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Multimodal Imaging of Posterior Corneal Opacities in Multicentric Osteolysis Nodulosis and Arthropathy (MONA)

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Abstract

Purpose: Multicentric osteolysis nodulosis and arthropathy (MONA) syndrome is a rare autosomal recessive skeletal dysplasia. Caused by mutations in the matrix metalloproteinase 2 gene (*MMP2*) on chromosome 16q12, this syndrome has infrequently been associated with ophthalmic manifestations. Corneal opacities have been reported but not described or documented in detail.

Methods: Complete ophthalmologic examination and multimodal anterior segment imaging were used to characterize the corneal findings in a patient with MONA syndrome.

Results: A 19-year-old with MONA syndrome was referred for an eye exam based upon MONA screening recommendations. Visually insignificant peripheral corneal opacities were noted. Anterior segment optical coherence tomography (AS-OCT) demonstrated posterior stromal and endothelial hyperreflectivity. Confocal microscopy demonstrated an acellular peripheral endothelium with a normal central endothelium.

Conclusions: Corneal opacities can occur with MONA syndrome, which is caused by mutations in the *MMP2* gene. In the patient presented here, the corneal opacities are peripheral, deep stromal, with sparing of the anterior stroma and epithelium.

Keywords

multicentric osteolysis nodulosis and arthropathy; matrix metalloproteinase 2; gelatinase; collagenase; corneal opacity

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Introduction

Multicentric osteolysis nodulosis with arthropathy (MONA) is a spectrum of rare, hereditary, primary skeletal dysplasias. It is inherited in an autosomal recessive fashion. Affected individuals have mutations in the *MMP2* gene on chromosome 16q12, which encodes matrix metalloproteinases (MMP) 2 protein.[1,2] MMP2 is also called type IV collagenase or gelatinase and is a 72 kDa zinc-dependent protein involved in tissue homeostasis, bone cell proliferation, craniofacial development, and modulation of the inflammatory response and collagen turnover.[3–5] One main function of MMP2 is cleavage of type IV collagen, a component of basement membrane. Many types of mutations have been reported including frameshift, small deletion, insertion, missense, and splice site variant mutations.[1,2,6–9]

To date, 52 patients and 23 genetic variants consistent with MONA syndrome have been reported.[6] The syndrome is characterized by progressive osteolysis of the carpal and tarsal bones with painful arthropathy and contractures starting in childhood. Subcutaneous nodules of the hands and feet and facial dysmorphism are common. A number of systemic manifestations have been described including cardiac, oral, dermatologic, and ophthalmologic.[1,2,6] Ocular features are variable and inconsistently described, ranging from vague mentions of “corneal opacities” to ptosis and strabismus.[1,2,7,10] In this report, peripheral corneal opacities present in this rare syndrome are demonstrated with multi-modal imaging for further characterization.

Case Report

A 19-year-old male with MONA syndrome and known biallelic splice site mutations (c.1770–1_1774 del) in the *MMP2* gene (16q12.2) was referred for corneal sub-specialty evaluation. The patient was originally referred to a pediatric ophthalmologist for a routine eye examination due to his diagnosis of MONA syndrome.

The patient was born with bilateral claw hand deformities (Figure 1). He is of short stature (<1%, Z = −3.35) with arthropathy of the hands and knees. There was no history of cardiac defects and he had a normal echocardiogram within the past year. He was undergoing treatment with zoledronic acid per his rheumatologist, and was taking calcium, vitamin D supplementation, naproxen, and topical diclofenac for his osteopenia and arthropathy. There was no significant ocular history. Subjectively, he reported no changes in vision and no ocular discomfort. His family history was unremarkable with no consanguinity.

On examination, the patient’s uncorrected visual acuity was 20/15 in each eye. His intraocular pressure, pupils, and extraocular movements were all normal. Ocular alignment was orthotropic. Corneal sensation on Cochet-Bonnet esthesiometry was 5/6 centrally and in all four corneal quadrants in both eyes, indicating symmetric and adequate corneal sensation. Slit lamp exam demonstrated clear central corneas and peripheral plaque-like opacities that appeared to involve the posterior stroma and endothelium (Figure 2). The anterior and posterior segment exams were otherwise normal.

Central corneal thickness was 589 μm and 593 μm in the right and left eyes, respectively. On corneal tomography, regular with-the-rule astigmatism was noted in both eyes. Anterior

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segment optical coherence tomography (AS-OCT) revealed a normal central cornea with hyperreflectivity of the peripheral posterior stroma and Descemet's membrane (Figure 3). On confocal microscopy, there is amorphous hyperreflective material immediately superior to endothelial cells. Endothelial cells are present just beneath this observed deposit in most but not all areas. The arrows in Figure 3 highlight a section where an amorphous hyperreflective deposit masks the clear visualization of endothelial cells. In these areas it appears the opacity is lying just superior to the otherwise normal appearing endothelial cells.

No corneal intervention was recommended and the patient was advised to return annually for eye exams with slit lamp photos to monitor the corneal opacities.

Discussion

We present a 19-year-old male with MONA and bilateral peripheral posterior corneal opacities involving the posterior stroma, Descemet membrane and endothelium. These opacities were not visually significant. The patient had a known biallelic splice site *MMP2* mutation, consistent with MONA syndrome.

Matrix metalloproteinases are a family of zinc-dependent endopeptidases in the extracellular matrix (ECM) that regulate both physiologic and pathologic inflammatory processes.[4,5] *MMP2,* the culprit gene in most cases of MONA syndrome, is on chromosome 16q12-q21 and consists of 13 exons.[3,8] It encodes the MMP2 enzyme, also called gelatinase A or type IV collagenase, which modulates the inflammatory response and degrades collagen and elastin to allow for collagen turnover in wound healing. MMP2 has been studied extensively in the context of skin and cornea wound healing, and MMP2 proenzyme (pro-MMP2) expression is up-regulated in injured corneal epithelium, including recurrent corneal erosions in humans.[4,11,12] MMP2 appears to play a role in corneal endothelial function, and endothelial cells in patients with Fuchs' dystrophy were found to secrete less MMP2 compared to healthy controls.[13]

Patients with MONA syndrome have decreased activity of serum MMP2, and measurement of the enzymatic activity is an alternative to genetic testing for diagnosing the syndrome.[2] Given the well-established role of MMP2 in corneal wound healing, it is not surprising that patients with MONA syndrome may develop corneal opacities. Unlike posterior polymorphous corneal dystrophy (PPCD), which classically presents as vesicle-like lesions, "snail track" band lesions, or diffuse scattered lesions, and unlike pre-Descemet corneal dystrophy (PDCD), which classical presents as numerous small, polymorphic opacities, our patient with MONA demonstrated a larger confluent plaque-like lesion.

MONA syndrome is rare and ocular manifestations of MONA are poorly characterized. Other eye findings such as ptosis and strabismus may also be associated. All patients with this rare syndrome should be evaluated for other MMP2 related ocular sequelae. Given the limited published data on posterior corneal opacities associated with MONA, we recommend at least annual screening to ensure no progression.

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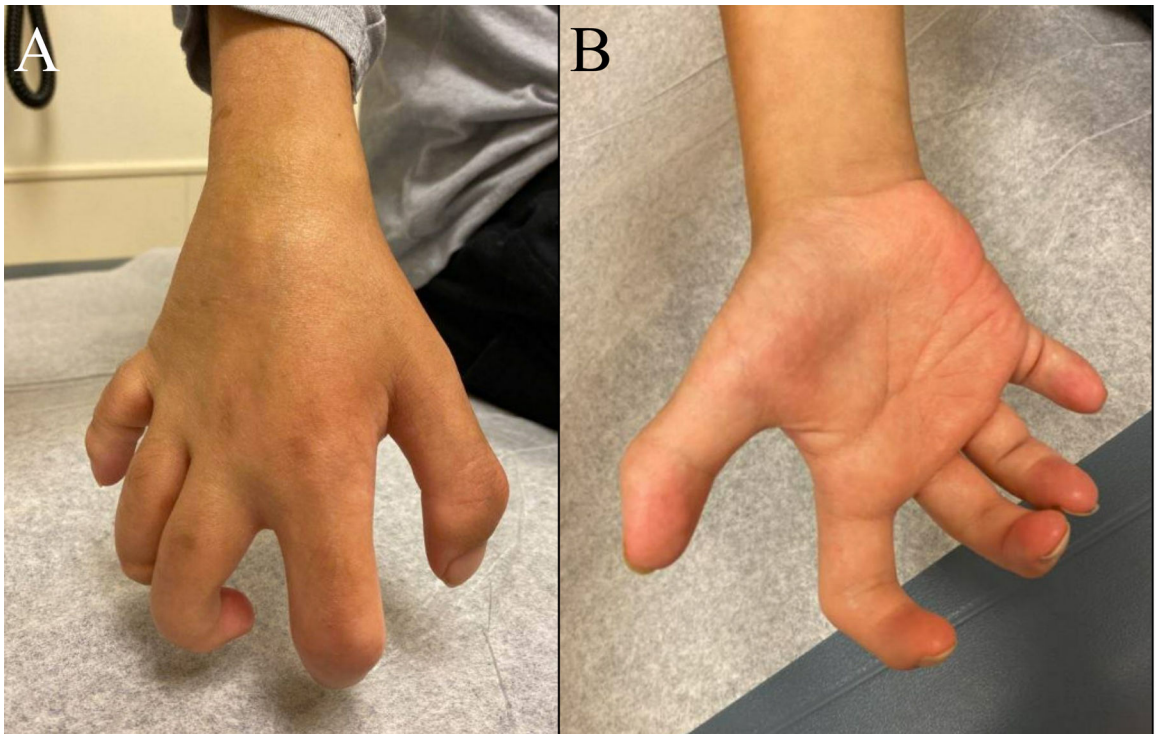

Figure 1.
Right hand of patient demonstrating claw deformity, common in MONA syndrome (A). The left hand had a similar appearance (B).

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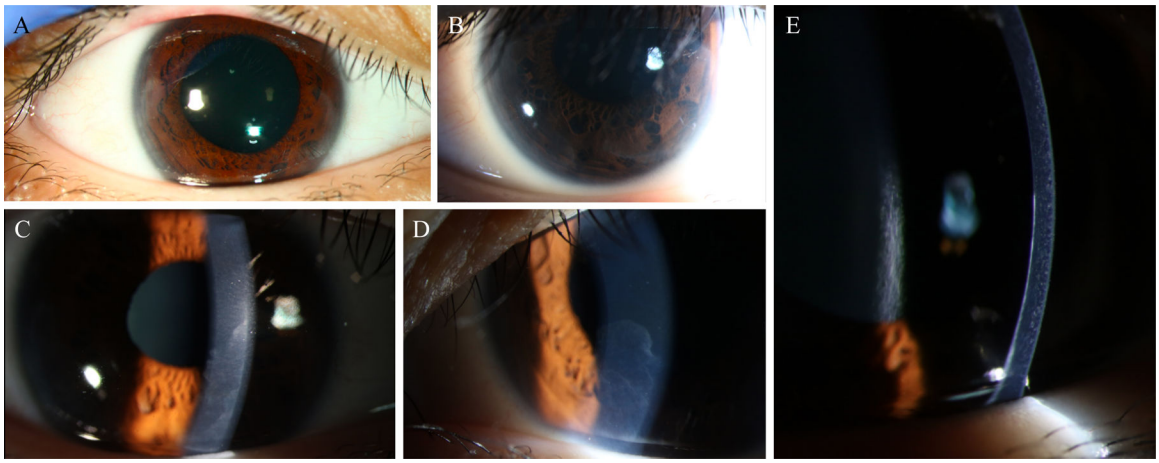

Figure 2.

Slit lamp photos of the patient's right eye. On diffuse illumination the corneal opacities are not readily apparent (A). Sclerotic scatter and broad slit beam highlight the smoky, plaque-like posterior corneal opacities found in the peripheral cornea (B-D). Thin slit beam reveals involvement of the posterior stroma and endothelium, sparing the anterior stroma and epithelium (E). The patient's left cornea had a similar appearance.

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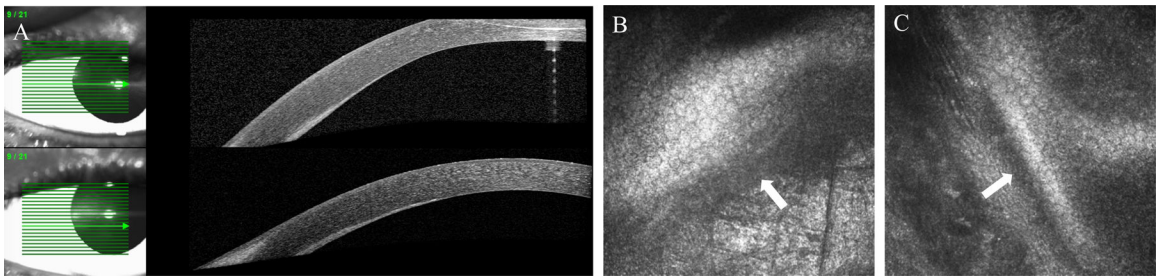

Figure 3.

Multimodal imaging further characterizes the bilateral posterior peripheral corneal opacities. AS-OCT of the right (A, top) and left (A, bottom) eyes showing hyperreflectivity of the posterior stroma and endothelium, with normal central cornea. On confocal microscopy of the right (B) and left (C) eyes, slightly oblique sections demonstrate the contrast between normal appearing endothelium centrally with the acellular depositional material just superior to the endothelium (arrows).