Phenotypic Variation in Ophthalmic Manifestations of MIDAS Syndrome (Microphthalmia, Dermal Aplasia, and Sclerocornea)

The term MIDAS syndrome was coined by Happle et al1 in 1993 to describe the predominant features of a genetic disorder with microphthalmia, dermal aplasia, and sclerocornea. This syndrome has also been called the “MLS syndrome,” which stands for “microphthalmia with linear skin defects.” The dermal aplasia in MIDAS syndrome consists of linear erythematous skin defects that typically involve the face, scalp, neck, and upper part of the thorax. In addition to the ocular and skin findings, there are multiple nonocular abnormalities commonly reported to be associated with MIDAS syndrome. Some of these include congenital heart defects, short stature, hypospadias, developmental delay, absence of the corpus callosum, nail dystrophy, and hydrocephalus.

The underlying defect in MIDAS syndrome is due to a deletion at Xp22.3. The disease is believed to be transmitted as an X-linked dominant trait that is lethal in the male hemizygous state. This theory has been supported by the fact that there have been no reported cases of XY males with this syndrome. The few reported cases of males with MIDAS syndrome have 46,XX karyotypes with a deletion of the Xp22.3 region due to an X/Y translocation. Although these patients are genotypically female, they are phenotypically male.

Recently we examined twin boys and 2 single-birth girls with genetically proven deletion of chromosome Xp22.3. Examination with the patient under anesthesia, including biometry and ultrasonography, was performed to detail the ocular findings associated with this syndrome. Other nonocular abnormalities were also noted.

Report of Cases. Cases 1 and 2. The twin males were born to a gravida 1, para 0, healthy 20-year-old single mother. The father was unrelated, and family history was unremarkable. Complications during the pregnancy included a positive maternal culture for group B streptococcus treated with amoxicillin and supraventricular tachycardia (SVT) of both fetuses treated with digoxin. The twins were born via an uncomplicated vaginal delivery. Estimated gestation was 35 weeks 4 days. Twin 1’s birth weight was 2.324 kg and twin 2’s birth weight was 2.350 kg.

In twin 1, external examination of the eyelids at birth was normal in both eyes. Intraocular pressure (IOP) obtained with a pneumotonometer was 36 and 33 mm Hg in the right and left eyes, respectively. Horizontal corneal diameter was 7.5 mm in each eye. Sclerocornea was noted in both eyes. The right and left corneas had central areas of less scleralized cornea measuring 4 and 5 mm, respectively (Figure 1). The fundus could not be visualized in the right eye, but funduscopic examination of the left eye showed a flat retina with a grossly normal optic disc and macula. Axial length was 15.17 mm in the right eye and 15.44 mm in the left eye. B-scan ultrasonography findings were normal in both eyes. A computed tomographic scan and mag-
nomic resonance images of the orbits showed that both globes were small but normal.

In twin 2, on external examination, a small eyelid fissure was noted on the right eye with normal fissures on the left. Examination of the right eye showed anophthalmia. Intraocular pressure obtained with a pneumotonometer was 26 mm Hg in the left eye. Horizontal corneal diameter was 10 mm in the left eye. The cornea of the left eye showed peripheral scleralization with dense opacification and vascularization centrally, consistent with Peters anomaly (Figure 2). No details could be discerned on funduscopic examination. Axial length of the left eye was 16.62 mm, and B-scan ultrasonography findings were normal. A computed tomographic scan and magnetic resonance images showed a normal globe on the left and no globe on the right.

Examination of the skin of both twins disclosed linear, erythematous lesions consistent with dermal aplasia. The lesions were located on the face, neck, and preauricular area. Several months later, an examination of the skin showed healing of the lesions with a small amount of scarring.

Both twins had episodes of SVT shortly after birth. Initial echocardiograms in both twins showed a patent ductus arteriosus, which had spontaneously closed on follow-up echocardiograms. No other cardiac abnormalities were found. The episodes of SVT in both twins were well controlled with β-blockers. By 6 months of age, all cardiac medications had been discontinued in both twins, without further episodes of SVT.

Both twins were noted to have distal penile hypospadias but otherwise had normal male genitalia. Chromosomal analysis of the male twins showed a 46,XX karyotype with a translocation between the X and Y chromosomes (Figure 3). The probe for the male determinant region of the Y chromosome was positive, indicating that the region of the Y chromosome that determines the male sex was present on the translocated X chromosome. Because of this translocation, the twins were phenotypically male, although genotypically XX or female. Chromosome analysis also showed a deletion at the Xp22.3 site. The karyotype of each of the twins was 46,XX,ish der(X)t(X;Y) (SRY+,Kallmann−, STS). Chromosome analysis was not performed on the patients’ parents.

Case 3. The first female patient was born to a gravida 1, para 0, healthy 37-year-old mother and her unrelated husband via normal spontaneous vaginal delivery. Estimated gestational age was 40 weeks, and birth weight was 3.015 kg. There were no complications during the pregnancy or birth.

Results of external examination were normal. The IOP in the right eye by pneumotonometer was 41 mm Hg. Because the left eye was severely microphthalmic, an accurate IOP measurement was not possible. The right cornea was bulging centrally and had a corneal diameter of 10 mm horizontally and vertically. Sclerocornea and diffuse vascularization were present. Centrally, a slightly less opacified area measuring 6.5 × 4 mm was noted, with a dense, white area measuring 4 × 4 mm within this clearer region. The left eye had a corneal diameter of 5 mm horizontally and vertically. Dense sclerocornea with a central clear zone of 2 mm was evident. No details of the anterior chamber or fundus could be discerned in either eye. B-scan ultrasonography findings in the right eye showed mild vitreous opacification. The retina was attached with evidence of choroidal thickening. Intraocular structures were otherwise normal. Ultrasoundography could not be performed on the left eye because of the severity of the microphthalmia.

Examination of the patient’s skin showed multiple areas of der-
mal aplasia on the face, neck, and upper extremities (Figure 4).

An echocardiogram demonstrated a patent ductus arteriosus with a right-to-left shunt but normal cardiac function. An ultrasound scan of the head showed a small intraventricular hemorrhage and moderate hydrocephalus, which required no treatment. This patient was also noted to have short fingers and nail dystrophy. Female genitalia were normal.

The patient's karyotype was 46,X,der(X)t(X;Y)(p22.3;q11),ish der(X)t(X;Y)(wcpY+,DYZ1+,DYZ3−,SRY−,STS−). Chromosomal analysis disclosed a translocation between the short arm of one X chromosome and the long arm of a Y chromosome. The STS probe, which is specific for the Xp22.3 region, did not hybridize with the abnormal X homologue, indicating a deletion of the Xp22.3 region. Chromosome analysis was performed on the patient's parents and results were normal in each case.

Case 4. The second female patient was born to a 27-year-old, gravida 2, para 0 mother and her unrelated husband. The mother had had an ectopic pregnancy in 1993 (approximately 5-6 years before the current pregnancy), but otherwise had no significant medical history. The infant was the product of an uncomplicated pregnancy and a normal spontaneous vaginal delivery. Birth weight was 3.892 kg.

Examination of the eyelids showed a slight mongoloid slant, but they were otherwise normal. Measurement with a Perkins applanator showed an IOP of 11 mm Hg in each eye. The right cornea was flat and oval with a horizontal diameter of 8.5 mm and a vertical diameter of 5.75 mm. The left cornea was also oval with a diameter of 6.75 mm horizontally and 4 mm vertically. The left eye had peripheral sclerocornea with a small area of increased clarity centrally. The right eye had a diffusely opaque cornea with a paracentral thinned area and an iridocorneal adhesion at the 4-o'clock position (Figure 5). Partial aniridia was noted in the left eye with peripheral adhesions of the iris to the cornea. The lens of the right eye was poorly visualized. In the left eye, a remnant of the anterior hyaloid system was seen extending to the posterior aspect of the lens. Under funduscopic examination, the retina of the right eye was not visible, but examination of the left eye showed a normal optic nerve with an attached retina. A-scan ultrason sound measurements demonstrated an axial length of 16.69 and 18.46 mm in the right and left eyes, respectively. B-scan ultrasonography findings were normal in both eyes.

No skin abnormalities were noted on examination. Results of the patient's cardiac examination and echocardiogram were normal, and she had normal female genitalia. By age 3 years, the patient was noted to have short stature.

Chromosome analysis showed a 46,XX karyotype. One X chromosome was normal and the other X chromosome had a translocation involving the distal short arm of the X chromosome and the long arm of the Y chromosome. This translocation resulted in a deletion of the Xp22.3 region, giving the patient a karyotype of 46,X,der(X)t(X;Y)(p22.3;q11.2). Results of chromosome analysis performed on each of the patient's parents were normal.

Results. Four patients with genetically proved deletion of chromosome Xp22.3 were examined (Table). Microphthalmia was noted in 4 of the 8 eyes (1 of the 4 was anophthalmic). Three of the 4 patients had dermal aplasia. Sclerocornea was noted in all 7 eyes, excluding the anophthalmic eye.

Five of the 7 eyes had microcornea, defined as a corneal diameter less than 10 mm. One eye was found to have Peters anomaly. Two of the 7 eyes had iridocorneal adhesions. One eye had partial aniridia.

Figure 3. Karyotypes of patients 1 (A) and 2 (B), obtained by GTG banding with a resolution level of 400 to 550 bands per haploid complement. The karyotype of patient 2 is identical to that of patient 1. Arrows indicate the region of the Y chromosome that is present on the translocated X chromosome.

Figure 4. Patient 3 at birth, showing areas of dermal aplasia around the nose, on the cheek, and on the neck.
and 1 eye had a remnant of the anterior hyaloid artery visible. Three of the 7 eyes had elevated IOP, 1 eye had a borderline elevated IOP, and 1 eye was too small to obtain an accurate IOP. The results of dilated fundus examination were normal in 2 of the 7 eyes, and no view was possible in 5 eyes. Of the 5 eyes in which there was no view of the fundus, 3 eyes had a normal B-scan findings, 1 eye was too microphthalmic to obtain a B-scan, and 1 eye had B-scan results that showed mild vitreous opacity with choroidal thickening. Computed tomographic scanning and magnetic resonance imaging were performed on 4 of the 8 orbits. Three of the 4 scans had normal findings and 1 scan result confirmed absence of the globe.

Comment. These 4 case studies demonstrate that the ocular manifestations associated with the deletion of Xp22.3 encompass a broader spectrum of findings than that originally described by the MIDAS syndrome. Although our patients had similar karyotypes, they exhibited a wide variety of ocular findings not included in the classic triad of microphthalmia, dermal aplasia, and sclerocornea. In addition, not all of our patients demonstrated the classic triad of abnormalities. As shown in the Table, only patient 1 had all 3 findings in both eyes. All eyes of the 4 patients (excluding the anophthalmic eye in patient 2) were noted to have various degrees of sclerocornea, but only 4 of the 8 eyes had microphthalmia (or anophthalmia), and only 3 of the 4 patients had dermal aplasia.

In a review of the literature, there have been 22 case reports of patients with a microdeletion at the distal Xp region. Seventeen of the reported cases were in females,\(^2,3\) whereas 5 of them were in 46,XX males.\(^2,4-7\) Previous case reports have noted phenotypic variability as seen in our patients. For example, al-Gazali et al\(^8\) in 1990 described a female patient with peripheral anterior synechiae and collarette adhesions. Lindor et al\(^9\) in 1992 described an infant with choroidal thickening in both eyes. Other atypical findings reported in patients with MIDAS syndrome include dense cataracts,\(^9\) blepharophimosis,\(^1\) and aphakia.\(^2\) To the best of our knowledge, the ophthalmic findings in our 4 patients not described in previous case reports include Peters anomaly, anophthalmia, partial aniridia, a remnant of the anterior hyaloid artery, and vitreous opacity.

Although 5 other 46,XX males with the MIDAS syndrome have been described in the literature, this study represents the first case report of identical twin boys (cases 1 and 2). These 2 cases demonstrate

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Abbreviations: MIDAS, microphthalmia, dermal aplasia, and sclerocornea; NA, not applicable (anophthalmic eye).
that, even with identical genetic deletions at the Xp22.3 locus, the phenotypes may vary. Patients 1 and 2 were similar in that both of them had microphthalmia, sclerocornea, and skin deformities. They also exhibited hypoplasia and a mild cardiac abnormality in the form of SVT. There were, however, several differences in the phenotypes of the twins. Patient 1 had a definite high elevation of IOP, while patient 2 had a borderline elevation of pressure. Patient 2 had a small right eyelid fissure and anophthalmia, neither of which was present in patient 1. Microcornea was present in patient 1, but the corneal diameter of the nonanophthalmic left eye of patient 2 was normal. These phenotypic differences found in identical twin boys with identical karyotypes lend further support to the current hypothesis that the variations found in MIDAS syndrome may be due to different patterns of X inactivation, or Lyonization, rather than due to subtle differences in genotypes.

Further research should be done to understand more completely how the Xp22.3 deletion is expressed because this research may lead to a better understanding of the role of this chromosomal locus in ocular development.

The clinical definition of MIDAS syndrome continues to be modified as more phenotypic variability is reported. The present study represents one of the largest case studies detailing the ocular findings in patients with an Xp22.3 deletion and serves to expand the current phenotypes associated with this syndrome. Providing additional descriptions of the phenotype should aid clinicians in identifying patients with this genetic syndrome and prompt early genetic testing in appropriate patients. It is apparent that the monikers “MIDAS syndrome” and “MLS syndrome” do not fully describe this disease. Therefore, consideration should be given to more accurately and genomically referring to the syndrome as the “Xp22.3 microdeletion syndrome.”

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A "Negative" Temporal Artery Biopsy, Positive for Arteritis

Ophthalmologists often participate in the diagnosis and treatment of patients with giant cell arteritis (GCA), typically when the diagnosis is heralded by a central retinal artery occlusion or ischemic optic neuropathy. However, even in the absence of eye symptoms or signs, ophthalmologists may be asked to examine the patient and perform a biopsy of the temporal artery. The microscopic findings in the patient described herein bear on the technique of temporal artery biopsy.

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Report of a Case. A previously healthy 81-year-old woman developed mandibular pain with chewing, low-grade fevers, night sweats, and proximal limb myalgias. She denied headache or visual changes. There were no abnormalities on results of physical examination, and her temporal arteries were pulsatile and neither indurated nor tender. A chest radiograph was unremarkable. The only abnormality on routine laboratory testing was microscopic hematuria. Her condition did not improve after a trial of antibiotics for the presumed diagnosis of sinusitis. Three weeks after onset of symptoms, an erythrocyte sedimentation rate of 131 mm/h and a C-reactive protein level of 7.9 mg/dL prompted referral for neuroophthalmic consultation and biopsy. Although no abnormalities were found on the examination results, we performed a biopsy of the left temporal artery.

The biopsy specimen was fixed and serially sectioned. Microscopic examination (Figure) showed a normal temporal artery in all sections, but several small adjacent arteries included in the biopsy specimen showed granulomatous angitis.

The patient’s symptoms improved with oral prednisone therapy, but further investigations prompted by persistent hematuria resulted in the diagnosis of Wegener granulomatosis.

Comment. As demonstrated by this case, symptoms, signs, and even histologic findings classically associated with GCA can be found with other systemic vasculitides. Features attributed to GCA, such as jaw claudication, amaurosis fugax, and an erythrocyte sedimentation rate greater than 100 mm/h, have been seen in patients with Wegener granulomatosis. Like patients with GCA, patients with Wegener granulomatosis can improve with corticosteroid treatment, at least initially. However, patients with Wegener granulomatosis who are misdiagnosed as having GCA and who are treated only with corticosteroids may develop acute renal failure and respiratory tract disease. When faced with a “positive” tem-