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Crystalline keratopathy due to intravenous immunoglobulin in a 12-year-old girl with Kawasaki disease

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Kawasaki disease (KD) is an acute, self-limiting, medium-vessel vasculitis that occurs predominantly in young children. The treatment of KD consists of intravenous immunoglobulin (IVIG) along with aspirin and, in IVIG-resistant cases, corticosteroids. Crystalline keratopathy with corneal deposition of the immunoglobulin is a rare complication of IVIG therapy. We report the case of a 12-year-old girl who received IVIG for KD and developed visual complaints, which were attributable to crystalline keratopathy and corneal edema. Cessation of IVIG and treatment with topical and systemic corticosteroids reversed the finding. At final follow-up, vision in both eyes was normal.

awasaki disease (KD) is an autoimmune disease that predominantly affects children under the age of 5 years and is characterized by mediumvessel vasculitis. Although it is largely self-limiting, some patients with KD develop abnormalities of the coronary vessels.¹ Ophthalmic manifestations of KD are common; in fact, bilateral, painless bulbar conjunctival injection is one of the principal diagnostic criteria for KD.¹ Intrave-

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nous immunoglobulin (IVIG) is the mainstay of therapy for KD.

Case Report

A 12-year-old girl presented at the Pediatric Ophthalmology Clinic at Advanced Eye Hospital & Institute of Navi Mumbai, with fever, arthralgia, and bilateral redness of the eyes of 8 days' duration. A pediatric rheumatology consult was sought in view of persistent pyrexia. The significant clinical findings included bilateral conjunctival congestion, mucositis involving the lips, arthritis involving the wrists, ankles, and metacarpophalangeal joints, and periungual desquamation. Because of a clinical suspicion of incomplete Kawasaki disease, a transthoracic 2-D echo-cardiogram of the heart was performed and revealed uniform dilatation of all coronary vessels, the right coronary artery being most significantly affected with Z-score of 3.5. Blood investigations showed leucocytosis, thrombocytosis, raised erythyrocyte sedimentation rate (90 mm), and elevated C-reactive protein (CRP) at 210 mg/l. This confirmed the diagnosis of Kawasaki disease. The patient was treated with IVIG infusion (2 g/kg) over 12 hours. The conjunctival injection resolved within a day of starting IVIG. She was discharged on low-dose aspirin as a part of the KD treatment protocol.

Five days after initiation of IVIG there was recurrence of fever, arthralgia, and redness in both eyes. She also complained of progressive blurring of vision and photophobia. On examination, visual acuity was 20/80 in each eye. Ciliary congestion and epithelial and stromal edema associated with superficial punctate keratopathy, which was visible on staining of the cornea with fluorescein, were also noted (eFigure 1A). Subtle nebulous, cloudlike, subepithelial crystalline opacities were seen extending into the midstroma (eFigure 1B). Intraocular pressures, pupillary examination, and fundus examination were normal. Anterior segment optical coherence tomography (AS-OCT) showed multiple highly reflective dots suggestive of intrastromal deposits, which were subepithelial in location (Figure 1A; eFigure 2A). Pachymetry readings of 792 μ in the right eye and 800 μ in the left eye were recorded. A possibility of IVIG-resistant KD with drug-induced keratopathy was suspected. Blood counts revealed only a mild reduction in disease activity, with falling acute phase markers (erythrocyte sedimentation rate, 55 mm; CRP, normal), but serum IgG levels were very high 2540 mg/dl (age-appropriate normal range, at 503-1,719 mg/dL). Because of a possibility of IVIGinduced keratopathy further IVIG was withheld; instead, intravenous methylprednisolone (30 mg/kg/dose) was administered. Topical fluoromethalone drops 4 times daily and tear substitutes were also prescribed. After 3 pulses of methyl prednisolone, she had a complete resolution of both systemic and ocular symptoms. Ten days after treatment, the patient's visual acuity had recovered completely to



FIG 1. Slit-lamp images of the right eye (above) and the corresponding anterior segment optical coherence tomography (below). Note the cornea appears thickened and hazy before treatment (A) and clear with reduced pachymetry (B) after treatment.

20/20 in each eye; pachymetry readings were 580 μ in the right eye and 572 μ in the left eye (Figure 1B; eFigure 2B). At 6 month's follow-up, the child was symptom free.

Discussion

The most common ocular findings in KD are nonexudative conjunctival injection with perilimbal sparing and anterior uveitis. Other manifestations include orbital cellulitis, ophthalmic artery obstruction, optic disk swelling, vitreous opacities, superficial punctuate keratitis, disciform keratitis, and global inflammatory involvement of the ocular segments.²

In this case, we suspect the keratopathy and corneal edema to be the result of the subepithelial deposition of immunoglobulin G, which was systemically administered as a part of KD treatment protocol. Causality between the drug and its adverse effect depends on the timing of the drug administration, onset of the reaction, pattern recognition, and ancillary investigations that may assist in establishing the association. We believe that the elevated serum IgG level in our patient at presentation, the absence of any concurrent medication, and the reversal of the pathology on discontinuation of the drug establishes beyond reasonable doubt that this relationship between the observed adverse effect (crystalline keratopathy) and the administration of IVIG was probable or likely.³

A similar case has been reported in a 7-year-old girl who developed almost identical symptoms 6 days after receiving IVIG.⁴ As was in our case, the patient recovered in a week's duration with topical steroids and tear substitutes. However, raised serum IgG levels were not documented in the previously reported case and it was a presumed diagnosis.

In experimental models, after subconjunctival application, IgG diffuses up to the corneal center with a delay of several days.⁵ We believe that this diffused immunoglobulin corresponds to the hyper-reflective dots seen on AS-OCT scans as well as the clinically seen diffuse stromal haze. Crystalline keratopathy has been previously observed with the use of immunoglobulin in the management of pyoderma gangrenosum where corneal deposition, which was thought to have originated from the limbal vessels, was noted.⁶ Crystalline keratopathy has also been reported in a case of monoclonal gammopathy of undetermined significance.7 Recent studies have also shown atypical corneal immunoglobulin deposition in a patient with dysproteinemia.⁸ Immunotactoid keratopathy, a different form of paraprotein crystalline keratopathy that is associated with a monoclonal immunoglobulin G kappa light chain protein has also been documented.^{9,10}

Rheumatologists and ophthalmologists alike should be sensitive to the possibility of IVIG-related keratopathy in children. Cessation of the drug and treatment with topical and systemic corticosteroids may have an additional role in treatment. After the encouraging reports from studies evaluating the efficacy of immunoglobulin along with prednisolone for prevention of coronary artery abnormalities in severe KD, corticosteroids have gained wide acceptance in treating IVIG-resistant KD. Ophthalmic evaluation in children especially those with ocular symptoms upon completion of initial therapy with IVIG is recommended.

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eFIG1. A, Fluorescein stained cornea in the right eye showing superficial punctate staining. B, Slit-beam through the hazy cornea showing the crystalline stromal deposits.



eFIG2. Slit-lamp images of the left eye (above) and the corresponding anterior segment optical coherence tomography images (AS-OCT; below) allow a comparison of the corneal thickness and clarity at presentation (A) and after withdrawal of intravenous immunoglobulin (IVIG) and treatment with steroids (B). The AS-OCT show multiple hyper-reflective dots in the anterior stroma corresponding to the diffuse crystalline immunoglobulin deposits.