

A Progressive Anterior Fibrosis Syndrome in Patients With Postsurgical Congenital Aniridia

JULIE H. TSAI, MD, JOHN M. FREEMAN, MD, CHI-CHAO CHAN, MD,
GARY S. SCHWARTZ, MD, ELIZABETH A. DERBY, MD, MICHAEL R. PETERSEN, MD, PhD,
AND EDWARD J. HOLLAND, MD

- **PURPOSE:** To report the characteristics of a newly recognized clinical entity in congenital aniridia that we have termed *aniridic fibrosis syndrome*.
- **DESIGN:** Interventional case series.
- **METHODS:** Retrospective chart review of 155 eyes in 80 patients with congenital aniridia was carried out to identify and characterize eyes that had anterior chamber fibrosis. Histopathologic evaluation was performed in three eyes.
- **RESULTS:** Seven eyes in six patients were identified to have aniridic fibrosis syndrome. All eyes had undergone previous intraocular anterior segment surgery, some eyes with multiple procedures. Seven eyes had undergone cataract surgery with posterior chamber intraocular lens; six eyes had undergone previous implantation of tube shunt devices, and four eyes had undergone previous penetrating keratoplasty. Clinically, the syndrome was characterized by a progressive retrolenticular and retrocorneal membrane that caused forward displacement of intraocular lenses. Surgical findings indicated that the fibrotic membrane also can involve the ciliary body and anterior retina. Histopathologic evidence from three eyes indicated that the extensive fibrotic tissue originated from the root of the rudimentary iris and entrapped the intraocular lens haptics. Endothelial decompensation that was subsequent to the formation of the aniridic fibrosis syndrome was seen in all eyes.
- **CONCLUSION:** Aniridic fibrosis syndrome is characterized by the development of a progressive anterior chamber fibrosis. A possible mechanism that promotes the formation of this fibrotic material may be the proximity or touching of intraocular devices on immature vessels in the rudimentary iris found in aniridia. Patients with aniridia with a history of penetrating keratoplasty, intraocular lenses, and tube shunts should be monitored for aniridic fibrosis syndrome; early surgical intervention is

recommended. (*Am J Ophthalmol* 2005;140:1075–1079. © 2005 by Elsevier Inc. All rights reserved.)

CLASSICALLY, CONGENITAL ANIRIDIA CONSISTS OF a clinical triad of foveal hypoplasia, aniridia, and nystagmus.^{1,2} However, the condition is defined more precisely as a spectrum of disease that results from various PAX6 gene mutations that affect a variety of ocular structures and actually may not involve significant changes in the iris structure.^{3–6} Foveal hypoplasia is the limiting factor that determines final visual acuity; however, many patients have cataracts, glaucoma, and aniridic keratopathy that may decrease baseline vision significantly.

Treatment of cataract, glaucoma, and aniridic keratopathy can be addressed successfully with traditional and advanced surgical techniques. Cataracts and glaucoma often require standard surgical treatment, but more difficult cases with zonular compromise necessitate more advanced techniques. Sutured lenses, capsular tension rings, and artificial irides for photophobia and appearance have been used successfully in these patients.^{7–9} Ocular surface reconstruction with limbal stem cell and corneal transplants also has been successful and has made the long-term treatment of aniridic keratopathy possible by restoring limbal stem cell function.^{3,10}

The present study characterizes the development of progressive fibrotic membrane in the anterior chamber of seven eyes in six patients with congenital aniridia who have undergone previous intraocular surgery. This fibrotic membrane appears to originate in the area of the rudimentary iris and can cause anterior displacement of posterior chamber intraocular lenses (PCIOLs) into the cornea and hypotony by posterior extension of the membrane over the ciliary body. We propose the term *aniridic fibrosis syndrome* to describe this clinical entity.

PATIENTS AND METHODS

A RETROSPECTIVE CHART REVIEW WAS COMPLETED ON 155 eyes of 80 patients with congenital aniridia who were seen

Accepted for publication July 9, 2005.

From the University of Cincinnati and Cincinnati Eye Institute, Cincinnati, Ohio (J.H.T., J.M.F., E.A.D., M.R.P., E.J.H.); National Eye Institute, Bethesda, Maryland (C.C.C.); and University of Minnesota, Minneapolis, Minnesota (G.S.S.).

Inquiries to: Edward J. Holland, MD, 580 South Loop Rd, Suite 200, Edgewood, KY 41017; fax: 859-331-9040; e-mail: eholland@fuse.net.

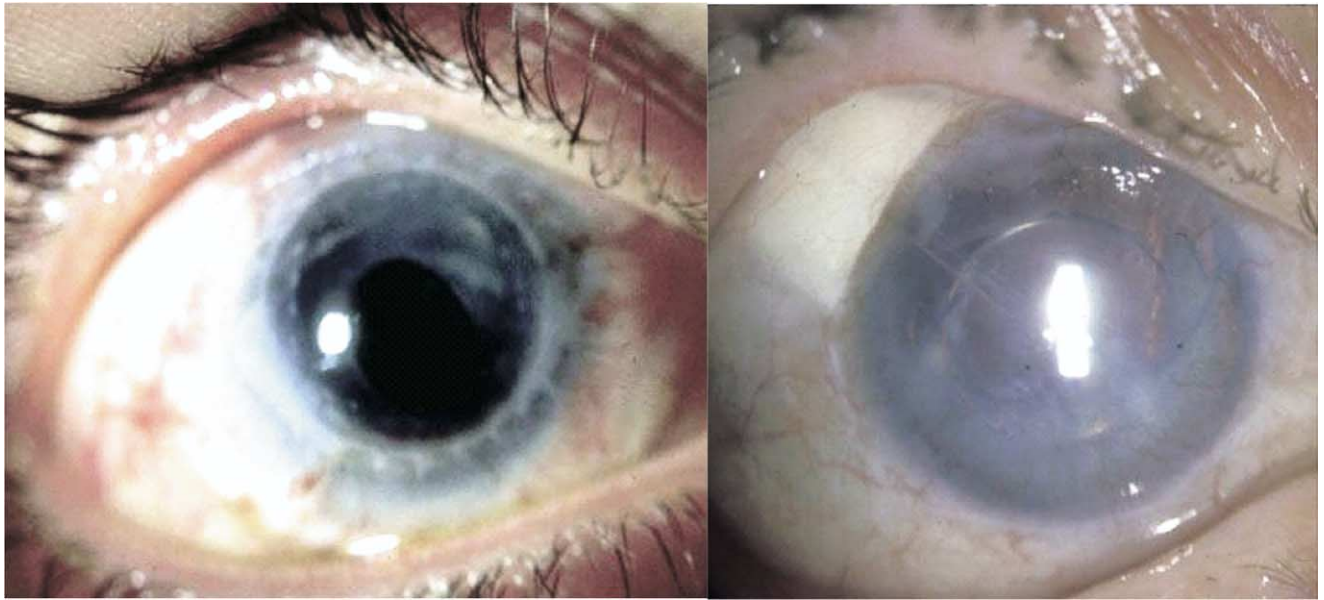


FIGURE 1. Early and late findings of aniridic fibrosis syndrome. (Left) Early fibrosis is noted around the posterior intraocular lens without significant forward displacement of lens. Corneal graft is still clear. (Right) Late fibrosis around posterior chamber intraocular lens results in forward displacement with the intraocular lens embedded in the cornea, which causes endothelial decompensation.

consecutively at the University of Cincinnati and Cincinnati Eye Institute from March of 2000 to June 2002. Five of the patients had undergone previous enucleation of one eye, and data on these eyes were not obtained. The charts of patients who had anterior chamber fibrosis were tagged, and pertinent data were recorded. Parameters that were recorded from the chart included age, sex, Snellen visual acuity, previous ocular surgery, presence of keratopathy, surgical interventions for anterior chamber fibrosis, clinical findings, visual acuity, and histopathologic condition (if available). Snellen visual acuity was recorded as best corrected visual acuity or pinhole visual acuity.

Surgical excision of the fibrotic tissues was performed on three patients. The excised tissue was immediately placed in 10% formalin for fixation and shipped to the National Eye Institute. The samples were bisected. One half of the samples were embedded in paraffin for routine histologic evaluation and immunohistochemistry; the other one half of the samples were embedded in epon for transmission electron microscopy.

RESULTS

- **CLINICAL SPECTRUM:** Seven eyes of six patients, all female, were identified to have aniridic fibrosis syndrome. The patients ranged in age from 9 to 65 years, with a mean age of 41.9 years. All but one eye had previous IOL placement in the ciliary sulcus with the use of an acrylic IOL; the remaining eye underwent implantation of a Morcher polymethylmethacrylate IOL (Morcher GmbH,

Stuttgart, Germany) with associated iris diaphragm. Early findings included thin membranes that covered the anterior and posterior surface of the PCIOL, fibrosis, and the contraction of the lens capsule with mild anterior displacement of the posterior chamber IOL (Figure 1). Late findings included progressive formation of fibrosis with extension of the membrane anteriorly that caused forward displacement and tilting of the PCIOL to and into the cornea and extension of the membrane posteriorly over the ciliary body that caused hypotony (Figure 2).

- **PREVIOUS SURGERY:** All seven of these eyes had undergone previous cataract extraction with posterior chamber intraocular implantation (Table 1). Six eyes had undergone previous tube shunt placement. Four eyes had undergone previous penetrating keratoplasty and keratolimbal allograft (limbal stem cell transplant).

- **HISTOPATHOLOGIC EVIDENCE:** Histopathologic evaluation was performed on three surgical specimens. All three specimens revealed the formation of a dense hypocellular fibrous membrane, with mild vascularization in two specimens (Figure 2). The IOL haptic imprints were present in the membrane. The fibrous membrane appeared to grow from the rudimentary iris. Immunohistochemistry revealed a relative scarcity of infiltrating T cells and macrophages in two of three specimens. Electron microscopy of the membranes indicated an admixture of immature collagen bundles within the mature collagen fibers (Figure 3). No glial, corneal

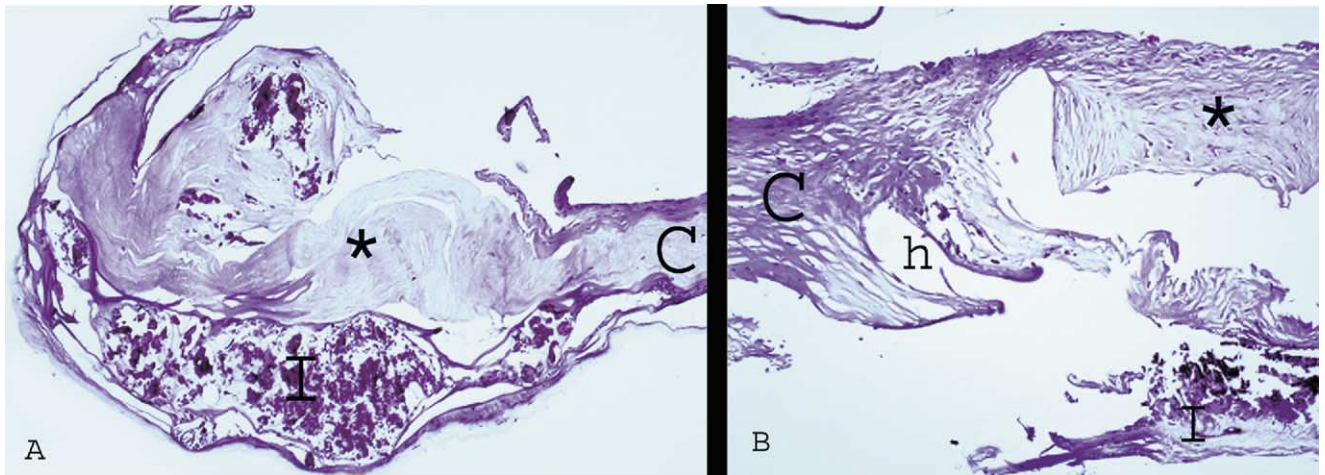


FIGURE 2. Light microscopy of fibrous membrane shows dense hypocellular fibrous membrane (asterisk) with mild vascularization. C = Cornea; h = lens haptic imprint; I = iris root. (Hematoxylin and eosin stain; original magnification, A, $\times 50$; B, $\times 100$).

TABLE 1. Previous Intraocular Surgery in Aniridic Eyes With Progressive Anterior Fibrosis

Previous Surgery	Total Eyes (n/N)
Cataract extraction with PCIOL	7/7
Penetrating keratoplasty	4/7
Glaucoma tube shunt	6/7
Limbal stem cell transplant	4/7

endothelial, lens epithelial, or lens capsular elements were observed.

• **CLINICAL COURSE:** All seven eyes had endothelial decompensation with the occurrence of the fibrosis syndrome. Two eyes had hypotony and traction retinal detachments that were likely secondary to the growth of the membrane posteriorly over the ciliary body and to the vitreous base. Five of seven eyes had surgical intervention, which consisted of penetrating keratoplasty and membranectomy combined with either PCIOL explantation or exchange. Two eyes with retinal involvement had retinal detachment repair at the time of intervention.

Two of the five eyes that underwent surgical intervention had recurrence of the anterior chamber fibrosis. PCIOL exchange and membranectomy were initially performed on the two eyes with recurrence. Subsequent surgical intervention on the eyes with recurrence involved PCIOL explantation combined with membranectomy. No eyes had more than one recurrence. In the two eyes with hypotony, one eye became normotensive after surgical excision of the membranes; the other eye maintained intraocular pressures between 5 and 10 mm Hg.

• **VISUAL ACUITY:** In the five eyes in which vision was recorded in our clinic before the development of aniridic

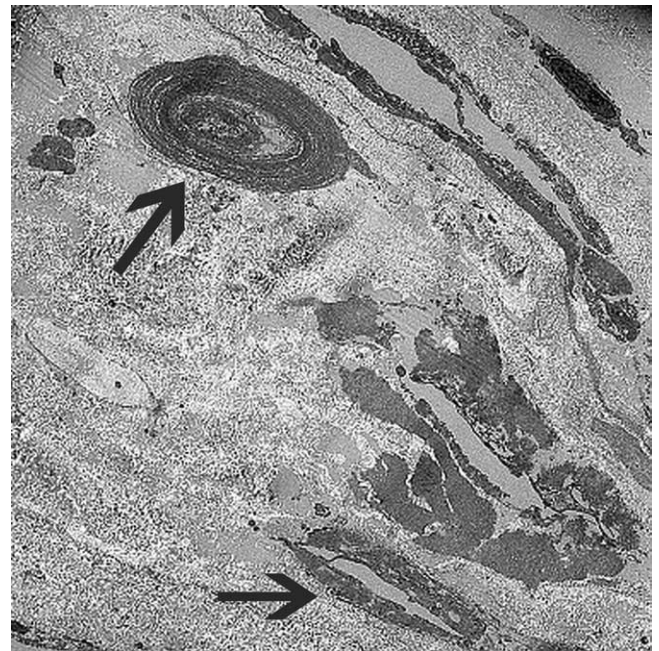


FIGURE 3. Electron microscopy (original magnification, $\times 1000$) of fibrous membrane indicates admixture of immature collagen bundles within the mature collagen fibers. Arrows denote bundles of immature collagen.

fibrosis syndrome, visual acuity declined with the development of aniridic fibrosis syndrome. Of the two eyes that did not have a prior visual acuity recorded (presented with aniridic fibrosis syndrome), per their clinical history, their vision had declined with the development of aniridic fibrosis syndrome (Table 2).

In the five eyes that had surgical intervention, the visual acuity of one eye improved to the previous baseline vision (Table 3). The visual acuity of two eyes improved but did not return to baseline. The two eyes that did have a

TABLE 2. Visual Acuity of Eyes Before and After the Development of Aniridic Fibrosis Syndrome (AFS)

Eye	Pre-AFS	With AFS
1	20/70	20/200
2	20/70	20/400
3	20/160	CF 2 feet
4A	NA	LP
4B	NA	HM
5	20/70	LP
6	20/250	20/400

CF = Counts fingers; HM = hand motion; LP = light projection; NA = not applicable.

TABLE 3. Visual Acuity of Eyes With Surgical Intervention for Aniridic Fibrosis Syndrome (AFS) Before and After Intervention

Eye	Pre-AFS	With AFS	After Intervention*
1	20/70	20/200	20/70
2	20/70	20/400	20/125
3	20/160	CF 2 feet	20/400
4A	NA	LP	HM
4B	NA	HM	20/400

CF = Counts fingers; HM = hand motion; LP = light projection; NA = not applicable.

*The two patients with recurrence of membranes and a second surgical intervention did recover similar visual acuity after the second surgical intervention.

baseline visual acuity recorded had modest improvement of visual acuity after surgical intervention.

DISCUSSION

MANY PATIENTS WITH CONGENITAL ANIRIDIA REQUIRE surgical intervention; most of these patients receive procedures that are related to glaucoma and cataract in their childhood or early adulthood to maintain their baseline vision.^{11,12} Although most patients have favorable outcomes after cataract, glaucoma, or corneal surgery, the authors present a series of eyes that had a fibrotic membrane in the anterior chamber that may represent a late complication of previous surgical procedures. We believe this to be a distinct clinical entity that can be identified properly as a syndrome in patients with congenital aniridia who have undergone previous intraocular surgery. Recognition and characterization of this syndrome provides a clinical benefit.

All of these eyes were pseudophakic, and most of the eyes (6/7) had undergone previous implantation of tube shunt devices for glaucoma. Most of the eyes (4/7) had undergone penetrating keratoplasty and limbal stem cell transplant surgery (that is, keratolimbal allograft). Thus, the syndrome is associated strongly with the presence of intraocular hardware and multiple intraocular surgeries.

This syndrome can be contrasted against other retrocorneal membranes and cyclitic membrane in that it causes the progressive forward displacement of the IOL, which can be dramatic with actual embedding of the IOL into the cornea. It can also involve posterior extension of the fibrosis over the ciliary body, which causes hypotony that is reversible with surgical removal of the membrane. Clinically, the fibrosis caused endothelial decompensation in all patients and, with its progressive nature and potential to extend posteriorly, requires surgical intervention.

On histopathologic evaluation, the membranes were not composed of glial, corneal endothelial, lens capsular, or lens epithelial elements but were composed of small vessels

and immature collagen fibrils. Two of three histologic specimens had a relative scarcity of inflammatory cells, unlike previously reported anterior chamber membranes¹³; one specimen did have associated inflammatory cells.

A possible mechanism for the development of aniridic fibrosis syndrome is the proximity or touching of intraocular hardware on immature vessels in the rudimentary iris of eyes with congenital aniridia. The hardware could provide a stimulus and a scaffold for the development and extension of the fibrotic membrane. A notable feature of aniridic fibrosis syndrome is that the fibrosis occurs in the absence of clinically observable inflammation, as has been reported with anterior fibrosis in noncongenital aniridic patients.¹⁴ Thus, a chronic inflammatory response may not be the essential pathophysiologic basis for the fibrosis. Instead, the fibrosis could be due to improperly regulated developmental mechanisms that are associated with PAX6 gene mutations.

Similar progressive fibrosis has been seen in children who have undergone intraocular surgery for congenital anterior chamber anomalies, such as Peters' anomaly, that are most likely due to PAX6 gene mutations¹⁵ (personal communication, Dr Michael Peterson, September 2003). One explanation for these findings is that PAX6 gene mutations result in a unique vulnerability to a progressive fibrosis in the presence of intraocular hardware and/or surgery. This would be in contrast to anterior chamber fibrosis that is seen after intraocular surgery in patients without PAX6 gene mutations.

Surgical intervention was carried out in five eyes of four patients. Surgical intervention consisted of penetrating keratoplasty, membranectomy, IOL explantation or exchange, and retinal surgery, if required. There were two recurrences after surgical intervention in two of three patients in whom the IOLs were exchanged instead of explanted. The two recurrences required additional surgery to explant the PCIOL. To date, there has not been a second recurrence after lens explantation.

To summarize, aniridic fibrosis syndrome describes a constellation of findings that can occur in patients with congenital aniridia who have undergone previous intraocular surgery. The progressive nature of the syndrome necessitates careful monitoring and surgical intervention. Although the small number of cases does not allow risk analysis for patients with congenital aniridia, we recommend some clinical guidelines for patients with congenital aniridia after intraocular surgery.

Patients with congenital aniridia should be monitored carefully for the development of intraocular fibrosis after intraocular surgery, because the risk of aniridic fibrosis syndrome likely increases with increasing intraocular hardware and/or procedures. Recognition of fibrotic changes should trigger careful monitoring that includes additional modalities (that is, serial A-scan measurements or ultrasonic biomicroscopy) to monitor for progression. If progression of fibrosis is noted, surgical intervention is highly recommended, because early surgical intervention can likely prevent complications that are associated with posterior and anterior extension of the fibrosis. Last, the reduction of intraocular devices (that is, the explantation of IOLs and/or artificial irises) should be strongly considered during surgical intervention.

REFERENCES

1. Nelson LB, Spaeth GL, Nowinski TS, et al. Aniridia: a review. *Surv Ophthalmol* 1984;28:621–642.
2. Gupta SK, De Becker I, Tremblay F, et al. Genotype/phenotype correlations in aniridia. *Am J Ophthalmol* 1998;126:203–210.
3. Holland EJ, Djalilian AR, Schwartz GS. Management of aniridic keratopathy with keratolimbal allograft: a limbal stem cell transplantation technique. *Ophthalmology* 2003;110:125–130.
4. Hill RE, Hanson IM. Molecular genetics of the PAX gene family. *Curr Opin Cell Biol* 1992;4:967–972.
5. MacDonald R, Wilson SW. PAX proteins and eye development. *Curr Opin Neurobiol* 1996;6:49–56.
6. Gomes JA, Eagle RC Jr, Gomes AK, et al. Recurrent keratopathy after penetrating keratoplasty for aniridia. *Cornea* 1996;15:457–462.
7. Burk SE, Da Mata AP, Snyder ME, et al. Prosthetic iris implantation for congenital, traumatic, or functional iris deficiencies. *J Cataract Refract Surg* 2001;27:1732–1740.
8. Osher RH, Burk SE. Cataract surgery combined with implantation of an artificial iris. *J Cataract Refract Surg* 1999;25:1540–1547.
9. Reinhard T, Engelhardt S, Sundmacher R. Black diaphragm aniridia intraocular lens for congenital aniridia: long-term follow-up. *J Cataract Refract Surg* 2000;26:375–381.
10. Mayer KL, Nordlund ML, Schwartz GS, et al. Keratopathy in congenital aniridia. *The Ocular Surface* 2003;1:74–79.
11. Mintz-Hittner H. Aniridia. In: Ritch R, Shields MD, Krupin T, editors. *The glaucomas*. St. Louis: Mosby; 1989. p. 869–884.
12. Mackman G, Brightbill FS, Optiz J. Corneal changes in aniridia. *Am J Ophthalmol* 1979;87:497–502.
13. Chan CC, Fujikawa LS, Rodrigues MM, et al. Immunohistochemistry and electron microscopy of cyclitic membrane: report of case. *Arch Ophthalmol* 1986;104:1040–1045.
14. Taneri S, Gerding HJ. Retinal detachment and phthisis bulbi after implantation of an iris prosthetic system. *J Cataract Refract Surg* 2003;29:1034–1038.
15. Baulmann DC, Ohlmann A, Flugel-Koch C, et al. PAX6 heterozygous eyes show defects in chamber angle differentiation that are associated with a wide spectrum of other anterior eye segment abnormalities. *Mech Dev* 2002;118:3–17.