobulin deposition as part of a multiple myeloma, which was excluded in our case.8

Corneal opacities may be secondary to a wide array of etiologies, including trauma, infection, or inflammation. They may also result from drug deposition, metabolic disorders, and corneal dystrophies or degenerations. It is important in such rare presentations to take an accurate history and to arrange appropriate investigations. The perfect circular shape and isolation in the midperipheral cornea suggest that this case likely represents deposition from an unknown material.

References