Congenital Duplication of the Anterior Segment With Central Hamartomatous Plaque

A child born of a full-term pregnancy had unilateral splitting of the anterior segment of the right eye associated with choristoma. No other craniofacial abnormalities were found. The globe was slightly increased in size but was normal in shape. The 2 corneas were separated by a choristoma. Pathological examination revealed splitting of the anterior segment with 2 corneas, 2 lenses, and 2 irides. Only 1 posterior segment was observed, including a hematic vitreous associated with a dysmorphic retina. As diplphalmosis, this congenital malformation may be induced by primary optic vesicle developmental disturbance.

Clinical History. A mature female infant was born at week 41 of gestation in December 1998 with a right eye malformation. The healthy mother, aged 34 years, had experienced only a fever during the first month of the pregnancy. Her 3 previous pregnancies were normal. There was no history of exposure to x-rays or drugs. Routine serologic test results were all negative. An ophthalmologic examination was performed 1 week later. A large, yellow-pink choristoma was localized in the middle of the eye, dividing the globe into a medial eye and a lateral eye (Figure 1). The lid apertures and eye mobility were normal. The cornea of the medial eye was hazy, but there was a noncolobomatous round iris. The cornea of the lateral eye was more transparent, and a noncolobomatous round iris with lens ectopia and cataract was detected. The fundus was not visible. Ultrasonography revealed 2 different lenses, with densification of the anterior vitreous, as seen by direct ophthalmoscopy. Only 1 optic nerve was present. After examination with the patient under general anesthesia, the choristoma was resected. Karyotype analysis was performed, and no anomalies were detected.

By age 6 months, the globe and the lids had increased in size. However, the child experienced ocular exposure. Both orbits were normal in size and shape as determined by computed tomography. Right-sided proptosis was noted, with increased globe size (right, 21 × 22 mm; left, 19.5 × 19.8 mm). A lateral tarsorrhaphy was therefore performed with the patient under general anesthesia.

When the child was 18 months old, she again experienced ocular exposure despite the previous lateral tarsorrhaphy. The palpebral apertures were large. Electrophysiologic features revealed no evoked potential in the right eye (data not shown). Enucleation was performed using a hydroxyapatite-polyglactin 910 (vicryl)–wrapped ball (FCI, Issy les Moulineaux, France) of 18 mm; 6 months later, a lateral canthoplasty was performed to adjust the position of the lids.

Pathological Examination. On gross examination, the first lesion corresponding to the choristoma was flattened and discoid, measuring 7 × 5 × 1 mm. Under light microscopy, the surface was lined by a squamous, poorly keratinized epithelium, devoid of keratohyalin granules. No Bowman membrane could be found between this epithelium and the underlying connective tissue, which contained many capillaries and did not exhibit corneal lamellar organization. The whole lesion was referred to as a dermoid.

On macroscopic examination, the formalin-fixed eye measured 19 mm in diameter (Figure 2). The insertion sites of the 6 external eye muscles were normal. The 2 corneas each measured 7 mm across, and there remained a thin white band between them, corresponding to the base of the previously removed dermoid. Examination of a horizontal section disclosed anterior splitting of the anterior segment. There were 2 distinct 3-mm-diameter lenses. The vitreous was retracted, and the retina was almost completely detached. The space between the detached retina and the sclera was filled with a serous, xanthochromic liquid. The retina was still attached to the optic nerve.
nerve head. Histologic examination disclosed the well-differentiated corneal epithelium, the Bowman membrane, the corneal stroma, and the posterior endothelium on both corneas. The Descemet membrane was normal in the lateral cornea but was irregularly thickened in the medial cornea. The remnant tissue between the corneas was similar to limbus, without the Bowman membrane. The 2 irides were atrophic, and there were histologic hallmarks consistent with a moderate white cataract. In both lenses, the posterior capsule was adherent to disorganized retinal tissue, which has been clinically called densification of the anterior vitreous (Figure 3). In this tissue, only 3 components of the normal retina could be recognized: the outer limiting membrane, the photoreceptor layer, and the outer nuclear layer. They were arranged in ribbons or tubes. “Rosettelike” tubes were empty and likely lined by outer granular layer cells. Other “pseudo-rosettelike” tubes had no lumen, the photoreceptor cells arranging around capillaries (Figure 4). There was 1 vitreous, and behind it was a dysmorphic retinalike tissue, situated in the first segment of the optic nerve, outside the uveal tract, and internal to the lamina cribrosa.

Comment. The eye is a complex structure that originates from primordial tissues derived from a variety of sources, including the wall of the diencephalon, the overlying surface ectoderm, and immigrating neural crest cells. Normal development of the eye depends inter alia on an ordered sequence of induction, so that growth, migration, and differentiation begin in the right place and at the right time and proceed in the right direction. Eye development occurs during the second week of gestation as 2 anterolateral, convex depressions of the neural plate, the optic grooves. They enlarge rapidly during the third or fourth week to form the primary optic vesicles. Throughout its development, the surface ectoderm and several layers of mesoderm form the future lens, cornea, stroma of the iris, and ciliary body structures of the anterior chamber filtration apparatus. Any disturbance in growth during this early period causes serious ocular anomalies. Defects arising later, after further differentiation of the eye has already been accomplished, usually cause less severe but more localized damage. Anophthalmia and congenital cystic eye, cyclopia, synophthalmia, or diplcephalos are classified in major defects. Unilateral diplcephalos is defined by 1 normal and 2 separate eyes from 2 anlagen in 2 orbits with 2 optic nerves, which differs from our case.

We report herein the first case of congenital duplication of the anterior segment associated with...
a dermoid. Dermoids are tumorous growths on the exterior of the eye derived from tissue not usually present. They occur in 1 to 3 of 10,000 live births. Associated ocular abnormalities include cataract and corneal staphyloma, aniridia, congenital aphakia, cataract, and microphthalmia. Experimental studies have described septation of the anterior segment. In 1937, Perri removed an optic vesicle with its ectodermal coverage in Ranu esculenta and Bufo vulgaris, turned it 180°, and reimplanted it. Almost regular double adult eyes were formed with doubling of lenticles, but with just one posterior segment, as a septation of the optic vesicle, which differs from diplophthalmos. Experimental studies suggest that this congenital malformation may be induced by primary optic vesicle development disturbance. Hyperthermia during the first trimester of pregnancy can disrupt normal organogenesis or growth of the primary optic vesicle, and we surmise that this may have been the cause of the malformation noted in our case.

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Papillary Adenocarcinoma of the Iris Transmitted by Corneal Transplantation

To our knowledge, there have been no reports of transmission of a systemic malignancy from a donor to a recipient by corneal transplantation. Known cases of transmission of disease by transplanted corneal tissue have involved infectious agents and 1 case of intraocular tumor. Corneal tissue from donors who have died of malignancy (with the exception of leukemia, lymphoma, and retinoblastoma) has been considered safe for transplantation. In contrast, there have been many reports of transmission of systemic malignancy from donor to recipient by solid organ transplantation. The donor origin of one case of tumor transmission by solid organ transplantation was proven conclusively by DNA typing. We report the first known instance, to our knowledge, of transmission of a systemic malignancy by corneal transplantation, proven by DNA analyses.

Report of a Case. A 22-year-old man sought treatment in June 1992 because of a 2-week history of slight irritation of his right eye and an area of discoloration of his right iris. He had undergone a right corneal graft for keratoconus in November 1990 (19 months previously). The left eye was densely amblyopic and had not been grafted. At a review 2 months prior to the June 1992 visit, the right eye was quiet, with no evidence of a mass, and a corrected visual acuity of 20/20.

Two months later, the visual acuity in the right eye was 20/40 with correction, improving with pinhole to 20/20. There was a vascularized, nonpigmented mass approximately 4.0 × 2.5 mm, arising from the inferotemporal iris between the 6- and 8-o’clock positions and extending into the angle (Figure 1 A). The eye was inflamed, with dilated episcleral vessels adjacent to the mass, keratic precipitates, anterior chamber cells, and an inferotemporal posterior synechiae. Indentent funduscopy revealed a localized retinal dialysis but no evidence of ciliary body involvement. There was no evidence of posterior segment involvement on ultrasound and computed tomography. Results of a full clinical examination were unremarkable, and an

Figure 1. A, Preoperative appearance of the right eye at the initial examination in June 1992. The vascularized, nonpigmented mass can be seen extending from the 6- to 8-o’clock positions on the face of the iris and into the anterior chamber angle. The corrected visual acuity was 20/40 (20/20 with pinhole). B, Postoperative appearance of the right eye in September 1992 showing the iris defect. The graft and the lens are relatively clear. The corrected visual acuity was 20/60.
intensive screen for systemic malignancy was negative. The provisional diagnosis was a granulomatous reaction to a foreign body, although malignancy could not be excluded. During the next week, the mass grew rapidly and it was decided in consultation with the patient and his family to proceed to excisional biopsy.

A partial-thickness scleral incision was made 2 mm from the limbus and a flap was raised, extending into clear cornea. A block of inner sclera including the scleral spur and the trabecular meshwork was excised. The iris was then prolapsed into the wound and a sector including the mass, the adjacent iris root, the face of the ciliary body, and the anterior ciliary processes was removed. The incision was closed and cryotherapy was applied to the posterior wound margin and the area of retinal dialysis. The immediate postoperative course was uneventful apart from a transient hyphema. Three weeks after the operation, the right eye was quiet and the visual acuity was 20/30 with pinhole.

Histologic examination of the iris mass revealed a poorly differentiated adenocarcinoma with associated inflammation. In view of the narrow margins around the mass and the probability of a persistent tumor in the adjacent angle, the patient’s right eye received 10000 rad (100 Gy) of 125Iodine plaque radiotherapy to a depth of 3 mm at the limbus from 4- to 10-o’clock position. At the time of removal of the plaque, a scleral buckle was placed at the site of the retinal dialysis.

At subsequent follow-up, there was a transient fall in visual acuity to 20/60 due to decreased clarity of the corneal graft (Figure 1B). The graft gradually cleared, and at the most recent follow-up nearly 10 years after the initial examination, the best-corrected visual acuity had improved to 20/30. There had been no evidence of primary adenocarcinoma in the recipient at any stage during this follow-up and no evidence of metastasis.

The corneal donor’s medical records were retrieved and reviewed. The donor had impaired vision in both eyes and it was established that an ophthalmic examination had been performed in the weeks prior to death. The results of that examination had revealed bilateral choroidal masses consistent with choroidal metastases. The donor died in November 1990 of disseminated, poorly differentiated adenocarcinoma. The primary tumor was thought to originate from the bowel. An autopsy was not carried out but a percutaneous biopsy of a lung lesion had been performed 6 months prior to the donor’s death. The histologic examination of the specimen showed adenocarcinoma. A small sample of this specimen was still available and, together with the lesion from the recipient’s iris and blood sample, was submitted for genetic analysis. Results of molecular analysis suggested that the recipient’s iris tumor had arisen from the corneal donor.

The recipient of the donor’s other cornea was traced and examined for evidence of tumor. The grafted eye was quiet and clear, with no evidence of tumor transmission. This recipient remained well in this and subsequent follow-up. No other tissues from the corneal donor were used for transplantation.

The biopsy tissue was submitted for routine pathologic examination. For light microscopy, the formalin-fixed tissue was embedded in paraffin and sections were stained with hematoxylin-eosin and a variety of specific commercial immunohistochemical stains.

The DNA was extracted from the tissue samples by incubation at 55°C in the presence of sodium dodecyl sulfate and protease K. Two extractions in phenol-chloroform were followed by a precipitation of the purified DNA in absolute alcohol at −70°C. Patient and donor tissue samples were extracted from paraffin blocks (fresh or fixed unprocessed tissue not required). DNA was amplified and typed at the DQα locus using the commercial Roche molecular systems typing kit (F. Hoffman La Roche Ltd, Basel, Switzerland). The DQ locus on chromosome 6 contains the genes that encode for HLA class II (HLA-D). There are 6 common DQ alleles detected by the kit (DQ 1.1, 1.2, 1.3, 2, 3, 4) that determine 21 possible genotypes. Appropriate negative (water) and positive (known 1.1, 4) controls were used. The reaction mix was amplified using 32 cycles of 94°C for 1 minute, 60°C for 30 seconds, 72°C for 30 seconds, and a final elongation of 72°C for 8 minutes. Amplified DNA was typed using the probing strips with 9 probes on their surfaces23 and a hybridization temperature of 55°C for 20 minutes.

The specimen consisted of a segment of iris and ciliary body structures and the mass, which measured approximately 5 × 3 × 3 mm (Figure 2). Arising from the anterior surface of the iris and extending into the loose iris stroma was a malignant neoplasm with well-
The tumor comprised fibrovascular cores surrounded by focally stratified large epithelial cells with lightly eosinophilic cytoplasm, large irregular ovoid nuclei, and 1 or 2 prominent nucleoli. The cells were nonpigmented and occasional cells were vacuolated. Deeper parts of the tumor contained small solid nests of cells and occasional multinucleated cells. There was a high mitotic rate but no necrosis. The scleral spur was sectioned separately and showed occasional tumor cells adherent to the endothelium and trabecular meshwork but no scleral invasion. The tumor cells stained for cytokeratin but were negative for S100 protein. The tumor was diagnosed as a poorly differentiated adenocarcinoma. Further histologic stains for placenta-like alkaline phosphatase and α-fetoprotein (for testicular carcinoma) and thyroid globulin (for thyroid carcinoma) were negative.

Genetic analysis of the recipient revealed alleles 1.1 and 1.3. The donor analysis revealed alleles 1.2 and 3. The alleles detected in the tumor sample contained both alleles from the recipient (1.1, 1.3) and allele 3, also found in the biopsy sample from the donor (Table and Figure 3). Because of the nature of this testing kit, the 1.2 allele can be hidden in this configuration; thus, its presence cannot be excluded or confirmed in the tumor specimen. To confirm the presence of the 1.2 allele in the iris tumor, DNA sequencing would be required. This was precluded by the small initial sample size.

Comment. The results of the molecular analyses almost conclusively demonstrate that the iris tumor, a poorly differentiated adenocarcinoma, arose from the corneal donor. The presence of the 3 allele in the tumor specimen can only be explained by the presence of donor cells in the tumor. The 1.2 allele was not detected in the tumor because of the typing kit methods. The tissue-typing kit is designed to detect 6 common DQ alleles. In normal circumstances, only 2 alleles would be present, and the kit relies partly on the exclusion of possible alleles for full typing (Table 1 and Figure 3). Therefore, there could have been as many as 4 alleles, the kit was not able to confirm or exclude the presence in the iris tumor of the 1.2 allele from the donor.

The only alternative explanation for the presence of the 3 allele in the iris tumor sample is that there was a mutation in the recipient’s iris tissue of either the 1.1 or 1.3 allele to a configuration that could be read by the 3 probe. Such a mutation would require 5 specific and independent replacement mutations, with the statistical probability that this could happen by chance in less than 1 in 10 million.

Transmission of systemic malignancy by solid organ transplantation has been recognized for many years.24-39 The Cincinnati Transplant Tumor Registry reported 142 cadaver organ donations from patients with unrecognized malignancies, leading to 64 cases of recipient disease (45%).38 Twenty-six (72%) of 36 recipients with distant metastases died of their tumors. Stringent criteria and procedures have been introduced in an attempt to reduce the incidence of this often-fatal complication but occasional cases are still reported.36,39 The tumors most likely to evade detection are small and clinically silent but capable of early metastasis.29,38

The use of closely matched donors and the systemic immunosuppression required for the survival of solid organ transplantations is thought to increase the viability of an inadvertently transmitted malignancy.24,25,29,36 There have been several cases of successful treatment of a transplanted tumor by removing the transplanted organ, withdrawing immunosuppression, and in some cases, adding chemotherapy or radiation.24,25,27,30,34,39 In a previous report, a 57-year-old woman received a closely matched (6 of 6 HLA antigen matched) renal transplant, but 3 months later began to develop complications from what proved to be a malignant melanoma originating from the kidney donor. She died despite treatment, and an autopsy revealed a widely disseminated tumor. The large amount of tissue available made identification of the HLA-DQ alleles and several other polymorphisms feasible. These showed that despite the close
antigen match, the donor and tumor differed from the recipient in 1 HLA-DQ allele. Three of 4 polymorphisms also showed that the donor and tumor were identical but differed from the recipient.20

Our case represents the first documented case of transmission of a systemic malignancy by corneal transplantation. The clarity, avascularity, and small mass of the cornea make the accidental transmission of a viable number of tumor cells very unlikely, and with the exception of 1 case of transmission of retinoblastoma by corneal transplantation reported more than 60 years ago,13 this has never been known to occur. Similarly, there has been no evidence of tumor transmission by transplantation of corneas from donor eyes with primary choroidal melanomas.46 In addition, corneal graft recipients very rarely receive systemic immunosuppression. For these reasons, the exclusion criteria for corneal donors have not been as strict as those for other organ donors.2,17,18

However, the avascularity of the cornea and anterior chamber and the postoperative use of topical steroids may favor tumor transmission. This risk was raised by Zakov et al,44 who described a case in which micrometastases were found close to the excision margin of the corneoscleral button in a donor eye. However, there was no evidence of transmission of malignancy in this case or in a retrospective analysis of 403 cases of corneal transplantation at the Massachusetts Eye and Ear Infirmary (Boston) between 1965 and 1968.45 Since these reports, it has been considered safe to use such donors for corneal transplantation,17,18 with further support from a recent retrospective review of 143 patients.19 However, direct evidence of the malignant potential of micrometastatic tumor cells has been shown.21 Furthermore, anterior chamber–associated immune deviation at least theoretically might explain how situations such as our patient’s arise. Experimentally it has been shown in mice that immune privilege is extended to foreign tumor cells in the anterior chamber. These foreign tumor cells survive and progressively grow in the immune deviant anterior chamber environment.43

In our case, the finding of bilateral choroidal masses in the donor during a clinical examination makes it highly likely that there was metastatic adenocarcinoma in both eyes at the time of death. Presumably there were small numbers of malignant cells adherent to the corneal endothelium at the time of harvesting, and some or all of these cells proliferated in the recipient anterior segment. To date there has been no evidence of extracocular spread.

It is interesting that the tumor did not become apparent for 19 months after the date of transplantation, despite the apparent rapid growth at presentation and the poorly differentiated histologic characteristics. It is well known that even some very aggressive tumors, such as poorly differentiated breast adenocarcinomas, may not recur for up to 5 years after excision of the primary tumor.44

Another factor that may have played a part in this case is that the original implanted tumor cell(s) may not have had a blood supply on the avascular graft endothelium. Their growth may have been slow until a cell reached a vascular supply on the iris or trabecular meshwork. The recipient’s immune system may have partially controlled the tumor while it was small, losing control as it grew bigger.

Evidence from patients with a solid organ tumor who have developed transplanted malignancies shows that it is possible for a competent immune system to overcome such a malignancy if the tumor load is not too great.24,25,27,30,34,39 Such immune modulation of tumor growth is thought to be mediated by natural killer–mediated mechanisms.45 The recommended management is to remove as much of the tumor as possible, withdraw immunosuppression, and consider the use of adjunctive radiation or chemotherapy.24,25,27,30,34,39 The graft recipient in this report had a competent immune system and a poorly matched donor, unlike most solid organ transplant recipients. There was evidence of an immune response to the tumor clinically, prior to excisional biopsy, and on histologic examination. After excision cryotherapy46 and local radiation, the residual tumor load was almost certainly negligible if not nil. After nearly 10 years of careful follow-up, the recipient has remained free of problems. Although we continue to be vigilant, we are increasingly confident that the tumor has been “cured” and that the patient’s immune response has eliminated any remaining tumor cells.

Eye bank procedures currently exclude all donors with proven10-15 or likely potential to transmit disease to recipients.13,17,18,47-49 Although this case demonstrates a new risk of transmission of donor disease to a recipient, it should be interpreted with caution. As many as 40% of donors in most eye banks have died of disseminated malignant tumors and therefore have potential micrometastases to the eye.43 Despite these large numbers of donors, no case of transmission has previously been noted.16,19

At this stage, on the evidence of 1 case, the risk of such transmission must be very low. Even if transmission occurs, the factors of probable poor tissue match, lack of immunosuppression, and small tumor load make the prognosis for patient survival excellent and for retention of the eye good. It would clearly be prudent, however, to exclude potential donors with known ocular metastases. All recipients need careful long-term follow-up and a high degree of suspicion for malignancy in unusual iris presentations.

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through hazy media. A total serous retinal detachment was present. Ultrasound performed a few days later showed a diffuse, irregular mass of the choroid and ciliary body with a maximum height of 9.5 mm (Figure A).

The patient had a 6-year history of chronic lymphocytic leukemia, RAI stage 0 (lymphocytosis only). At an examination by her oncologist 6 months prior to onset of ocular symptoms, she was without symptoms of the disease and taking no systemic medications. Her white blood cell count at that time was 17,000/mm³ (normal, 4,800–10,800/mm³) and her hematocrit was 36.9% (normal, 37%–40%). Three months before the onset of ocular symptoms, her white blood cell count had
decreased to 9900/mm³, and her hematocrit had decreased to 33.7%.

Because of the hypopyon and keratic precipitates, which are rarely found in patients with uveal melanoma, the presumptive diagnosis was leukemic infiltrate of the uveal tract. However, uveal melanoma could not be ruled out. In view of the pain and no potential for vision, and because the uveal tumors were too large for radiotherapy, the right eye was enucleated 7 weeks after the onset of symptoms (Figure, B).

Findings from histologic evaluation showed that the uveal tumor (Figure, C and D) was composed of medium to large cells with scant cytoplasm and vesicular nuclei with areas of clumped chromatin and prominent nucleoli. There were more than 2 mitoses per high-power field (Figure D). Scattered among these tumor cells were tingible body macrophages that produced the starry-sky pattern seen in some high-grade lymphomas, especially those of Burkitt lymphoma (Figure, E).

Immunoperoxidase studies showed that the tumor cells expressed bcl2 (an oncoprotein that inhibits apoptosis) and the B-lymphocyte antigen CD20. They lacked the lymphocyte subset–associated markers CD10, CD5, and TdT, as well as the melanoma markers HMB45 and MART1. Depending on the region of the tumor evaluated, 60% to 90% of the tumor cells were positive for Ki67, indicating a high fraction of proliferating cells. A few admixed nonneoplastic, small T cells (expressing the pan-T-cell antigens CD3 and CD5) were present. The diagnosis was high-grade B-cell lymphoma. The immunophenotype excluded Burkitt lymphoma (which typically expresses CD20, CD10, and, in 100% of cells, Ki67, and which lacks bcl2) and precursor B lymphoblastic lymphoma (which typically expresses CD10 and TdT but not CD20).

Six weeks after the enucleation the patient felt weak and had palpebral axiality and inguinal lymph nodes and splenomegaly. The hematocrit fell to 20% and the white blood cell count rose to 146 000/mm³. Review of a peripheral blood smear revealed 27% neutrophils, 1% bands, 27% lymphocytes, 5% monocytes, 38% blasts, and 2% nucleated red blood cells. The cells counted as blasts were medium to large cells with deep-blue agranular cytoplasm and ovoid nuclei with chromatin that was usually irregularly clumped. Most lacked discrete nucleoli, but occasional cells had prominent nucleoli (Figure, F). The appearance was that of abnormal lymphoid cells similar to those seen in the eye, but not typical of prolymphocytes. Only palliative treatment was administered, and the patient died 4 months after the enucleation.

Comment. About 3% of patients with chronic lymphocytic leukemia develop non-Hodgkin lymphoma (usually large B-cell lymphoma); this sequence of malignancies is called Richter syndrome.1,2 The onset of the lymphoma is usually abrupt. Clinical features include fever, weight loss, increasing lymphadenopathy, lymphocytopenia, and dysglobulinemia.3 Based on studies of immunoglobulin isotypes and gene rearrangements, the lymphoma in most cases of Richter syndrome appears to be the progression of chronic lymphocytic leukemia into a more aggressive tumor; however, in a minority of cases, the lymphoma likely represents a second independently arising tumor.4 We know of only 2 previously reported cases of Richter syndrome that involved the eye. In one case the malignant lymphocytes were confined to the vitreous; in the other, the tumor was in the vitreous and the subretinal space.5 This pattern of involvement is characteristic of retinal/central nervous system lymphoma, a form of lymphoma that is not usually associated with disease outside the central nervous system. Neither case had clinically apparent uveal involvement, and neither case had the rapid downhill course typical after the development of Richter syndrome. In contrast, the lymphoma in our case predominately involved the uveal tract, a feature that correlates with systemic lymphomas.6 The clinical findings mimicked uveal melanoma rather than retinal/central nervous system lymphoma. The patient had a rapid downhill course and died soon after the diagnosis was made. Our case represents what we consider to be a novel presentation of Richter syndrome and demonstrates that Richter syndrome should be included in the differential diagnosis of uveal melanoma.

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Multiple Anterior Chamber Cystic Lesions as the First Sign of Advanced Retinoblastoma

Retinoblastoma (RB) is the most frequently occurring intraocular malignant tumor of childhood.1-3 It occurs bilaterally in 30% to 35% of cases.1,2 A few adult cases have been reported, but onset is very rare in patients older than 5 years.3 Generally, RB is seen with leukocoria or strabismus, and the anterior chamber (AC) is usually clear. In rare instances, the AC may have a pseudo-hypopyon. Cysts in the AC are very rare. We report the case of a 4-year-old boy with bilateral cysts in the AC that was the first sign of RB.
old boy with multiple anterior chamber cystic lesions as the first sign of advanced RB.

Report of a Case. A 4-year-old boy was referred by an ophthalmologist from another hospital for an emergent ophthalmic examination. The child's mother reported a history of a few hours duration of mydriasis and decreased vision in her son's right eye, in which “little white things” were present. The child had no significant natal, medical, developmental, or family history and no previous ocular trauma.

At the time of the examination, the patient's best-corrected visual acuity was counting fingers OD and 20/20 OS. His intraocular pressure was 48 mm Hg OD and 14 mm Hg OS. Mydriasis that was not induced pharmacologically was present in his right eye; extraocular movements were full, and alignment was straight. The left eye was healthy.

Slitlamp examination showed conjunctival hyperemia with papillae and scant purulent discharge. The cornea was clear. There were 4+ cells in the anterior chamber of the right eye, with 20 to 25 small (<0.5 mm), round to oval, white to translucent formations. These lesions moved in the anterior chamber (Figure 1). These lesions were within normal limits, and all serologic studies to detect Toxocara, Toxoplasm, Taenia solium, Taenia echinococcus, Richettsia, Listeria, and Leishmanias were negative.

The child was hospitalized and treated with intravenous mannitol 20%, oral acetazolamide, and topical timolol maleate and dorzolamide hydrochloride to decrease the intraocular pressure. A mass in the right eye, imaged with both computed tomography and ultrasonography, was shown to be a unilateral intraocular calcified lesion. The diagnosis of RB was then made. To our knowledge, the association of this tumor and AC cystic lesions is unique. At this point, we decided to perform a fine-needle aspiration biopsy of the cystic lesions through the cornea to confirm the diagnosis and to rule out an associated disease (eg, parasitic disease or ciliary body medulloepithelioma). Cytologic examination of an aspiration biopsy specimen of the AC revealed atypical cells highly suggestive of RB. Surgical enucleation of the right eye was performed after no metastatic disease was found. We began treatment with 3 cycles of chemotherapy, consisting of vincristine sulfate (1.5 mg/m²), carboplatin (500 mg/m²), and etoposide (150 mg/m² twice daily) in association with amifostine. The patient has been reexamined regularly, and 10 months postoperatively, has had no recurrence, metastasis, or development of a new tumor in the other eye.

On histopathologic examination, the AC showed iris neovascularization and a small amount of loose, brown, rounded cystlike lesions occupying the inferior third. The cystic appearance of the AC lesions was altered during fine-needle aspiration biopsy because of their considerable size. Microscopically, they were composed of small neoplastic cells with hyperchromatic nuclei, scant cytoplasm, and increased mitotic activity (Figure 2).

After surgical excision, gross examination revealed that the ocular tumor was a large mass that filled most of the posterior segment of the right eye. On the cut surface, the mass was firm and grayish-white and had a myxoid appearance. There was extensive retinal detachment (Figure 3). Extensive iris neovascularization and residual distorted cysts were observed in the anterior chamber.

Microscopical features of tumor cells from the enucleated eye were identical to those observed in the cystic lesions. No typical Flexner-Wintersteiner rosettes were present (Figure 4). Immunohistochemical stains for neuron-specific enolase and S100 protein confirmed that the tumor was a neuronal neoplasm consistent with RB. There was no focus of choroidal invasion by neoplastic cells, and the optic nerve was free of tumor.

Comment. The initial signs and symptoms of RB are determined by the extent of the tumor at diagnosis. Clinically, leukokoria and strabismus are the 2 most frequent clinical signs in children with typical RB. More than 50% of all RB is diagnosed following observation of leukokoria. Strabismus is the initial sign in 1 of every 5 patients with RB.1-3

Figure 1. The anterior chamber of the right eye (A and B) contains multiple, small, round to oval, white to translucent formations with a cystic appearance (B, original magnification ×3).
Other less common signs and symptoms include a red, painful eye with glaucoma, poor vision, an orbital cellulitis–like condition, or diffuse ocular infiltration involving the iris, ciliary body, and anterior vitreous. Atypical manifestations of RB, such as pseudohypopyon, hypHEMA, or vitreous hemorrhage, can result in misdiagnosis.

Pseudohypopyon is a level of tumor cells in the AC. A few cases with pseudohypopyon and RB have been reported, but we have not found any cases with cystic lesions in the AC, as in the present case; RB may be mistaken for inflammatory ocular disease, especially if the vitreous has tumor seedings obscuring the view of the retinal mass.

The diagnosis of RB is usually made by fundus examination through a dilated pupil. Noninvasive diagnosis is very important to avoid the potential dissemination of malignant cells. The present case was first misdiagnosed as parasitic endophthalmitis because of the AC lesions and problems visualizing the retinal mass as a result of vitreous haze. Ciliary body medulloepithelioma was also initially suspected because of the cystic formations, but the aspiration biopsy specimen for cytologic analysis of the cysts provided the diagnosis. We believe that through-cornea fine-needle aspiration biopsy has not been reported to increase the risk of dissemination, but it should be avoided if possible.

It is useful to perform a computed tomographic scan of the orbit to determine if the tumor extends to the optic nerve or orbit and whether calcification is present, although in 75% of patients, flocculent calcification is already apparent in plain orbital radiographs.

Different treatment modalities are available for RB, depending primarily on the extent of the tumor. Enucleation, radiotherapy, thermotherapy, cryotherapy, and chemotherapy are used alone or in combination. Enucleation is the treatment of choice for advanced unilateral, nonfamilial disease.

Multiple AC cystic lesions are an unusual initial sign of advanced RB. To our knowledge, this association is unique. A child who seeks treatment with clinical signs and symptoms of any kind of endophthalmitis, including parasitic, should be considered to have RB until proven otherwise. Avoidance of fine-needle aspiration biopsy in these cases is very important.

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Figure 2. Cytologic examination of the anterior chamber cystic lesions after fine-needle aspiration biopsy shows groups of neoplastic cells and red corpuscles (hematoxylin-eosin, original magnification ×100).

Figure 3. Gross examination of the enucleated eye shows an extensive retinal detachment and a large mass filling most of the posterior segment.

Figure 4. High magnification of the retinal tumor shows neoplastic cells with hyperchromatic nuclei, scant cytoplasm, and increased mitotic activity (hematoxylin-eosin, original magnification ×250).
Evaluation of Lenticular Irregular Astigmatism Using Wavefront Analysis in Patients With Lenticonus

Analysis of corneal topography is becoming more common for evaluating corneal irregular astigmatism. However, irregular astigmatism can also arise from the crystalline lens. An irregular reflex on retinoscopy with normal corneal topography or an abnormal lens contour on slitlamp examination strongly suggests the existence, and gives an estimate of the degree, of lenticular irregular astigmatism. However, it is difficult to evaluate lenticular irregular astigmatism qualitatively and quantitatively. Two cases of lenticonus in patients with Alport syndrome are presented to show that wavefront sensing can be used to evaluate lenticular irregular astigmatism.

Report of Cases. Case 1. A 52-year-old man sought treatment at our clinic because of a gradual decrease in his vision. His visual acuity was 20/20 OD with a refractive error of −13.5 diopters (D) sphere and −3.5 D cylinder at 5° and 20/25 OS with a refractive error of −14.5 D sphere and −0.75 D cylinder at 170°. Slitlamp examination revealed bilateral anterior lenticonus (Figure 1A).

Case 2. A 21-year-old man was diagnosed with Alport syndrome. He had received a kidney transplant from his father to treat renal failure. He sought treatment for ocular complications at our clinic. His vi-

Figure 1. Digitally processed slitlamp photographs of the anterior lenticonus show marked anterior protrusion of the anterior surface of the lens in patients 1 (A) and 2 (B).
indicates spherical-like aberrations. These findings indicate that the irregular astigmatism in lenticonus arises from the lens.

For both patients, videokeratography and wavefront aberrometry were performed with a wavefront analyzer (KR-9000PW; Topcon Corporation, Tokyo, Japan) to determine simultaneously the corneal irregular astigmatism and the irregular astigmatism in refraction (Figure 2 and Figure 3). Maps of higher-order aberrations due to the anterior corneal surface (C) indicates minimum higher-order aberrations, and the map of ocular higher-order aberrations (F) indicates spherical-like aberrations. These findings indicate that the irregular astigmatism in lenticonus arises from the lens.

Figure 2. A mire image (A), color-coded maps of the anterior corneal surface (axial power) (B) and corneal higher-order aberrations (C), a Hartmann-Shack data image (D), and color-coded maps of total ocular wavefront (E) and ocular higher-order (F) aberrations in a patient with lenticonus (patient 1). The map of higher-order aberrations due to the anterior corneal surface (C) indicates minimum higher-order aberrations, and the map of ocular higher-order aberrations (F) indicates spherical-like aberrations. These findings indicate that the irregular astigmatism in lenticonus arises from the lens.

Snellen acuity was 20/25 OD with a refractive error of −2.5 D sphere and −0.25 D cylinder at 180° and 20/20 OS with a refractive error of −2.25 D sphere and −0.75 D cylinder at 175°. Slitlamp examination revealed bilateral anterior lenticonus (Figure 1B). Dot-and-fleck retinopathy was detected in both eyes.

For both patients, videokeratography and wavefront aberrometry were performed with a wavefront analyzer (KR-9000PW; Topcon Corporation, Tokyo, Japan) to determine simultaneously the corneal irregular astigmatism and the irregular astigmatism in refraction (Figure 2 and Figure 3). Maps...
from a patient with keratoconus (Figure 4) and maps of an emmetropic eye (Figure 5) are shown as examples of a corneal irregular astigmatism and a healthy control, respectively.

The maps of the eyes with lenticous showed a relatively uniform pattern, indicating that the corneal higher-order aberrations were within the normal range (Figure 2C and Figure 3C). The map of the keratoconic eye showed a faster wavefront superiorly and a slower wavefront inferiorly, indicating corneal irregular astigmatism with a dominance of coma-like aberration (Figure 4C).
For all patients except the patient with emmetropia, the maps for total ocular aberrations showed cooler colors in the center, indicating that the refractions of these eyes were myopic (Figures 2E, 3E, and 4E). The map of ocular higher-order aberrations for the keratoconic eye (Figure 4F) had a pattern similar to the one seen on the corneal higher-order aberrations map (Figure 4C), suggesting that the irregular astigmatism in keratoconus arises from the cornea.

In the lenticular eyes, however, the maps of the higher-order ocular aberrations showed a domi-
of the irregular astigmatism in re-
expression of spherical-like aberrations
(Figure 2F and Figure 3F). Because the corneal irregular astigmatisms were within the normal range in these eyes, we deduce that most of the irregular astigmatism in refraction originated from a lenticular component.
The root mean square values of the higher-order aberrations for 4-mm- and 6-mm-diameter pupils are shown in the Table. As shown in the color-coded maps, ocular spherical-like aberrations were dominant in the lenticular eyes, and corneal and ocular coma-like aberrations were dominant in the keratoconic eye.

Figure 5. A mire image (A), color-coded maps of the anterior corneal surface (axial power) (B) and corneal higher-order aberrations (C), a Hartmann-Shack data image (D), and color-coded maps of total ocular wavefront (E) and ocular higher-order (F) aberrations in a patient with emmetropia. The maps of corneal (C) and ocular (F) higher-order aberrations show no signs of irregular astigmatism.
**Higher-Order Aberrations in 2 Patients With Lenticonus, a Patient With Keratoconus, and a Healthy Control**

<table>
<thead>
<tr>
<th>Vision</th>
<th>Corneal Coma S3</th>
<th>Spherical S4</th>
<th>Total S3+S4</th>
<th>Ocular Coma S3</th>
<th>Spherical S4</th>
<th>Total S3+S4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day, 4-mm-diameter pupil</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenticonus, patient 1</td>
<td>0.02</td>
<td>0.10</td>
<td>0.10</td>
<td>0.41</td>
<td>0.88</td>
<td>0.97</td>
</tr>
<tr>
<td>Lenticonus, patient 2</td>
<td>0.10</td>
<td>0.08</td>
<td>0.13</td>
<td>0.47</td>
<td>0.72</td>
<td>0.86</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>1.06</td>
<td>0.32</td>
<td>1.10</td>
<td>1.02</td>
<td>0.41</td>
<td>1.10</td>
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<tr>
<td>Control</td>
<td>0.08</td>
<td>0.07</td>
<td>0.11</td>
<td>0.14</td>
<td>0.06</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Night, 6-mm-diameter pupil</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenticonus, patient 1</td>
<td>0.15</td>
<td>0.44</td>
<td>0.47</td>
<td>0.64</td>
<td>2.24</td>
<td>2.33</td>
</tr>
<tr>
<td>Lenticonus, patient 2</td>
<td>0.35</td>
<td>0.34</td>
<td>0.49</td>
<td>0.70</td>
<td>1.31</td>
<td>1.48</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>4.46</td>
<td>1.05</td>
<td>4.59</td>
<td>3.97</td>
<td>0.78</td>
<td>4.05</td>
</tr>
<tr>
<td>Control</td>
<td>0.41</td>
<td>0.28</td>
<td>0.50</td>
<td>0.42</td>
<td>0.24</td>
<td>0.48</td>
</tr>
</tbody>
</table>

S indicates the root mean square of x-order aberrations.

**Comment.** Wavefront sensing enables us to evaluate irregular astigmatism qualitatively, from the color-coded maps of the higher-order wavefront aberrations, or quantitatively, as a set of Zernike coefficients. However, the higher-order aberrations or irregular astigmatism are made up of corneal and lenticular components. Although corneal topography is usually designated by powers, higher-order wavefront aberrations due to the cornea can be quantified by calculating a set of Zernike coefficients. By comparing higher-order aberrations in refraction with those due to the cornea, lenticular irregular astigmatism can be estimated.

It is clinically important that we easily recognize the relationship between the characteristics of the higher-order aberrations and the location of the shape abnormality by using color-coded maps of ocular higher-order aberrations. Irregular astigmatism induced by lenticonus is a relatively symmetrical, spherical-like aberration because the protrusion of the anterior lens surface and under sclerosis are the center. In contrast, irregular astigmatism in typical keratoconus is an asymmetrical, coma-like aberration due to the displacement of the cone.

To determine the source of irregular astigmatism, it is important to separate the higher-order aberrations of the cornea from those of the lens. For this purpose, we believe that it is very important to view simultaneously the map of corneal higher-order aberrations produced by corneal topographic analysis and the map of ocular higher-order aberrations produced by wavefront sensing. In our study, a combination of anterior corneal topography and wavefront aberrometry was used. Therefore, higher-order aberrations due to the lens were estimated indirectly. Artal et al. more accurately showed the relative contribution of the corneal surface and the internal optics of the eye to the ocular aberrations by immersing the eye in isotonic sodium chloride solution during wavefront sensing. Many questions about lenticular irregular astigmatism, such as the aging effect of the lens, residual irregular astigmatism with contact lens wear, and the effects of intraocular lens design, are still unanswered. Studies of the simultaneous measurements of corneal higher-order aberrations and higher-order aberrations of the eye will make it possible to answer these questions.

**Lens Subluxation Following Contact Transscleral Cycloidiode**

Diode laser cyclophotocoagulation is increasingly used in the treatment of refractory glaucoma due to its simplicity of use and effectiveness. Complications include iritis, hyphema, pupillary distortion, staphyloma formation, scleral perforation, and phthisis bulb. We report a case of lens subluxation following transscleral cycloidiode laser treatment.

The table above shows the higher-order aberrations in 2 patients with lenticonus, a patient with keratoconus, and a healthy control. The values are given in micrometers (µm) and indicate the root mean square (RMS) of each aberration type. Higher-order aberrations are discussed in detail in the text, with a focus on the differences between corneal and lenticular contributions. The Comment section highlights the importance of wavefront sensing in evaluating irregular astigmatism and compares it with corneal topography. The Lens Subluxation Following Contact Transscleral Cycloidiode section mentions complications of this procedure and presents a case report.

Report of a Case. A 61-year-old woman with hypermetropia came to the eye casualty with a 3-week history of reduced vision (hand movements) in her left eye due to neovascular glaucoma secondary to central retinal vein occlusion. Her fellow eye was normal. She underwent argon laser panretinal photocoagulation twice, with no regression of rubeosis. Because the cornea showed signs of early decompensation due to persistently raised intraocular pressure (IOP), transscleral cyclodiode laser was performed. The standard probe (quartz G-probe attachment of the Iris medical-Oculight SLx diode laser; Iris Medical Instruments Inc, Mountain View, Calif) was used for 15 applications of 1.5 seconds' duration, to a total of 2 treatments but lens subluxation followed the ciliary body. The IOP remained raised and laser treatment was repeated with settings of 2.5 to 3 W, each of 1.5 seconds' duration, to a total of 2 treatments superiorly and 2 inferiorly (80 laser burns) during a 6-month period. No blood or pigment was noted on the probe during any treatments. There was no history of ocular trauma at any time.

Following the fourth application, the IOP was well controlled without treatment and the cornea was clear. Seven weeks after the last laser treatment, the patient was found to have a 180° superior zonular dehiscence and lens subluxation inferonasally (Figure), with vitreous prolapse into the anterior chamber. The limbal sclera was then noted to be thinned superiorly and inferonasally. There were no signs of phacolytic glaucoma or persistent uveitis.

Comment. Transscleral diode cyclophotocoagulation is an effective and popular method of management of glaucoma that is unresponsive to conventional treatment. Its IOP-lowering effect is due to coagulation necrosis of the ciliary epithelium. Laser treatment can be performed in a contact or noncontact mode but the former has better scleral transmission and thus uses less energy.1 Owing to the rarity of severe adverse effects, repeated use of this treatment is common.

Staphyloma formation,2 scleral perforation,3 and phthisis bulbi caused by scarring of the angle structures3 are recognized complications but lens subluxation following contact cyclodiode has not been reported to our knowledge. Our patient did not have preexisting risk factors, ie, zonule weakness and scleral thinning. Laser treatment was repeated to reduce IOP and prevent bullous keratopathy. Zonular dehiscence and lens subluxation presumably occurred because of laser-induced damage of the ciliary body and zonules.

At the time of this report, since our patient has no useful vision in this eye, isolated lens subluxation has not caused her significant problems. However, diode laser is used to treat glaucoma in eyes with good vision. Where repeated treatments are necessary, the patient should be warned of the risk of lens subluxation and secondary complications, such as pupil block, corneal touch, phacolytic glaucoma, and uveitis. Avoiding contact laser in patients with zonular abnormality and scleral thinning has been recommended.3 If absolutely necessary, lower energy should be used and care should be taken to avoid pathologic areas.

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Cartilage in the Anterior Lens Capsule of a Diabetic Patient

Posterior capsular opacification (PCO) is the most common complication of cataract surgery. It occurs in as many as 30% of patients within the first 2 to 3 years following the procedure.1

Lens capsule opacification appears to be caused by lens epithelial cells (LEC) retained in the capsular bag after surgery. Remnant LEC may undergo regression or, alternatively, proliferate, migrate, and transdifferentiate to myofibroblasts in a process called epithelial-mesenchymal transition. Myofibroblasts are spindle-shaped cells that express the α smooth muscle actin.
α-SMA) and secrete large amounts of extracellular matrix, including collagen types I, III, and IV. Epithelial-mesenchymal transition is usually associated with fibrosis and wrinkling of the lens capsule. Unaltered nontransformed LEC do not produce extracellular matrix and do not express α-SMA.

The clinical and histopathologic findings in a diabetic patient with marked anterior and posterior capsule opacification are presented. Histopathologic evaluation of a specimen obtained from the anterior lens capsule disclosed the unusual finding of cartilaginous tissue.

Report of a Case. A 54-year-old white woman with a 10-year history of type 2 diabetes mellitus was referred to the Medical Retina Service at Aberdeen Royal Infirmary (Aberdeen, Scotland) in October 2000 for evaluation of bilateral diabetic macular edema. Her ocular history was remarkable for bilateral cataract extractions for congenital cataracts, which were performed in 1991 (right eye) and 1994 (left eye).

A polymethyl methacrylate intraocular lens (IOL) had been implanted following extracapsular cataract extraction by nuclear expression in the right eye. A silicone IOL (S30; Allergan Medical Optics, Irvine, Calif) had been used following phacoemulsification in the left eye. No other congenital or developmental eye abnormalities, such as persistent hyperplastic primary vitreous, had been detected. Posterior capsule opacification occurred in both eyes 1 year after cataract surgery, requiring bilateral Nd:YAG laser posterior capsulotomies. Twelve months after this procedure, PCO was again noted in both eyes, and Nd:YAG posterior capsulotomies had to be repeated.

On examination, her best-corrected visual acuity was measured at 20/120 OU. Intraocular pressures were normal. Slitlamp examination disclosed bilateral pseudophakia and severe bilateral anterior capsular thickening and phimosis that was more pronounced in the left eye. A small posterior capsulotomy was present in each eye. On fundus examination, bilateral clinically significant macular edema was suspected, although the view of the retina was poor owing to anterior and posterior capsular thickening and phimosis.

A Nd:YAG anterior capsulotomy was performed in the left eye in an attempt to enlarge the anterior capsule opening prior to retinal photocoagulation for clinically significant macular edema. However, the Nd:YAG laser failed to achieve any rupture of the anterior capsule, and surgical discission was required. Intraoperatively, the anterior capsule appeared white, had a rubbery consistency, and was extremely thick and hard (Figure 1), making it very difficult to excise. A specimen of the anterior lens capsule was sent for histopathologic evaluation.

Light microscopy revealed a thickened anterior lens capsule and mature hyaline cartilage (Figure 2).

Comment. The patient described in this report had marked anterior and posterior lens capsule opacification and severe capsular phimosis. Rapid proliferation of LEC and capsule opacification following Nd:YAG
laser capsulotomy in patients with retinal pathology has been reported. Thus, the diabetic maculopathy present in this case and the fact that Nd:YAG capsulotomies had been performed twice might have been contributing factors to the pronounced capsule opacification present. It has also been shown that, in organ cultures, LEC proliferate more rapidly when a high concentration of protein is present in the culture medium. This could explain the increased rate of PCO observed in patients with diabetes, in whom an increased protein content in the aqueous humor has been detected, and it is likely that it could have contributed to the capsular thickening observed in our case. Furthermore, patients with diabetes seem to be more prone to developing fibrotic changes in the lens capsule, rather than Elschnig pearls.

Fibrotic changes in the lens capsule occur in the process of epithelial-mesenchymal transition, a well-known phenomenon observed in many ocular tissues and in tissue cultures. Epithelial-mesenchymal transition appears to be involved in the pathogenesis of anterior subcapsular cataract and PCO. The process of epithelial-mesenchymal transition seems to be driven by cytokines, of which transforming growth factor β, which is also present in the aqueous humor, is the most important. Studies on human capsular bags have shown that different parts of the lens capsule have different histopathologic characteristics, which could be at least partially related to being exposed to different environments (ie, the anterior capsule is probably more exposed to the aqueous humor and its cytokines than the posterior capsule, which is relatively protected by the IOL).

To our knowledge, the finding of cartilage in the anterior lens capsule in humans has not been previously reported. It could be hypothesized that residual LEC could have undergone metaplasia when stimulated by various intraocular cytokines, becoming chondrocytes. In this regard, it is interesting to note that cartilage matrix proteins, including proteoglycan core protein, link protein, and cartilage-matrix protein (CMP) have been found in the embryonic chick lens capsule. It is unknown whether LEC can undergo transformation into cartilage cells under the influence of an altered microenvironment. Since lens capsules from diabetic patients with capsule thickening are rarely available for histopathologic evaluation, it is also difficult to judge whether this was an exceptional case or whether cartilage can be found in some patients with marked lens capsule opacification. Further clinico-pathologic studies may give more insight into this unusual phenomenon.

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Bilateral Epithelial Downgrowth Managed in One Eye With Intraocular 5-Fluorouracil

Epithelial downgrowth into the anterior chamber is an extremely rare complication of intraocular surgery. Epithelial cells gain access via incisional defects or by direct implantation at the time of surgery. The tissue can grow in the form of cysts or as layered sheets. If these sheets are left untreated, devastating complications such as intractable glaucoma and retinal detachment result in destruction of the eye.

Historically, the preferred treatment methods are surgical. Weiner et al suggested that combining antimetabolites with surgical treatments might be superior to surgery alone in controlling the disease. There are reported cases of the use of multiple subconjunctival injections of substantial amounts of 5-fluorouracil to control the disease. However, these failed once the injections were stopped.

Report of a Case. A 70-year-old, aphakic white woman underwent penetrating keratoplasty (PKP) for interstitial keratitis in 1994 in the right eye and 2 years later in the left eye. In 1997, slitlamp examination of the left eye showed a retrocorneal membrane without a clear site of origin. Argon laser photoagulation confirmed the presence of epithelial downgrowth, and ultrasonic biomicroscopy showed anterior synchiae. Repeat PKP was performed in combination with anterior vitrectomy, release of anterior synchiae, and cryopexy. Histopathological examination of the host corneal button showed stratified epithelial tissue extending along the posterior surface of the cornea. Epithelial downgrowth occurred in 1998, and a repeat PKP combined with anterior vitrectomy and cryopexy were done but failed to prevent recurrence. In 1999, cyclotherapy and repeat PKP were performed. Histopathological examination of each of the corneal buttons showed the typical extensive stratified squamous epithelium along the posterior corneal...
The left eye was ultimately lost to epithelial downgrowth and secondary retinal detachment.

In 1999, the patient experienced graft rejection in the right eye and a repeat PKP was done. Postoperatively, vitreous incarceration in the superior aspect of the graft was managed with pars plana vitrectomy. Thereafter, the intraocular pressure remained elevated despite maximum medical therapy and was successfully controlled with implantation of an Ahmed valve in October 2000. The patient returned 1 month later with complaints of blurry vision. Slitlamp examination showed a retrocorneal membrane. The membrane originated temporally and was thought to be from the site of the paracentesis done at the time of the suture surgery. Internal cryopexy was performed but failed to halt extension of the membrane (Figure 1). In December 2000, one anterior chamber injection of a low dose (0.2 mg) of 5-fluorouracil,4 with a sodium hyaluronate (Healon-GV; Pharmacia Canada Inc, Mississauga, Ontario) pupillary plug, was performed in an attempt to retain the 5-fluorouracil in the anterior chamber and minimize its diffusion into the vitreous. This failed to halt the extension of the membrane. The injection was repeated with a higher dose of 5-fluorouracil (1 mg) mixed with chondroitin sulfate–sodium hyaluronate (Viscoat; Alcon Laboratories, Fort Worth, Tex) after a temporal paracentesis. The mixture was applied directly to the epithelial membrane, which was viscodissected from the posterior corneal surface (Figure 2). Viscodissection was achieved by lifting the edge of the membrane with the cannula and using the viscoelastic–5-fluorouracil mixture to separate the epithelial membrane free of the posterior corner. The chondroitin sulfate–sodium hyaluronate was left in the eye, and there were no problems with elevated intraocular pressure after this treatment. Five months after this treatment, there was no recurrence of the membrane, but a repeat PKP was done in May 2001 for graft failure. Histopathological examination of the host corneal button did not show epithelial downgrowth but showed remnants of a fibrous network. There was no recurrence after this second treatment with 5-fluorouracil during 14 months of follow-up.

Comment. To our knowledge, there are no previous reports of noncongenital bilateral epithelial downgrowth and no reports of treatment using anterior chamber injections of 5-fluorouracil. In the present case, surgical treatment of epithelial downgrowth in the left eye failed to control the disease, resulting in loss of that eye. However, in the right eye, 2 anterior chamber injections of a total of 1.2 mg of 5-fluorouracil, the latter mixed with a viscoelastic and combined with viscodissection of the membrane itself, were successful in halting the disease process and preventing recurrence 14 months after the treatment. The advantages of intraocular injections include direct delivery of 5-fluorouracil to the actively proliferating membrane. This allowed use of a substantially smaller effective dose of 5-fluorouracil, compared with subconjunctival injections, and potentially decreased the risk of toxic side effects to the cornea.2,3 Finally, the small number of injections was easily performed and well tolerated. Intraocular injections of 5-fluorouracil may be a viable treatment option for epithelial downgrowth in selected patients.
Bilateral Subperiosteal Orbital Hematomas and Henoch-Schönlein Purpura

There are few reports of nontraumatic bilateral subperiosteal orbital hematomas in the ophthalmic literature. None exist on subperiosteal orbital hematomas associated with Henoch-Schönlein purpura.

Report of a Case. A 5-year-old boy with a known case of infantile spasms since birth visited with bilateral exophthalmos of a few days’ duration. Ocular examination revealed bilateral upper eyelid ecchymosis and exophthalmos mostly on the right side, with no afferent pupillary defect (Figure 1). There was no history of trauma. Physical examination revealed a purpuric rash on the buttocks and lower extremities, abdominal tenderness, and bilateral ankle swelling and tenderness. Computed tomography (CT) scans of the orbits revealed well-defined, nonenhancing, bilateral superior orbital masses with no bone erosion (Figure 2). Hematuria was noted on urinalysis, but systemic workup, including coagulation studies, was normal. A diagnosis of Henoch-Schönlein purpura with bilateral orbital hematomas was entertained. Orbital magnetic resonance imaging (MRI) at follow-up confirmed the diagnosis and showed improvement. There was an uneventful recovery, with marked resolution of the exophthalmos 2 weeks following initial visit.

Comment. Henoch-Schönlein purpura is a systemic hypersensitivity disease of unknown origin, with common vasculitis in childhood. The clinical diagnosis relies on a classic tetrad of purpuric rash, arthralgias, abdominal pain, and renal involvement. A kidney or skin biopsy specimen demonstrating IgA deposition can be helpful in atypical cases. Although Henoch-Schönlein purpura is not usually associated with frank bleeding, there are reports of associated intracerebral, scrotal, intestinal, and adrenal gland hematomas. To our knowledge, there are no previous reports on Henoch-Schönlein purpura and orbital hematomas.

Orbital hematomas are most commonly traumatic in origin but can occasionally be spontaneous or secondary to increased central venous pressure, extension from chronic sinusitis, and blood dyscrasias. Few reports of bilateral nontraumatic orbital hematomas are found in the literature, and they are mainly in association with alcoholic liver disease, scurvy, and disseminated intravascular coagulation.
travascular coagulation. The resulting exophthalmos in children can sometimes pose a diagnostic challenge, as the rapid presentation might resemble an orbital malignancy.

The subperiosteal space is a potential space bridged by small irregular diploic vessels. Bleeding into this space commonly manifests as painful proptosis with eyelid edema and conjunctival chemosis. The most common location for subperiosteal hematomas is the superior orbit. However, rare reports of medial and lateral subperiosteal orbital hematomas are present. Orbital hematomas most commonly occur in children and young adults because the periorbita is less firmly adherent to bone in this age group. On CT scan, appearance of acute subperiosteal orbital hematoma is a biconvex, well-defined, nonenhancing mass of homogeneous density that is slightly higher than that of the brain. In most cases, CT scan images are sufficient to seal the diagnosis. Confirmation can be obtained on MRI, which can characterize the different stages of blood degradation.

Because most of these hematomas usually resolve within a few weeks, conservative management is acceptable as long as normal optic nerve function is documented. Fine-needle aspiration and surgical drainage should be considered in cases of compression of the optic nerve.

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Temporary Tarsorrhaphy: A Valuable Procedure in Hansen Disease

The temporary tarsorrhaphy technique described by Kitchens et al in the February 2002 issue of the ARCHIVES1 is, in our experience,2 a remarkably useful technique to promote corneal healing, particularly in patients with Hansen disease. Corneal anesthesia and impaired orbicularis oculi function with secondary impairment of tear drainage can culminate in severe corneal ulceration, which often fails to respond to conventional therapy. Temporary tarsorrhaphy, which can easily be opened for inspection and reclosed, promotes rapid healing in almost every case when other strategies have failed. We have even seen large descemetoceles heal without additional intervention. In our practice, we use a bow to allow frequent opening, inspection, and reclosure. The drawstring method of securing the suture described by Kitchens et al represents an innovative and useful development of the technique.

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Error in Signature. In the Clinicopathologic Reports, Case Reports, and Small Case Series by Mouriaux et al titled “Congenital Duplication of the Anterior Segment With Central Hamartomatous Plaque,” published in the October 2002 issue of the ARCHIVES (2002;120:1377-1379), an error occurred in the signature. On page 1379, the signature should have appeared as follows: Frédéric Mouriaux, MD, Marie-Paule Leroy-Rattier, MD, Claude-Alain Maurage, MD, and Françoise Guilbert, MD, Lille, France; Ian Cree, PhD, FRCPath, Portsmouth, England; and Jean François Rouland, MD, Lille. The journal regrets the error.