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Grand Rounds

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

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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 (Triton; Topcon, Tokyo, Japan), and Pentacam HR (Oculus, Wetzlar, Germany). See Figures 2–3. Optical coherence tomography scans of the macula and optic disc were normal in both eyes. Extensive blood investigations were ordered, including urea and electrolytes, full blood

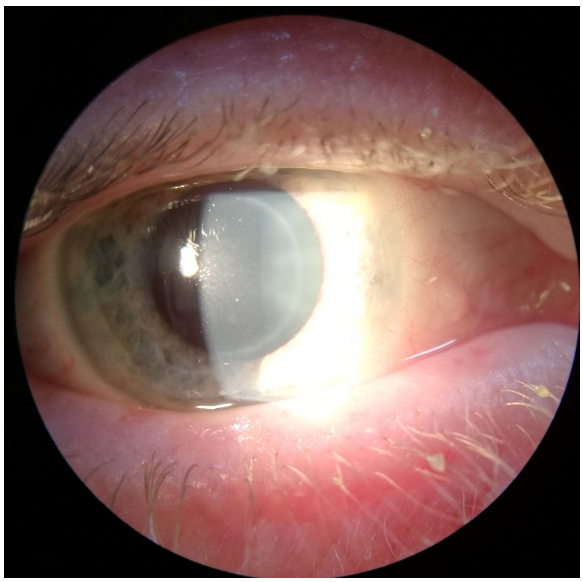

Figure 1. Slit-lamp photograph of the right eye showing intrastromal corneal circular opacity.

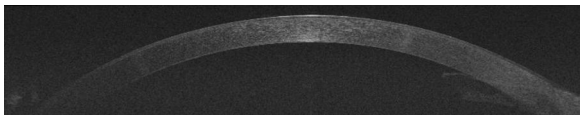

Figure 2. Optical coherence tomography image demonstrating the stromal opacity sparing the epithelium and endothelium.

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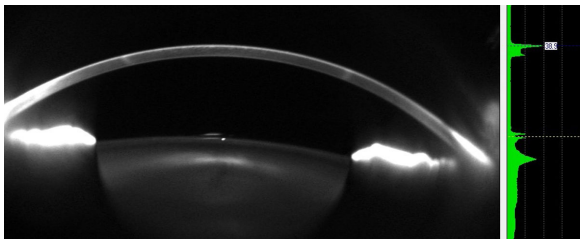

Figure 3. Scheimpflug Pentacam HR image demonstrating the stromal opacity sparing the epithelium and endothelium.

count, liver function, bone profile, random glucose, C-reactive protein, erythrocyte sedimentation rate, Borrelia burgdorferi antibodies, lipid panel (including apolipoprotein 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 nonprgogressive, 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,[1] the first being described by Ascher in 1963.[2]

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.[3,4] Furthermore, one would expect drug depositions to involve the peripheral and central cornea,[5] 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 alkaptonuria, 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.[6] 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 corneal dystrophy.[7] 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.

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Table 1. Differential diagnosis of circular/ring-shaped corneal opacities

Main classification	Examples	Key relevant clinical features	Appropriate work-up	Treatment
Infection	Acanthamoeba keratitis	• 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[9-12]	• Confocal microscopy • Culture and PCR[9-12]	• G. PHMB 0.02% or G. chlorhexidine 0.025% AND • G. propamidine 0.1% or G. hexamidine 0.1%[9-12]
	Herpetic keratitis	• *Simplex*: hypoesthesia, can be epithelial, stromal or endothelial • *Zoster*: headache, pyrexia, immunosuppression, systemic illness, V1 skin vesicles, conjunctivitis, elevated dendrites (lack terminal bulbs and stain poorly), may develop disciform, interstitial, necrotic or peripheral ulcerative keratitis; risk of posterior segment involvement and cranial nerve palsies[11-15]	• PCR in epithelial disease • Can culture vesicles[11-15]	*Simplex* • Oc. ganciclovir 0.15% • PO aciclovir/valaciclovir • Prophylactic antibiotics[11-17] *Zoster* • PO aciclovir/valaciclovir[11-17]
	Interstitial keratitis	• Corneal stromal inflammation with/without stromal vascularization • Redness, tearing, photophobia, irritation, visual loss depending on location[11,12,15,18-20]	• Syphilis serology, serum ACE (sarcoid), chest X-ray (tuberculosis, sarcoid), tuberculin skin test[11,12,15,18-20]	• Treat underlying cause • Topical steroids and cycloplegics[11,12,15,18-20]
Immunological	Wessely immune ring	• Sterile intrastromal immune reactions to foreign antigens • Ring-shaped infiltrate[21-23]	• Nil	• Nil
	Cogan syndrome	• Systemic autoimmune vasculitis • Typically young adults • Intraocular inflammation (redness, photophobia, pain, blurred vision) and vestibuloauditory dysfunction (tinnitus, vertigo, hearing loss) • Corneal signs: peripheral anterior stromal opacities and neovascularization • Systemic features in about 30%[15,24-29]	• Multidisciplinary involvement • ESR, CRP, FBC[15,24-29]	• PO immunosuppression • Topical steroids for keratitis[15,24-28]
Drugs	Gold (chrysiasis)	• Yellow-brown deposits in the corneal stroma (may be deposited in the corneal epithelium or lens)[15,30,31]	• Not usually required	• Not usually required
	Silver (argyrosis)	• Pigmentation of the conjunctiva, cornea, skin, and external mucosal membranes with silver • Occupational exposure or topical silver-containing medicines[15,32-34]	• Consider biopsy[35] (mucous membranes)	• Avoid exposure[34]
Metabolic	Wilson disease (hepatolenticular degeneration)	• Rare, autosomal recession • 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[15,36,37]	• Multidisciplinary involvement • Bloods including liver function tests, renal function, full blood count, clotting and serum ceruloplasmin • Other investigations guided by presentation[15,38]	• Chelation therapy[15,39]
	Lysosomal storage disorders: • Cystinosis • Mucopolysaccharidoses • Fabry disease	• *Cystinosis*: autosomal recession, widespread tissue deposition of cysteine crystals, including cornea, causing renal impairment in childhood[15,40,41] • *Mucopolysaccharidoses*: mainly autosomal recession, absence	All require multidisciplinary involvement; specific investigations to consider: • Cystinosis – white cell cysteine[15,40,41] • Mucopolysaccharidoses – urine GAGs pattern	• Cystinosis – cysteamine[15,40,41] • Mucopolysaccharidoses – allogeneic hematopoietic stem cell transplantation and enzyme

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Table 1. (Continued)

Main classification	Examples	Key relevant clinical features	Appropriate work-up	Treatment
		of enzymes needed to break down glycosaminoglycans; causes punctate corneal opacification and diffuse stromal haze; may cause optic atrophy and pigmentary retinopathy[15,42,43] • *Fabry disease*: X-linked, deficiency of the enzyme α-galactosidase A, which leads to accumulation of a glycolipid; ocular signs include golden brown corneal vortex keratopathy, spokelike posterior cataract, corkscrew conjunctival vessels, retinal tortuosity[15,44,45]	and alpha-L-iduronidase enzyme assay[15,42,43] • Fabry disease – Alpha-galactosidase A in leukocytes, plasma or cultured fibroblasts and urine microscopy[15,44,45]	replacement therapy[15,42,43] • Fabry disease – enzyme replacement therapy[15,44,45]
	Hemochromatosis	• Genetic or acquired, iron deposition in the sclera, conjunctiva and cornea[15,46,47]	• Assessment of iron overload, genetics and organ damage[15,46,47]	• Phlebotomy • Treatment of complications[15,46,47]
	Lecithin-cholesterol-acyltransferase deficiency	• 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)[15,48-51]	• Lipid panel (including apolipoprotein A-1) • Genetic testing[15,48-51]	• Treatment of complications[15,48-51]
Hematological disorders	Copper deposition in • Multiple myeloma[52,53] • Benign monoclonal gammopathy[54] • Monoclonal gammopathy of undetermined significance[55] • IgG monoclonal gammopathy associated with pulmonary carcinoma[56]	• Copper deposition in the central Descemet membrane along with anterior and posterior lens capsule	Referral to hematology; specific investigations to consider: • Serum protein electrophoresis • ESR	• Various treatment options depending on underlying cause
Stromal dystrophies	• Macular corneal dystrophy • Congenital stromal corneal dystrophy • Fleck corneal dystrophy • Posterior amorphous corneal dystrophy • Central cloudy dystrophy of François • Pre-Descemet corneal dystrophy • Schnyder corneal dystrophy[7]	• Schnyder corneal dystrophy is the only one that may produce ring-shaped stromal opacification • Onset childhood, midperipheral panstromal haze also develops, causing the entire cornea to appear hazy • About 50% patients demonstrate corneal crystals • Reduced vision[7]	• Nil	• Consider penetrating keratoplasty
Miscellaneous	Anterior embryotoxon (arcus)	• Stromal lipid accumulation, ring shaped, separated from the limbus by a clear zone • Common in elderly patients, occasionally associated with dyslipidemia in younger patients[57,58]	• Nil	• Treatment of dyslipidemia in younger patients
	Posterior embryotoxon	• Thickened and anteriorly displaced Schwalbe line • Normal variant in about 15% • Associations include: Axenfeld-Rieger anomaly[59,60]	• Gonioscopy	• Treatment of glaucoma if present
	Coats white ring	• Typically small whitish stromal opacity often associated with previous corneal foreign body[61]	• Nil	• Nil

CRP, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *FBC*, full blood count; *G*, guttae; *GAGs*, glycosaminoglycans; *IgG*, Immunoglobulin G; *Oc*, oculentum; *PCR*, polymerase chain reaction; *PHMB*, polyhexamethylene biguanide; *PO*, per os.

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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.

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