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SHORT COMMUNICATION

Case report

Eight-year follow-up of Axenfeld-Rieger syndrome with Turner syndrome

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PURPOSE. *To report a case of Turner syndrome associated with iridogoniodysgenesis accompanied by somatic malformations.*
METHODS. *A 29-year-old woman underwent complete ophthalmologic and general examination. Incomplete development of the angle with iris stromal hypoplasia and prominent posterior embryotoxon with iris adhesions were noted. Disc drusen was confirmed by ultrasonography. Visual fields were normal other than bilateral enlargement of blind spot. Intraocular pressure was under 21 mm Hg during 8 years of follow-up without medication. The patient had atrial septal defect, sensorineural hearing loss, polycystic ovaries, hirsutism, glomerulosclerosis, dental anomalies, and low intelligence. A chromosome analysis revealed that she had mosaic Turner syndrome with a 45,X/46,XX karyotype.*
CONCLUSIONS. *Few reported cases in the literature describe the coexistence of Axenfeld-Rieger syndrome and Turner syndrome mosaicism. Somatic and anterior chamber malformations in this patient represent a developmental disorder of the neural crest. General examination and chromosomal analysis are indicated in patients presenting with anterior chamber dysgenesis. (Eur J Ophthalmol 2003; 13: 580-3)*

KEY WORDS. *Axenfeld-Rieger syndrome, Turner syndrome mosaicism*

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INTRODUCTION

Axenfeld-Rieger anomaly is an autosomal dominant inherited ocular disorder characterized by anteriorly displaced and prominent Schwalbe's line with attached strands of iris, stromal hypoplasia, and corectopia (1,2). If somatic defects including maxillary hypoplasia, hypodentia, umbilical hernia, hypospadias, sensorineural hearing loss, and cardiac anomalies accompany Axenfeld-Rieger anomaly, it is termed Axenfeld-Rieger syndrome (ARS) (3-5). Glaucoma occurs in 50% of patients with each condition (1).

Turner syndrome is a condition in which there is an absence or structural abnormality of one X chromosome in phenotypic females and occurs in 1 in 1500–2000 live-born girls (6,7). The cardinal features of Turner syndrome are short stature, webbing of the neck, cubitus valgus and ovarian failure resulting in absence of secondary sexual characteristics, and congenital heart defects. Other clinical manifestations include a low posterior hairline, small mandible, prominent ears, epicanthic folds, high arched palate, a broad chest presenting the illusion of widely spaced nipples, and hyperconvex fingernails. Sensorineural hearing deficit is common and the frequency increases with age. In patients with 45,X/46,XX mosaicism, the abnormalities are attenuated and fewer (6-8).

We report ophthalmic, systemic, and genetic findings in a patient with polycystic ovaries, ARS, and mosaic Turner syndrome (45,X/46,XX).

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Case report

The patient, the oldest of two siblings, was born in 1964 to unrelated parents at term after an uncomplicated pregnancy. Medical history revealed that the patient was 3500 g and 52 cm at birth, the product of a full-term gestation of a 20-year-old primagravida. She was operated on at 4 years of age owing to open patent ductus arteriosus. Duplex collecting system with glomerulosclerosis on left kidney was noted at 28 years of age. There was no family history of ARS.

She received no ophthalmic attention until 29 years of age. In 1993, she presented with photophobia. Her visual acuity was 20/20 in each eye. She had no ocular motility problem. Slit-lamp and gonioscopic examination revealed allergic conjunctivitis, clear cornea, and incomplete development of the anterior chamber with iris stromal hypoplasia and prominent posterior embryotoxon with iris adhesions (Fig. 1). The lens and vitreous were clear bilaterally. Intraocular pressures were 16 mm Hg in the right eye and 15 mm Hg in the left eye and remained under 21 mm Hg without ophthalmic mediation during 8 years of follow-up. Funduscopic examination revealed an indistinctness of the margins of the optic disc, absent optic cupping, elevated optic nerve head surface above the plane of the retina, and a yellow-pink disc (Fig. 2). B-scan ultrasonography showed optic disc drusen bilaterally. Computerized brain tomography showed no intracranial abnormality. Enlarged blind spot and no glaucomatous defect in the visual field examinations were noted during the follow-up.

She was referred to the genetics department at 36 years of age owing to sensorineural hearing loss, short stature, obesity, oligomenorrhea, hirsutism, and mental retardation. Physical examination revealed the following typical features of Turner syndrome: short statue (150 cm) with a weight of 80 kg, webbing of the neck, cubitus valgus, low posterior hairline, widely spaced nipples, stage 1 breasts and axillary hair, excessive pubic hair, extended umbilicus, and maxillary hypoplasia, which was accompanied by such dental anomalies as microdontia, hypodontia, and cone-shaped teeth. Pelvic ultrasound showed an adult uterus with bilateral polycystic pattern of ovaries.

Chromosomes were prepared from phytohemagglutinin antigen–stimulated peripheral blood lymphocyte culture following harvest using the standard procedures. Chromosome analysis showed a normal 46,XX karyotype in 88% of cells and a 45,X karyotype in 12% of the cells (Fig. 3).

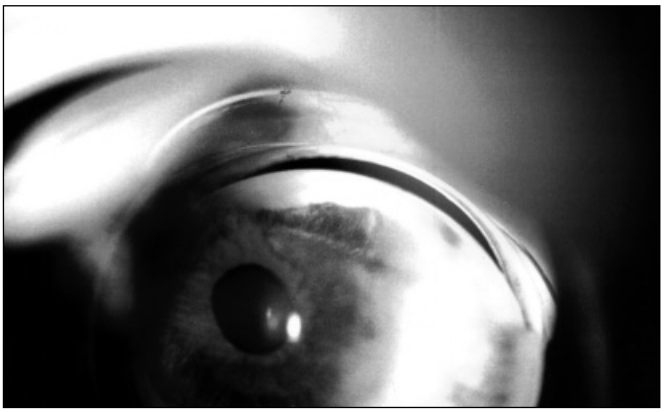

Fig. 1 - *Gonioscopic appearance of anterior chamber with iris stromal hypoplasia, prominent posterior embryotoxon, and iris adhesions.*

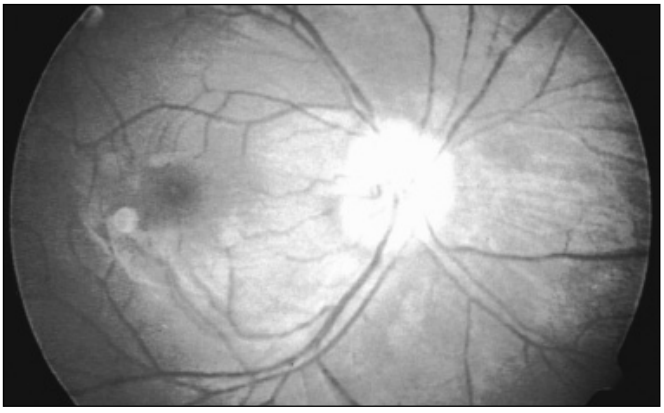

Fig. 2 - *Optic disc drusen.*

Fig. 3 - *Metaphases demonstrate one missing X chromosome. Arrow indicates single X chromosome.*

DISCUSSION

We report a patient with somatic findings and anterior segment dysgenesis who had a karyotype consistent with mosaic Turner syndrome. Iridogoniodysgenesis in association with Turner syndrome has been reported only in a few patients with a mosaic karyotype with a 45,X cell line and a further abnormal cell line (7). Among those patients reported by Lloyd et al (7), two had a 46,X,idic (Y) cell line, one had a ring X cell line, and one had a 47, XXX cell line. However, only one with 45,X/46,X,r(X) karyotype was suggestive of Rieger anomaly. Additionally, that reported patient had some minor dysmorphic features including downslanting palpebral fissures, prominent ears, and cardiac problems. Because of the presence of maxillary hypoplasia and dental anomalies in addition to prominent posterior embryotoxon with iris strands to cornea and iris stromal hypoplasia, that patient was considered to have ARS rather than just the anomaly.

Our patient had classical findings of Turner syndrome, including short stature, cubitus valgus, webbing of the neck, absence of secondary sexual characteristics except excessive pubic hair, extended umbilicus, obesity, oligomenorrhea, hirsutism, and polycystic pattern of ovaries compatible with polycystic ovarian disease. Polycystic ovaries in association with mosaic Turner syndrome has been reported previously (9,10).

Common ophthalmologic findings associated with Turner syndrome are amblyopia, strabismus, blepharoptosis, epicanthus cataract, hypertelorism, and red-green deficiency (6,8,11). Isolated anterior and posterior segment features have been mentioned in previous reports of Turner syndrome, including conjunctival lymphedema (12), intraocular melanoma (13), infectious crystalline keratopathy (14), anterior segment dysgenesis (6), Coats' disease (15), and retinal detachment (11).

Noonan syndrome is a genetic condition inherited in an autosomal dominant manner characterized by the somatic features of Turner syndrome but with a normal karyotype (16). The ophthalmologic and orthoptic findings on 58 patients were investigated by Lee et al (16): hypertelorism, strabismus, amblyopia, prominent corneal nerves, and fundal changes were the leading associated findings.

The incidence of optic disk drusen is 0.1% in the normal population. Swollen discs or disc drusen or both were seen in Noonan syndrome in 4% (16). There is no such reported association with ARS or Turner syndrome. Optic disc drusen in that patient was diagnosed by funduscopic examination with a +90-diopter lens and by B-scan ultrasonography. Additionally, computerized tomography was performed to investigate any intracranial pathology and had normal results.

Approximately 25% of reported cases with ARS might be considered to be sporadic (3). Genetic studies have shown that there is a genetic heterogeneity in this group of disorders including involvement of chromosomes 4, 6, 9, 13, 18, and 21 (17-19). Genetic linkage analysis confirmed mutated gene for ARS (RIEG/PITX2) on chromosome 4 (4q25) (20).

The neural crest cells and mesoderm migrate in to the developing eye after the basement membrane of the surface ectoderm and the lens vesicle separate and the crest cells differentiate to form the trabecular meshwork, corneal endothelium and Descemet membrane, keratocytes, and iris stroma in three waves between the sixth and eighth weeks of embryogenic life (1). It has been proposed that disorders such as Axenfeld-Rieger anomaly and Peters anomaly arise as a result of defective migration of neural crest cells.

The mesodermal derivatives of the anterior segment of the eye, as well as a large portion of the cardiac intraventricular septum, have been shown to arise from neural crest anlage (2). Sensory neurons of the vestibuloacoustic ganglia, which are themselves derived from cephalic ectoderm, seem to rely heavily on underlying neural crest derivatives for appropriate development (2). It has been postulated that defective neural crest migration could be the cause of the secondary anomalies in neighboring ectoderm through the indirect mechanisms leading to associative defects to anterior segment dysgenesis (2). Genetic study of our patient revealed X-chromosome mosaicism. There might be another undetected mutation that is responsible for abnormal neural crest migration within the anterior segment. Congenital heart defects and sensorineural hearing loss can be associated with both Axenfeld-Rieger syndrome and Turner syndrome (2,5,6,8).

It has been suggested that the presence of more than one differing cell line could lead to defective neural crest cell migration that would result in anterior segment dysgenesis. A chromosome analysis is recommended to patients presenting with iridocorneal dys-

genesis or congenital glaucoma. Because ARS is a systemic hereditary disorder, recognition of the ocular malformation should alert the ophthalmologist to investigate possible extraocular malformation in affected individuals, to suggest genetic counseling, and to examine the relatives of the presenting patient.

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