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Hereditary Lymphedema and Distichiasis

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Abstract

Two patients with lymphedema-distichiasis syndrome illustrate that both Milroy's disease and late-onset hereditary lymphedema are sometimes associated with distichiasis. It is important for ophthalmologists to be aware of the lymphedema-distichiasis syndrome because of its ophthalmic manifestations and the associated systemic abnormalities that can be potentially life threatening.

Lymphedema-distichiasis syndrome is an autosomal-dominant condition causing ocular and systemic complications, including spinal arachnoid cysts and congenital heart defects. Prompt recognition of these associated lesions leads to proper evaluation and treatment.

Chronic hereditary lymphedema (Milroy's disease) is relatively rare. The association between distichiasis and hereditary lymphedema was first reported by Campbell.¹ Distichiasis, an aberrant second row of cilia arising from or near the meibomian orifices, may present as photophobia, blepharospasm, tearing, or a recurrent red eye. Additional ocular and systemic abnormalities have been described with lymphedema-distichiasis syndrome. We describe two patients with hereditary lymphedema and distichiasis. The two cases illustrate the variety of forms lymphedema that may be associated with distichiasis. We also describe the association of Milroy's disease with the corneal iron line. To our knowledge, this association has not been previously described.

REPORT OF CASES

CASE 1.—A 17-year-old Mexican-American girl presented to the Los Angeles County/University of Southern California Eye Clinic with a 3-month history of intermittent redness, itching, and burning in both eyes. Results of the eye examination revealed visual acuity of 20/20 bilaterally with correction. The lid margin showed distichiasis of all lids. These cilia were fine and directed in random fashion. The conjunctiva was chemotic in both eyes, with

fleshy swelling more prominent inferiorly (Fig 1). Results of corneal examination showed superficial vascularization of the peripheral cornea and a perilimbal iron pigment line inferiorly. Results of the eye examination were otherwise unremarkable.

Results of general physical examination revealed edema of the lower extremities extending to the knees (Fig 2). This swelling was noted at birth. Pitting was demonstrated with application of hard and sustained pressure. There was no history of acute erysipelas-type attacks.

Results of laboratory studies, including calculation of erythrocyte sedimentation rate, urinalysis, complete blood chemistry tests, liver function tests, serologic tests to detect syphilis, titers to detect toxoplasmosis or cysticercosis, chromosomal banding studies, and roentgenograms of the chest and skull were all within normal limits. Lymphangiography was attempted, but no lymphatic vessels were identified despite multiple attempts. This was believed to be presumptive evidence of lymphatic hypoplasia.

Results of biopsy of the conjunctiva revealed chronic inflammation and scarring of the conjunctival stroma. Plasma cells, lymphocytes, and mast cells were prominent along the epithelial stromal junction. Collagenization of the conjunctival stroma was also noted.

The patient's family history was significant in that one of seven siblings also had congenital lymphedema, but family members were unavailable for examination.

CASE 2.—A 15-year-old boy presented with a 6-month history of recurrent lymphedema of both lower extremities. He also had a history of distichiasis bilaterally, which the family treated with epilation. The family history was significant for lower leg lymphedema in a paternal uncle.

Results of a general physical examination revealed 2+ pitting edema of both lower extremities distal to the knees and good pulses. Results of cardiac examination and Doppler studies of the lower extremities were within normal limits.¹ Despite the history of epilation, a second row of cilia was seen on all four eyelids emanating from the meibomian orifices. No corneal scarring or ulceration was seen. Results of the remainder of the general physical and ocular examination were normal.

COMMENT

Chronic hereditary lymphedema of the lower extremities was first described by Letressier in 1865² and again by Nonne in 1891³ In 1892, Milroy⁴ reported lymphedema in six generations of one family. All forms of hereditary lymphedema are considered Milroy's disease. Unfortunately, this obscures the differences between Milroy's disease and other forms of primary lymphedema. Milroy's original description of the disease is quite precise: "It is congenital in onset. It is not painful or tender. It occurs in both sexes."⁵ Kinmonth⁶ concludes that Milroy's disease should describe only those cases of primary lymphedema that are congenital and hereditary. Lymphangiographic examination of patients with Milroy's disease shows abnormal, hypoplastic lymph pathways with obstructed lymphatic trees distal to the limb. Patient 1 had painless hereditary lymphedema at birth. Presumptive

evidence of lymphatic hypoplasia was the inability to cannulate a lymphatic vessel despite multiple attempts in this patient. Therefore, Milroy's disease was diagnosed.

Distichiasis has been described only in association with delayed-onset lymphedema.^{6–8} Distichiasis in a patient with Milroy's disease has not been described. Distichiasis has been reported only in patients with histories similar to that of patient 2 who developed edema at or near adolescence. Furthermore, previous patients with delayed-onset lymphedema and distichiasis have had bilateral hyperplasia of the lymphatics in the lower extremities on lymphographic examination.⁹

The classification and nomenclature of primary lymphedema has been a subject of confusion for decades. Based on our cases, it appears that distichiasis may be associated with both Milroy's disease (hypoplastic lymphatics) and late-onset hereditary lymphedema (hyperplastic lymphatics). Further examination of all patients presenting with chronic edema verified lymphangiographically will more clearly delineate the cause of the primary lymphedema associated with distichiasis.

Patient 1 presented with chemosis and a corneal iron line. Iron precipitates from the tear film when poor tear film exchange and stasis occurs. Chemosis is a known ocular manifestation of Milroy's disease.¹⁰ This chemotic state causes stasis of fluid and pooling of tears at the limbus. This stasis allows iron to precipitate from the tear film, causing an iron line. Interestingly, chemosis has not been described with delayed-onset lymphedema. This is consistent with our findings of chemosis in patient 1 (with Milroy's disease), but not in patient 2 (with delayed-onset lymphedema).

Lymphedema-distichiasis syndrome is important in pediatric ophthalmology. Knowledge of this syndrome allows the ophthalmologist to recognize subtle lymphedema, institute earlier treatment, and, hence, prevent disability. The ocular manifestations and their complications (eg, corneal ulceration and scarring) can also be managed expeditiously. Most importantly, associated abnormalities (Tables 1 and 2), which are potentially life threatening, can be diagnosed and treated. For example, children who present with this syndrome and vague neurologic complaints should be evaluated for spinal arachnoid cysts immediately. Timely recognition and surgical excision can often prevent severe neurologic sequelae.^{11,12} These patients must also be evaluated to detect congenital heart defects. Cardiac defects associated with this syndrome include pulmonary stenosis, absent inferior vena cava, coarctation of the aorta, atrial and ventricular septal defects, and arrhythmias.

Chronic hereditary lymphedema and distichiasis are inherited as autosomal-dominant traits.^{11–14} As is characteristic of autosomal-dominant genes, penetrance can be incomplete and expression variable. This is evident in our patients, and genetic counseling is advised for these patients.

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Fig 1.—
Distichiasis of lower eyelashes and chemosis in case 1.

Fig 2.—
Lymphedema of the lower extremities in case 1.

Table 1.—

Reported Anomalies Associated With Distichiasis and Lymphedema

Anomaly	Source, y
Strabismus	Campbell, ¹ 1945
Pterygium coli, lower lid ectropion	Falls and Kertesz, ²⁰ 1964
Fusion of various thoracic vertebrae and extradural cysts	Chynn, ¹¹ 1967
	Bergland, ¹² 1968
	Robinow et al., ⁷ 1970
Bifid uvula and submucous cleft palate	Jester, ¹⁵ 1977
Pterygium coli and ptosis	Shammas et al., ¹⁴ 1979
Congenital heart defects	Goldstein et al., ¹³ 1985

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Table 2.—

Reported Anomalies Associated With Lymphedema

Anomaly	Source, y
Yellow nails and pleural effusions	Allen, ¹⁶ 1934
Primary pulmonary tension and cerebrovascular malformation	Avasthey and Roy, ¹⁷ 1968
Obstructive jaundice	Sharp and Krivit, ¹⁸ 1971
Intestinal lymphangiectasia	Vardy et al., ¹⁹ 1975