

Late Malignant Melanoma After Treatment of Rhabdomyosarcoma of the Orbit During Childhood

A 27-year-old woman developed malignant orbitoconjunctival melanoma in her left eye 21 years after treatment of a left orbital embryonal sarcoma with systemic chemotherapy and radiation therapy to the orbit. The coexistence of these 2 malignancies in the same orbit is very rare. It may be coincidental, but a genetic predisposition or late adverse effects of childhood cancer treatments cannot be excluded.

Second malignant tumors can occur in patients treated for retino-

blastoma during childhood,¹ but other multiple ophthalmic malignancies in the same patient are a very rare occurrence. We report the case of a patient who had 2 distinct tumors involving her left orbit. A childhood sarcoma was followed 21 years later by a malignant melanoma.

Report of a Case. In 1971, a 6-year-old girl developed a tumor in her left orbit. A specimen from an incisional biopsy of the mass showed evidence of embryonal sarcoma (**Figure 1** A and B). The patient received multidrug systemic chemotherapy (including dactinomycin) and radiation therapy to the orbit. Radiation therapy consisted of an exclusive anterior beam with a de-

livered dose of 5000 rad (50 Gy; 330 rad [3.3 Gy] per fraction) with good local tumor control. During follow-up, the patient developed cataract and strabismus and underwent uneventful surgical treatment for cataract. Her final visual acuity was 20/200 because of macular retinal alterations that were probably secondary to radiation retinopathy. A surgical procedure to correct strabismus was then performed in 1982, and regular follow-up was performed by her ophthalmologist.

In July 1992, at age 27 years, the patient developed a slowly growing, painless, temporal conjunctival mass of the left eye. The patient was then referred to our clinic in September 1992. At that time, she had a slightly

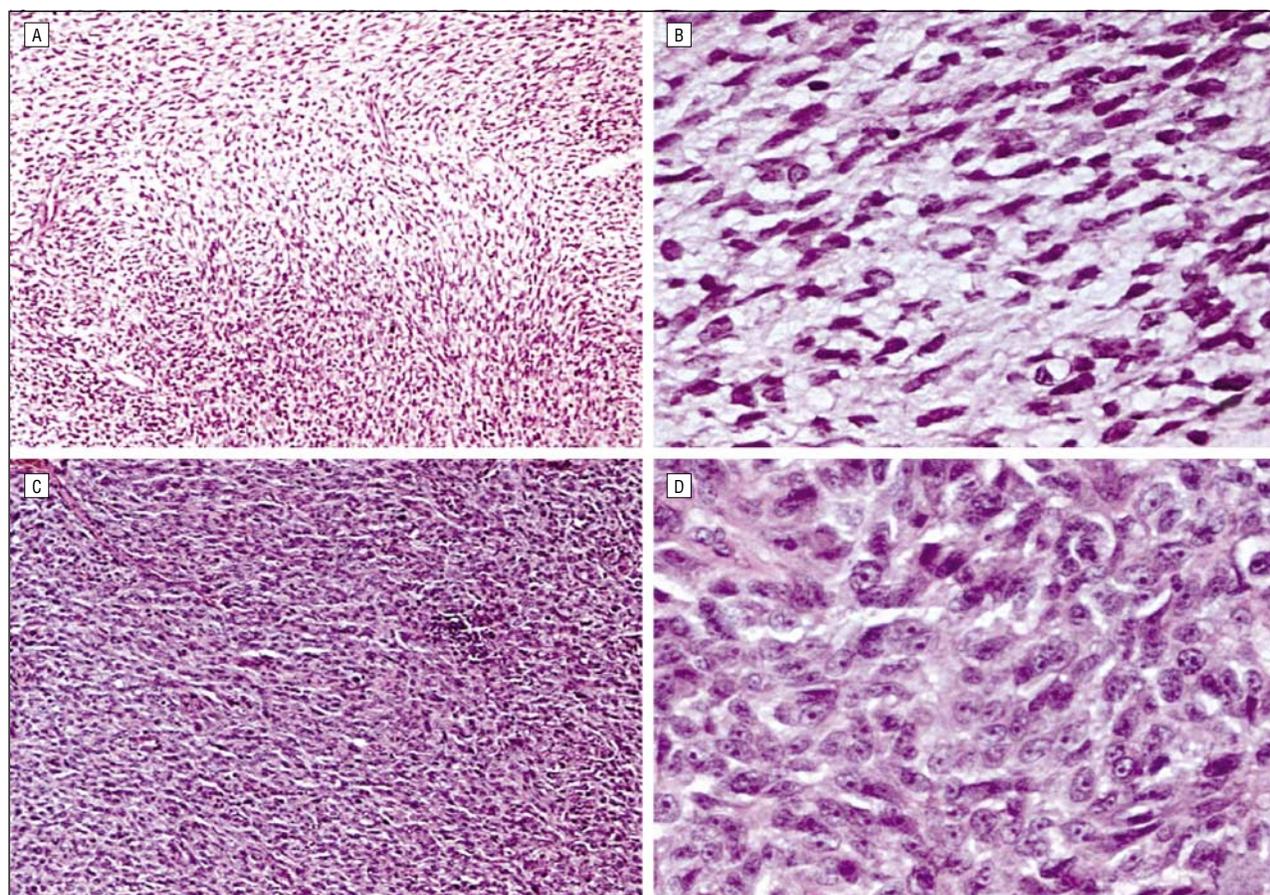


Figure 1. A and B, Biopsy specimen of an orbital lesion, embryonal sarcoma, shows syncytial arrangement of poorly differentiated embryonic mesenchymal cells dispersed in edematous or fibrous stroma (hematein-eosin saffron, original magnification $\times 10$ [A] and $\times 40$ [B]). C and D, Orbital exenteration because of malignant melanoma shows highly cellular proliferation of fusiform malignant cells with atypical nuclei and prominent nucleoli (hematein-eosin saffron, original magnification $\times 10$ [A] and $\times 40$ [B]).

pigmented bulbar conjunctival mass in the temporal area (**Figure 2**) with posterior extension on computed tomography (**Figure 3**). There were no palpable preauricular or submandibular nodes. Systemic workup ruled out metastasis. A biopsy specimen of the lesion revealed a conjunctival malignant melanoma, and the patient underwent orbital exenteration in October 1992. Histological examination of the biopsy specimen showed proliferation of malignant pleomorphic cells whose morpho-

logic features and immunophenotype were compatible with the diagnosis of malignant amelanotic melanoma (tumor cells were positive for S100 protein and negative for vimentin, desmin, actin, myoglobin, and cytokeratin). The pathological characteristics of the exenteration specimen confirmed the diagnosis of melanoma (Figure 1C and D). The mass was located in the lower conjunctival fornix and extended inferiorly to involve the orbicularis muscle and bulbar conjunc-

tiva as far as the limbus. The surgical margins were free of tumor.

The patient was then fitted with transcutaneous implants and a magnetic retained prosthesis with satisfactory aesthetic results. Regular systemic and ophthalmologic follow-up was uneventful until January 1999, at which time the patient complained of persistent nasal obstruction. Examination revealed a mass in the left nasal fossa and maxillary sinus (**Figure 4**). Surgical treatment consisted of maxillectomy with immediate reconstruction with latissimus dorsi free-flap, and pathological examination confirmed the presence of malignant melanoma (**Figure 5A and B**).

One year later, a sinus relapse was observed on a follow-up computed tomographic scan. The patient underwent a salvage operation, and pathological examination confirmed the presence of melanoma (Figure 5C and D). Disseminated hepatic and bone metastases appeared in August 2000. The patient is currently receiving systemic chemotherapy with interferon and temozolomide.

Comment. The association of embryonal sarcoma and melanoma in the same orbit is a very rare occurrence;

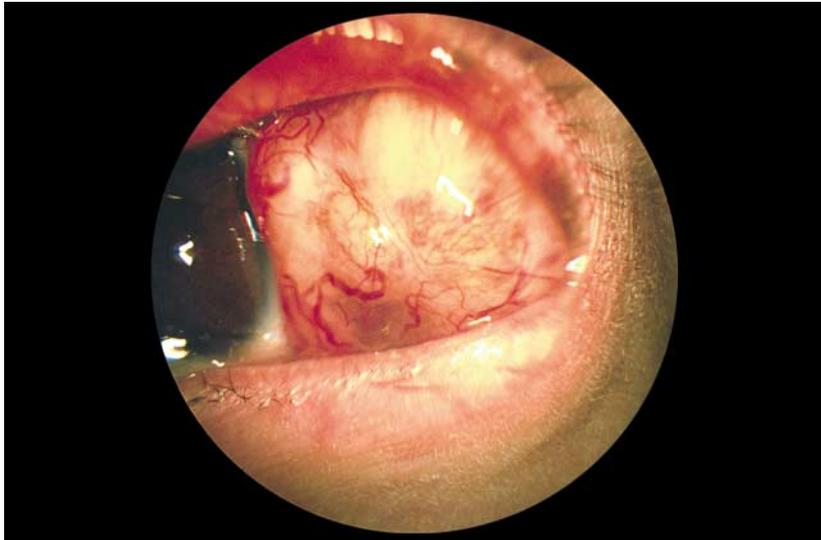


Figure 2. Slightly pigmented mass adjacent to the temporal region of the left eye.



Figure 3. Computed tomographic scan of the left orbit shows posterior extension of the mass.



Figure 4. Computed tomographic image shows recurrent malignant melanoma involving the orbital apex, left ethmoidal and maxillary sinuses, and nasal fossa.

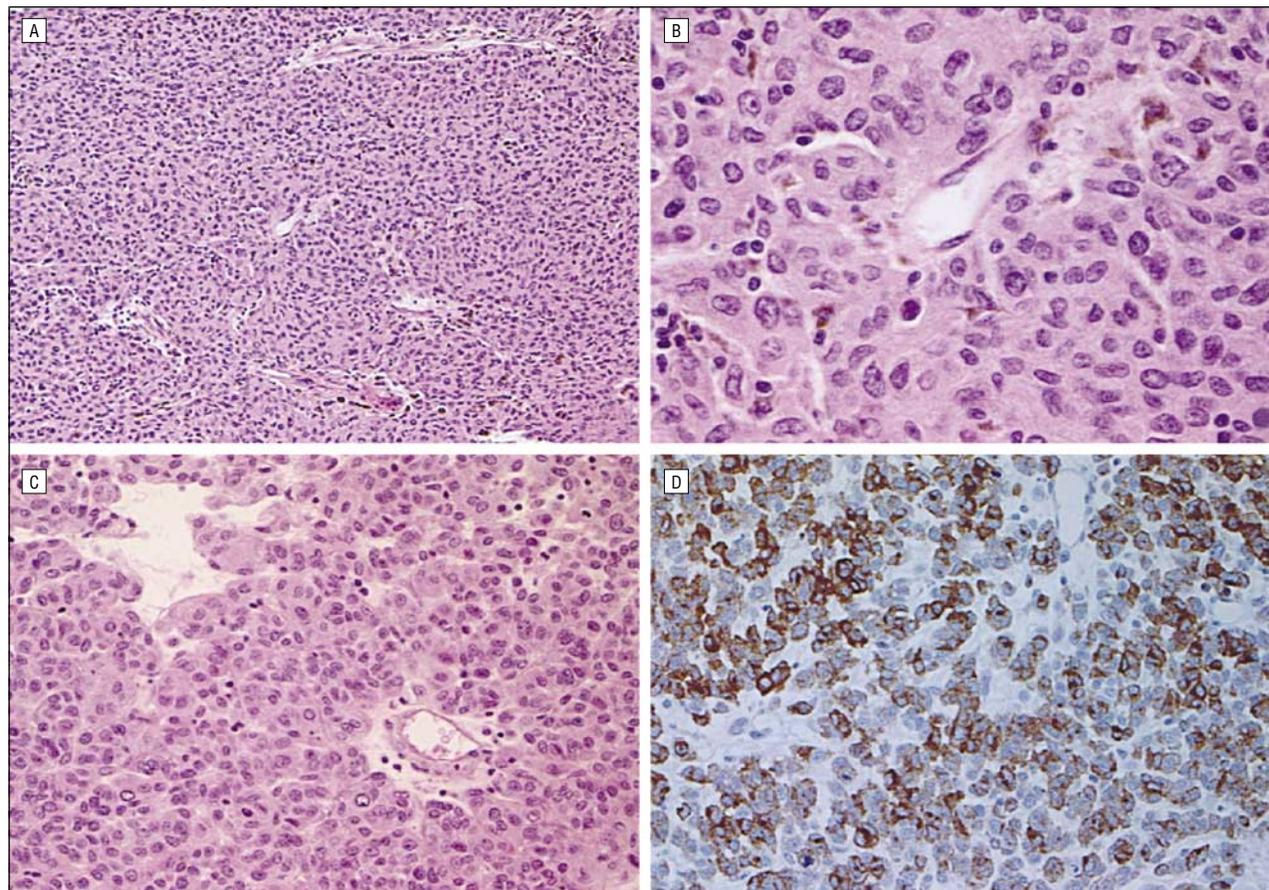


Figure 5. A and B, Maxillary recurrence of malignant melanoma shows proliferation of large epithelioid cells (hematein-eosin saffron, original magnification $\times 10$ [A] and $\times 40$ [B]). C, Sinus relapse of malignant melanoma shows epithelioid-type cells (hematein-eosin saffron, original magnification $\times 20$). D, Significant expression of a melanoma-related antigen (HMB 45, $\times 20$).

to the best of our knowledge, the literature reports only 1 other case of orbital melanoma 45 years after successful treatment of rhabdomyosarcoma.² The appearance of second tumors after treatment of rhabdomyosarcoma is also a very rare event. In their series describing long-term follow-up of children treated for orbital rhabdomyosarcoma, Oberlin et al³ did not describe any patient with a second neoplasm (median follow-up, 8 years). Paulino et al,⁴ in a smaller series but with a longer follow-up, described a mucoepidermoid carcinoma of the parotid gland occurring at the border of the radiation field after radiotherapy of the supraglottic larynx. An epidermoid carcinoma was described 9 years after chemotherapy and radiation therapy for rhabdomyosarcoma, and this lesion was attributed to radiation therapy.⁵ However, the various second malignant neoplasms described after treatment of rhabdomyosarcoma do not include malignant melanoma.^{4,5} In a recent study on chil-

dren with soft-tissue sarcomas, the incidence of second malignant neoplasms was estimated to be 7.5%, but these authors reported only 1 case of melanoma.⁶

The metachronous appearance of 2 primary malignancies may be due to several causes. It could be an incidental occurrence, or it may be related to a genetic predisposition. The role of previous cancer treatments (chemotherapy and radiation therapy) cannot be excluded.

The possibility of a radioinduced tumor is supported by the pre-existing homolateral lesion treated by a combination of radiation therapy and chemotherapy; the lesion also occurred in the radiation field several years after initial treatment. However, the possibility of a genetic predisposition cannot be excluded in our patient, despite the absence of a family history of cancer.

This case report describes and documents the very rare occurrence of 2 distinct orbital malignancies

(rhabdomyosarcoma and malignant melanoma) occurring in the same patient at an interval of 20 years; it further emphasizes the current concern about childhood cancer treatments that might cause severe late effects, especially second cancers.

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Unilateral Multifocal Uveal Melanoma With Occult Ring Melanoma

Unilateral multifocal uveal melanoma is a neoplastic curiosity that needs to be clinically distinguished from metastatic carcinoma and metastases of cutaneous melanoma. We describe a patient with a small posterior choroidal melanoma who developed 2 separate nonpigmented

angle tumors in the same eye after treatment. The angle tumors simulated metastases of either the primary choroidal melanoma or an unrecognized systemic malignancy. When the eye was removed, we found an occult ring melanoma of the ciliary body with invasion of the angle.

Report of a Case. A 71-year-old woman was referred for the evaluation of a pigmented tumor in her right eye. An examination revealed a visual acuity of counting fingers at 3 ft OD and 20/40 OS. Positive findings included bilateral cataracts and a 6-mm heart-shaped, pigmented choroidal tumor above the right optic disc (Figure 1A). A 3-mm flat, pigmented nevus was present temporal to the left macula. A standardized A-scan of the right choroidal tumor showed low internal reflectivity and a tumor height of 2.5 mm. A general medical evaluation and laboratory studies showed no evidence

of systemic malignancy. The tumor was treated with a radioactive plaque. A week after surgery, 2 light-gray lesions approximately 1 mm in size were seen at the root of the right iris at the 7- to 8-o'clock and 10-o'clock positions (Figure 1B). The lesions were observed for 4 months but did not enlarge; an iris biopsy was performed and showed spindle melanoma cells. Further evaluation found no evidence of malignancy elsewhere, including the skin. The patient opted for removal of the eye. A histopathologic examination revealed a largely necrotic (>95%) choroidal melanoma above the optic nerve (Figure 2A). No mitotic figures were seen among the residual spindle and epithelioid cells. A mixed cell-type melanoma had encircled the ciliary body and focally invaded the angle (Figure 2B). When 40 fields were viewed under high-power magnification, 2 mitotic figures were seen. Both tumors were positive for the HMB-45 antigen. Results of serial sections confirmed that the 2 melanomas were not contiguous.

Comment. At least 16 cases of unilateral multifocal uveal melanoma have been reported in the literature.^{1,2} Our patient had no predisposing risks for uveal melanoma such as melanosis oculi or neurofibromatosis. She did not have bilateral diffuse uveal melanocytic tumors. The near-simultaneous recognition of both an anterior and posterior segment melanoma in the same eye is highly unusual.³ The time sequence in which 2 discrete anterior segment tumors were detected in our patient raised the possibility of ocular metastasis of either the recently treated choroidal melanoma or an occult systemic malignancy. Prior to biopsy, the second possibility seemed more likely because the angle tumors were nonpigmented. The ring melanoma, which was clinically undetected because of minimal elevation, probably represents a primary uveal malignancy.

The biological basis for multifocal uveal melanoma is unknown. The possibility of occult ring melanoma needs to be considered when multiple angle tumors are found,

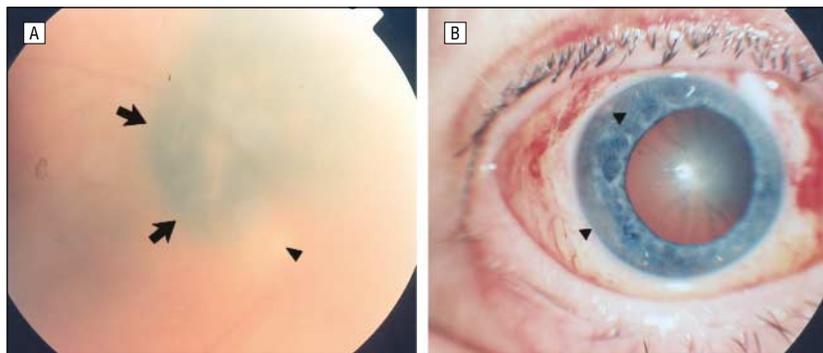


Figure 1. A, A 6-mm pigmented tumor (arrows) is present above the right optic disc (arrowhead). The view of the fundus is hazy as a result of cataract. B, Two light-gray tumors (arrowheads) are barely discernible in the angle of the right eye.

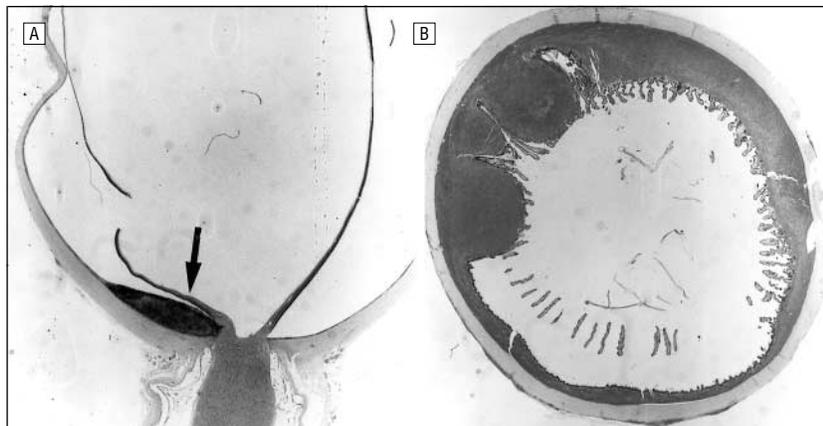


Figure 2. A, The enucleated right eye reveals a predominately necrotic melanoma (arrow) adjacent to but not involving the optic nerve (hematoxylin-eosin; original magnification $\times 6$). B, A coronal section several millimeters behind the limbus shows the ciliary body entirely replaced with a mixed cell-type melanoma (hematoxylin-eosin; original magnification $\times 12$).

even in an eye harboring a discrete posterior melanoma.

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Infectious Keratitis Manifesting as a White Plaque on the Cornea

We experienced a cluster of 3 cases of culture-proved infectious keratitis that, although caused by different organisms, each had a white plaque attached to the corneal surface without the typical findings associated with an infectious corneal ulcer.

Report of Cases. *Case 1.* A 68-year-old woman visited our clinic complaining of a foreign body sensation and epiphora for 3 weeks in her right eye. She had no history of ocular disease or trauma. On slitlamp examination, a white plaque of gelatinous texture with sharply demarcated and elevated margins was seen on the nasal paracentral cornea in conjunc-

tion with a pterygium (**Figure 1A**). There was no epithelial defect, stromal infiltration around the plaque, or cellular reaction in the anterior chamber. Specimens were collected from the periphery of the plaque for smear and culture, and hourly administration of fortified antibiotic eyedrops was initiated. However, no resolution of the corneal plaque was observed for 1 week. Plaque removal was tried and the lesion was easily removed, leaving an almost clear stromal bed underneath. Assuming a diagnosis of a sterile corneal ulcer because of the quiet ocular findings and negative culture report, the fortified topical antibiotic regimen was changed to ofloxacin, 4 times daily, with hourly nonpreserved artificial tears. An epithelial defect at the plaque removal site persisted for 2 weeks, so we applied human amniotic membrane (HAM) and removed the pterygium. However, the epithelial defect slowly enlarged into the central cornea despite a lateral tarsorrhaphy. A white plaque reappeared on the epithelial defect during the next 3 months. Four months after her initial examination, we repeated removal of the corneal plaque and microbiologic testing from the stromal bed. The corneal plaque showed a roughened surface that appeared calcific in nature (**Figure 1B**) and was easily detached. The culture result disclosed *Comamonas acidovorans* with susceptibility to several antibiotics, including cefotaxime sodium, ceftriaxone sodium, ceftazidime, imipenem, and pefloxacin, although the patient did not return during the follow-up for treatment. Three months later, she sought care for a corneal perforation at another clinic and underwent evisceration (**Figure 1C**).

Case 2. A 66-year-old woman was referred to us for a 1-month history of a foreign body sensation in her left eye. Initial slitlamp examination showed a white, calcific-appearing plaque with an elevated and well-outlined border (**Figure 2**). The cornea was otherwise quiet with no cellular reaction in the anterior chamber. The plaque was removed surgically and scraping for culture was performed from the underlying stromal bed. HAM was transplanted with the basement membrane layer up to prevent a persistent epithelial defect. Corneal epithelium, initially growing over the periphery of the HAM, failed to cover the center of the HAM, which showed signs of dissolution. At that time, pathologic examination of the plaque disclosed suspicious filamentous organisms embedded within severely degenerative tissue, and the microbiology laboratory reported the growth of *Microsporium* species. Treatment was begun with 0.15% amphotericin B eye-drops, and the HAM was covered slowly with epithelium, with no sign of recurrence at 3 months after discontinuation of treatment.

Case 3. A 57-year-old man was referred for a possible corneal ulcer. He had complained of a gritty sensation in his left eye for 3 weeks. He also had a white and apparently calcific plaque, which had a well-demarcated and elevated margin (**Figure 3A**). A mild cellular reaction (1+) was seen in the anterior chamber. Excisional biopsy of the plaque, scrapings from the stromal bed for smear and culture, and transplantation of HAM over the denuded stroma were performed, followed by initiation of treatment with fortified antibiotics. One week later, the HAM started to dissolve, reveal-

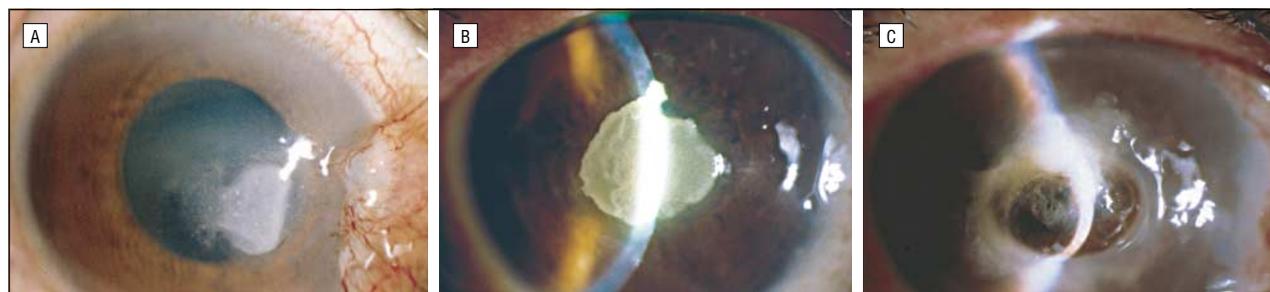


Figure 1. A, A white plaque of gelatinous texture with sharply demarcated and elevated margins is seen on the nasal paracentral cornea in conjunction with a pterygium. B, The corneal plaque, which slowly reappeared after the removal of the original plaque in part A, exhibits a roughened surface and an apparently calcific nature and was easily detached. C, Perforation is seen in the central cornea where the white plaque was attached in part B.

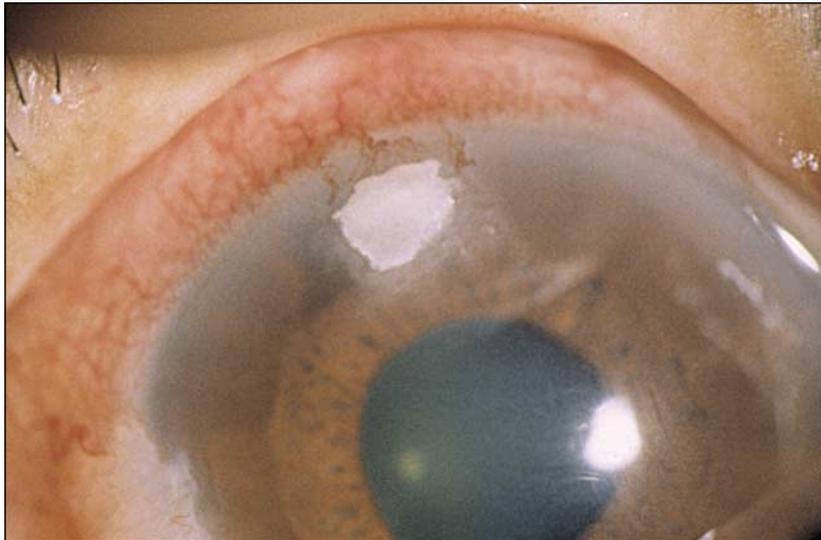


Figure 2. A white plaque, apparently calcific in nature, is seen with elevated and well-defined margins. Otherwise, the cornea appears to be quiet and the anterior chamber is clear.

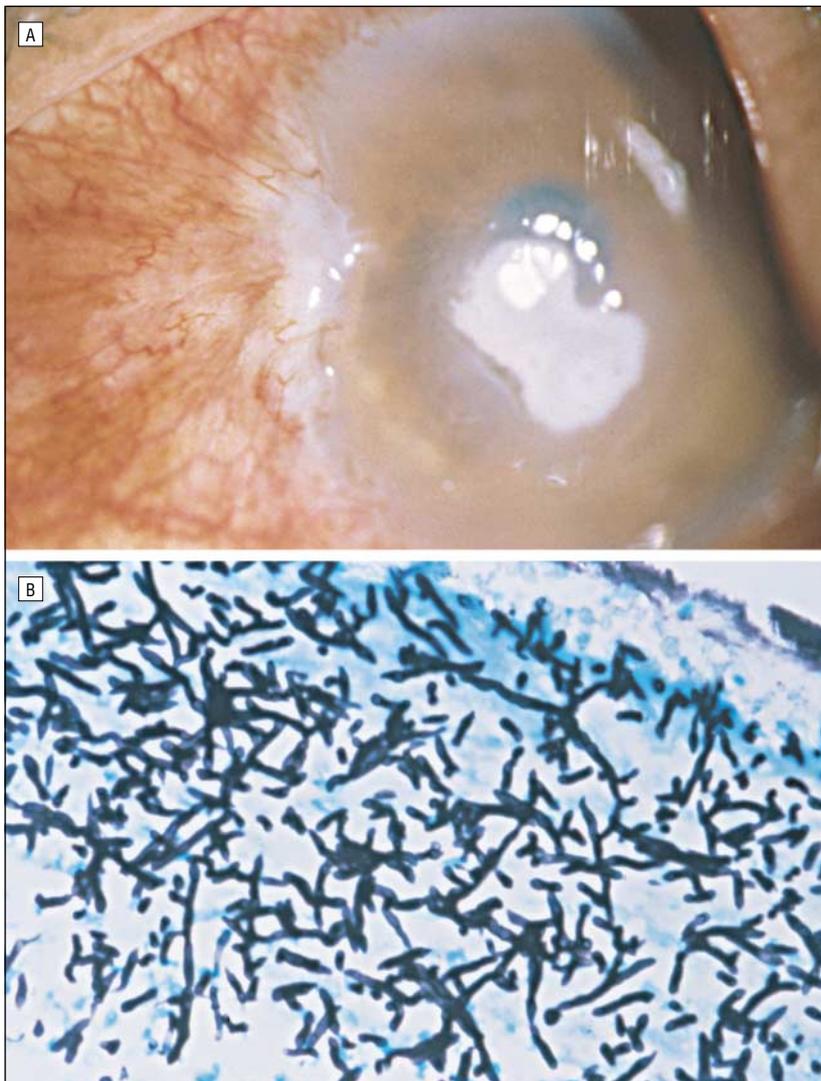


Figure 3. A, A white and apparently calcific plaque shows a well-demarcated and elevated margin. B, The filamentous fungal organisms that were within the excised plaque (Gomori methenamine silver, original magnification $\times 200$).

ing a puslike fluid accumulation underneath. Natamycin eyedrops were added according to the biopsy result, which showed many filamentous fungal organisms within the plaque (Figure 3B). *Acromonium* species were cultured from the stromal bed. The corneal lesion improved gradually without any sequelae except for opacity that was limited to the HAM.

Comment. Although caused by different organisms, our 3 cases of infectious keratitis were characterized by the shared manifestations of a white corneal plaque, slow progression, and mild clinical inflammatory features relative to most cases of infectious keratitis. Entrapment of less virulent microorganisms within the plaques, which were formed by an unknown mechanism, might be the reason for the slow and mild clinical features. However, corneal perforation is possible if the correct diagnosis and proper management are delayed as in case 1, where pathological examination of the plaque was not performed owing to our inexperience.

We performed immediate HAM transplantation in cases 2 and 3 because of the problem of the persistent epithelial defect in case 1, where the initial negative microbiologic report influenced us not to be suspicious of an infection in cases 2 and 3. In retrospect, we do not think that HAM transplantation was essential to healing. In fact, the HAM might have acted to some extent as a barrier against the penetration of antimicrobial eyedrops. The best management option would probably be an excisional biopsy of the plaque and the administration of antibiotics guided by an in vitro drug sensitivity test, without HAM transplantation. HAM could be used later if an epithelial defect persists after treatment of the infectious component.

As for the cultured microorganisms in this report, *C acidovorans* is a ubiquitous gram-negative rod and is generally considered nonpathogenic. Keratitis caused by *C acidovorans* has been rarely reported, and no reported cases showed clinical features that were similar to our case 1.^{1,2} *Microsporium*, although one

of the most common causative organisms for dermatomycoses, has not been reported to cause infectious keratitis to the best of our knowledge. *Acromonium*-caused keratitis is also rare compared with other fungal infections.³ Further microbiologic evidence may be needed to confirm the true role of these organisms in corneal ulcers. We believe, however, that corneal perforation, as in case 1, and a healing response to antifungal drops, as in cases 2 and 3, suggest the infectious nature whatever the actual causative organism might have been.

In conclusion, these were all cases of indolent corneal infections that manifested as white plaques on the cornea. It is important to perform culture and histopathologic studies on the plaque in addition to the stromal bed for this kind of atypical infectious keratitis.

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Infectious Scleritis After Use of Immunomodulators

Infectious scleritis, typically occurring in eyes having predisposing risk factors, is vision-threatening. We present a case of infectious scleritis after chemotherapy, which, to our knowledge, has not been previously reported as a risk factor.

Report of a Case. A 58-year-old woman manifested symptoms of a red, painful right eye for 1 day. Four months previously, she had undergone right mastectomy for breast cancer and was receiving chemotherapy with cyclophosphamide and epidoxorubicin. She had completed the fifth course of chemotherapy 3 weeks before this visit. Her medical history, including surgery and trauma, was otherwise unremarkable.

At presentation, slitlamp examination showed conjunctival congestion with a 2 × 2-mm scleral nodule surrounded by episcleral vessels (**Figure 1A**). Other ocular findings were unremarkable. Infectious scleritis was suspected. She was placed on a regimen of fortified topical cefazolin sodium (25 mg/mL) and gentamicin sulfate (14 mg/mL) every hour and systemic gentamicin sulfate, (60 mg) every 8 hours. On the next day, we performed peritomy to verify the scleral nodule. Cultures were obtained, and

the necrotic sclera was debrided and irrigated with gentamicin. A gram stain of the scleral nodule showed gram-negative rods (**Figure 2**). The culture report disclosed heavy growth of *Serratia marcescens* that was sensitive to gentamicin, amikacin, ciprofloxacin, piperacillin sodium, imipenem, ceftizoxime sodium, and ceftazidime, but resistant to cefuroxime, ampicillin, and cephalothin sodium. Therapy with topical and systemic gentamicin was continued, then tapered during the next 2 weeks until the lesion was resolved (**Figure 1B**). No recurrence or visual impairment was found during the 1-year follow-up.

A rheumatologic evaluation performed at presentation showed normal findings. The leukocyte count was 6200/μL, with a decreased percentage of polymorphonuclear cells and lymphocytes (polymorphonuclear cells, 48%; lymphocytes, 18%). The patient's leukocyte count had been decreasing during 4 months of chemotherapy. In particular, the percentage of polymorphonuclear cells had decreased from 77% to 48%. However, there was no associated systemic infection.

Comment. Trauma and surgery are important risk factors for infectious scleritis.^{1,2} Two cases of infectious scleritis without history of trauma or surgery have been reported elsewhere.^{3,4} Maskin³ described a diabetic patient with infectious scleritis; the culture report was the same as that from the patient's foot ulcer. Maskin speculated it was probably

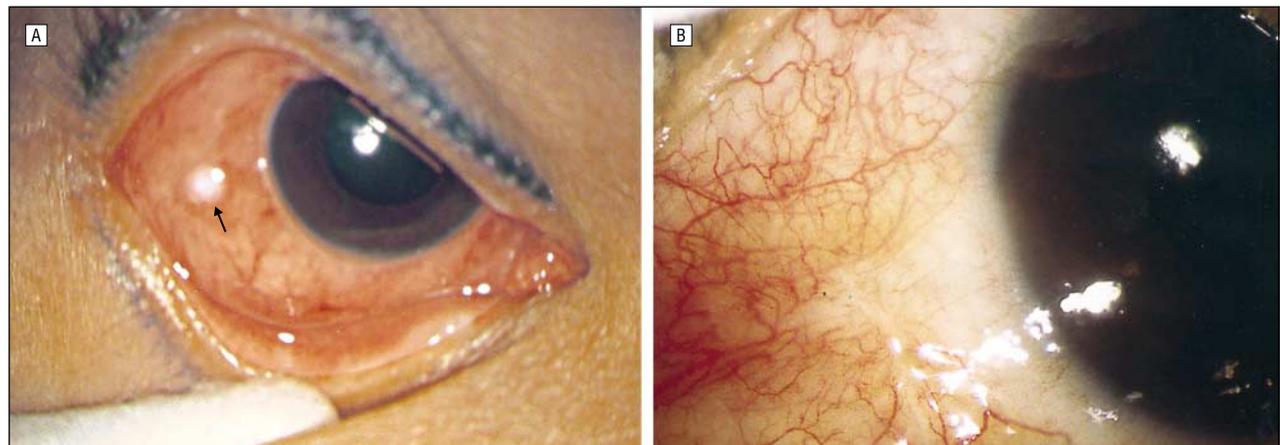


Figure 1. A, A 2 × 2-mm scleral nodule (arrow) surrounded by engorged episcleral vessels. B, The abscess subsided after debridement and antibiotic treatment.

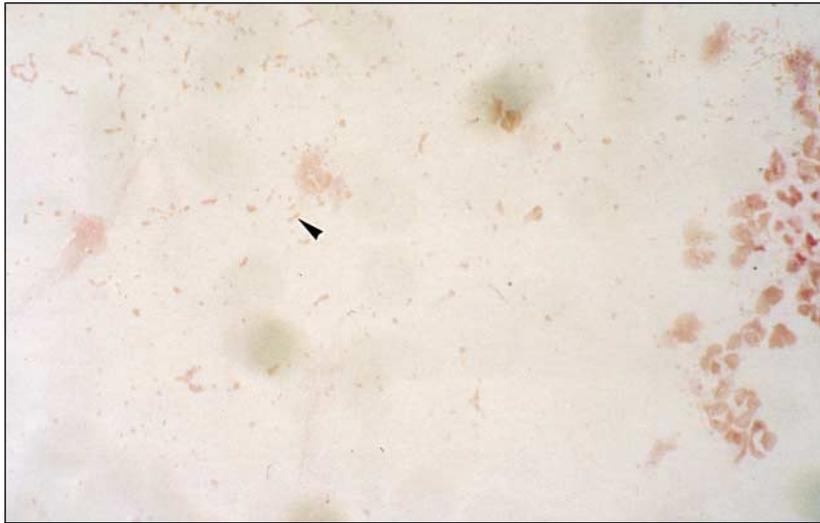


Figure 2. The gram stain from the scleral nodule showed gram-negative rods (arrowhead) (original magnification $\times 400$).

due to self-inoculation. Reynolds and Alfonso⁴ reported infectious scleritis in a patient with acquired immunodeficiency syndrome. Unfortunately, a detailed history of the patient was not available. We found no known risk factors of infectious scleritis in our patient. The only possible clue was the patient's immune status. Cyclophosphamide-related bone marrow suppression applies to all elements of the bone marrow but affects leukocytes to the greatest degree.⁵ Such a condition may increase the risk of infection before suppression of neutrophil production is evident. Serious infection has been found to develop in 12% to 32% of patients receiving high-dose cyclophosphamide.⁵ In addition, epidoxorubicin also contributes to myelosuppression. In our patient, chemotherapy might have suppressed the immune system, allowing subsequent development of infection. However, we cannot identify whether the infection source was exogenous or endogenous.

To our knowledge, this is the first report of infectious scleritis after systemic immunosuppressive therapy. This case demonstrates that microbial scleritis may imitate nodular scleritis, even though there may be no history of trauma or surgery to implicate infection. The diagnosis of infectious scleritis may be delayed and mistaken for an autoimmune process. In patients at risk of infections, such as our patient who was undergoing chemotherapy, it is

of primary importance to prevent devastating consequences.

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Congenital Restrictive External Ophthalmoplegia and Gustatory Epiphora Associated With Fetal Isotretinoin Toxicity

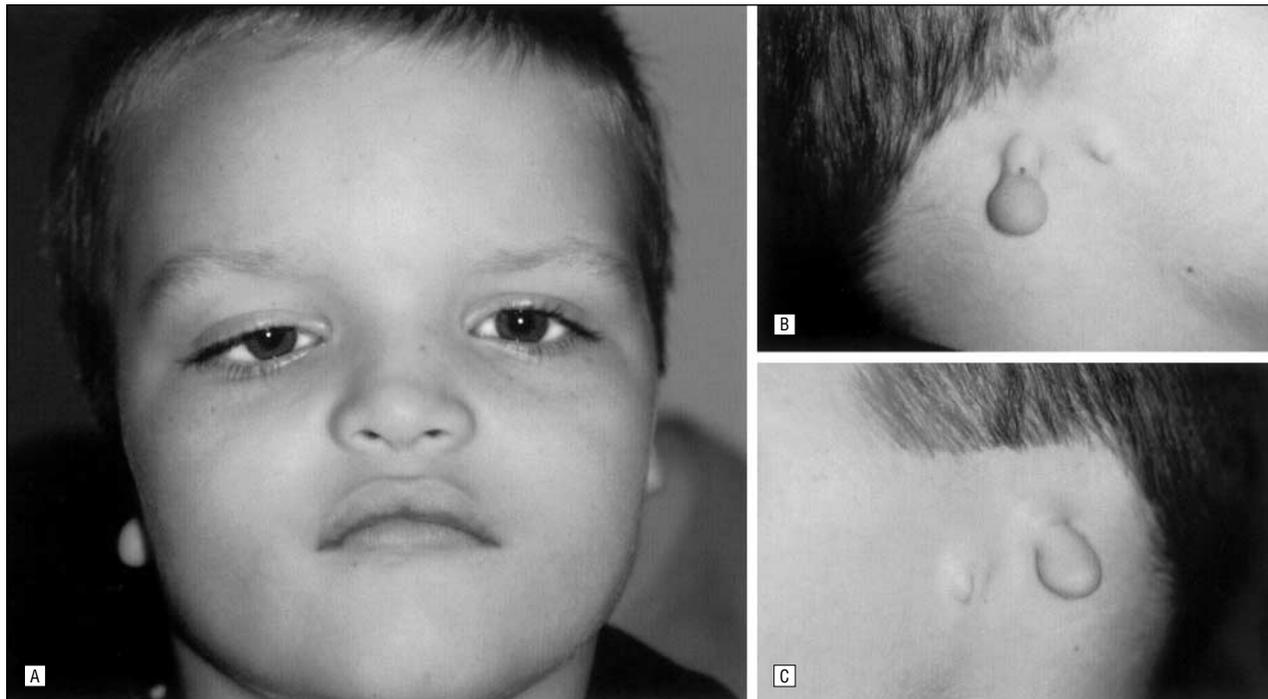
Isotretinoin or Accutane (Hoffman-La Roche Inc, Nutley, NJ; 13-

cis-retinoic acid) is a vitamin A analogue that was first licensed in the United States in 1982 for the treatment of cystic acne. Use of isotretinoin during pregnancy is teratogenic and is associated with a constellation of fetal malformations collectively termed retinoic acid embryopathy.¹

Retinoic acid embryopathy is characterized by craniofacial abnormalities in the form of hydrocephalus, microcephaly, a narrow, sloping forehead, hypertelorism, ear deformities, cleft palate, and micrognathia.¹ Systemic anomalies include congenital heart defects and thymic malformation. Reported ophthalmic findings are microphthalmos, optic nerve hypoplasia, and cortical blindness.² We describe a child exposed to isotretinoin during gestation who sought treatment for congenital restrictive ophthalmoplegia and gustatory epiphora (crocodile tears syndrome).

Report of a Case. An 11-week-old boy with numerous malformations came to our unit with a history of poor visual tracking from birth. The child's mother had used isotretinoin (mean daily oral dosage, 53.3 mg) for acne during the first 9 weeks of her pregnancy. There was no family history of parental consanguinity or hereditary ocular or systemic disease. The infant was born at term weighing 2.9 kg and was found to have external and middle ear malformations, patent ductus arteriosus, patent foramen ovale, and gastroesophageal reflux. At age 1 month, he had a seizure. Electroencephalography results were unremarkable, and magnetic resonance imaging of the orbits and brain revealed no malformations of the brainstem or cerebral structures; extraocular muscles appeared normal in size and configuration. Karyotype and fluorescence in situ hybridization analysis for chromosome 22 deletion demonstrated no abnormalities.

The infant was hypotonic. Craniofacial abnormalities included a prominent calvaria, a tall forehead, an oblique facial plane, micrognathia, anotia, and preauricular skin tags (**Figure**). He had mild bilateral blepharoptosis. Ocular motor examination revealed a striking limi-



Photographs of our patient at age 6½ years. Craniofacial abnormalities characteristic of isotretinoin embryopathy are apparent, including a prominent calvaria, a tall forehead, an oblique facial plane, micrognathia (A), anotia, and preauricular skin tags (B and C).

tation in the amplitude and velocity of saccadic, pursuit, and vestibulo-ocular reflex eye movements in both the horizontal and vertical planes. Large-angle (30 prism diopters) alternating exotropia was noted with deficient convergence. Pupillary responses were normal. Cycloplegic retinoscopy revealed significant hyperopia (+5.00 diopters OU). No funduscopic abnormalities were noted. Flash visually evoked potential and photopic and scotopic electroretinography responses were normal for the patient's age. Spectacles were prescribed to correct the hyperopia.

By 10 months of age, the patient was noted to have epiphora when feeding (crocodile tear syndrome) and a lack of tear production when crying (emotional alacrima). At 11 months of age, bilateral lateral-rectus recessions were performed to correct the exotropia. Forced duction testing during surgery revealed marked restriction to passive rotation in both horizontal and vertical directions in each eye, consistent with restrictive myopathy. At age 6 years, he had a best-corrected visual acuity of 20/30 OU and an intermittent esotropia of 10 prism diopters. The mild bilateral blepharoptosis and the limitation of

versional and vergence eye movements were unchanged.

Comment. Our patient exhibits 2 previously unreported ocular manifestations of fetal isotretinoin exposure: congenital restrictive external ophthalmoplegia and gustatory epiphora. The cause of the ophthalmoplegia is not known, but it may represent a sporadic form of congenital ocular fibrosis syndrome. Congenital ocular fibrosis syndrome is a collection of nonprogressive, inherited motility disturbances characterized by "stiff" fibrotic extraocular muscles.³ It is unclear whether congenital ocular fibrosis syndrome represents a primary congenital myopathy or neuropathy. Recent evidence suggests that congenital ocular fibrosis syndrome may arise from a loss of neurons within brainstem ocular motor nuclei during embryologic development.³ The neuronal loss secondarily disrupts myogenesis, resulting in anomalous muscle development. The presence of congenital gustatory epiphora in our patient, caused by maldevelopment of the salivary and lacrimal nuclei within the pons and medulla, suggests a primary brainstem neuropathy as the cause of the ophthalmoplegia.⁴

Concomitant gustatory epiphora and ocular motility disturbances have been reported with fetal thalidomide exposure.⁵ The thalidomide abnormalities have been ascribed to a toxic insult to the ocular motor and facial brainstem nuclei before the fifth week of gestation. The findings in our patient suggest that exposure to isotretinoin during the early stages of fetal development can produce similar ocular motor abnormalities.

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Orbital Cellulitis and Abscess Secondary to Dacryocystitis

The symptoms of nasolacrimal duct obstruction include epiphora, conjunctivitis, and mucoid discharge. Dacryocystitis may develop when bacterial overgrowth occurs in the stagnant fluid of the lacrimal sac. Whereas acute dacryocystitis is usually characterized by tender preseptal cellulitis, chronic dacryocystitis typically manifests as painless purulent reflux from the lacrimal sac. Antibiotic therapy is indicated for acute infections, and dacryocystorhinostomy is the definitive treatment.

Although anterior extension into the preseptal soft tissues occurs more often in acute dacryocystitis, orbital extension can occur, although rarely, and result in orbital cellulitis and abscess formation.¹⁻⁹ Posterior extension into the orbit can result in devastating visual compromise. We describe a series of 4 patients with orbital cellulitis and abscesses secondary to dacryocystitis (**Table 1**).

Report of Cases. *Case 1.* A 38-year-old woman had a history of epiphora for many years but declined surgical treatment. She had 1 previous episode of dacryocystitis that resolved with systemic antibiotics. She sought care because of a 1-week history of painful swelling and decreased vision in her left eye.

On examination, her visual acuity was 20/20 OD and no light perception OS. A left afferent pupillary defect was present. Her left globe was markedly proptotic, tense to retropulsion, and restricted in all fields of gaze. Dilated funduscopy examination revealed hyperemia of the left disc. A computed tomographic scan

revealed a medial orbital abscess. No sinus disease was noted.

The patient was started on intravenous cefazolin and gentamicin sulfate. She underwent an emergent orbitotomy with abscess drainage through a medial Lynch incision. Copious amounts of necrotic purulent material were drained. A direct communication was noted between the posterior aspect of the lacrimal sac and the intraconal space. The intraconal abscess was also evacuated. A dacryocystorhinostomy was performed. Cultures grew *Staphylococcus aureus*. Postoperatively, the patient had resolution of the orbital inflammation and proptosis, but her visual acuity remained no light perception OS.

Case 2. A 64-year-old woman was hospitalized with jaundice, anorexia, and hepatic failure secondary to chronic alcoholism. Two days after admission, swelling of the right upper and lower eyelids was noted. She was afebrile but had a white blood cell count of $22.5 \times 10^3/\mu\text{L}$ with leukocytosis. Empiric intravenous vancomycin hydrochloride was started by the admitting service. Ophthalmic consultation was obtained.

Her visual acuity was light perception OD. An afferent pupillary defect was present. Marked right proptosis, diminished extraocular motility, chemosis, and conjunctival hyperemia were also noted. Dilated fundus examination showed right choroidal folds and retinal edema. A computed tomographic scan showed a large, irregular mass in the medial and posterior orbit displacing the globe and optic nerve. There was enlargement of the medial rectus muscle and contrast enhancement of the posterior sclera. The bony orbit was intact, and the sinuses were clear.

A differential diagnosis of orbital cellulitis with abscess, idiopathic orbital inflammation, hematogenous dissemination, and malignancy was considered. Intravenous antibiotics were continued with minimal improvement. During the next several days, the patient's medical condition deteriorated due to gastrointestinal bleeding and ascites. Once the patient was medically stable, a medial orbitotomy through a Lynch incision was performed. Upon dissection between the medial and superior recti muscles into the intraconal space, an abscess was encountered surrounding the optic nerve. The abscess was noted to be extending from the area of the lacrimal sac. Purulent material was drained, and a communication with the abscess was identified. Several dacryoliths were removed. An osteotomy into the nasal cavity and a dacryocystorhinostomy with silicone stents were performed. Cultures grew nonenterococcal group D streptococci, *Streptococcus viridans*, and *Streptococcus intermedius*. Postoperatively, the patient had resolution of proptosis and improved ocular motility, except for an adduction deficit. Her visual acuity remained light perception OD.

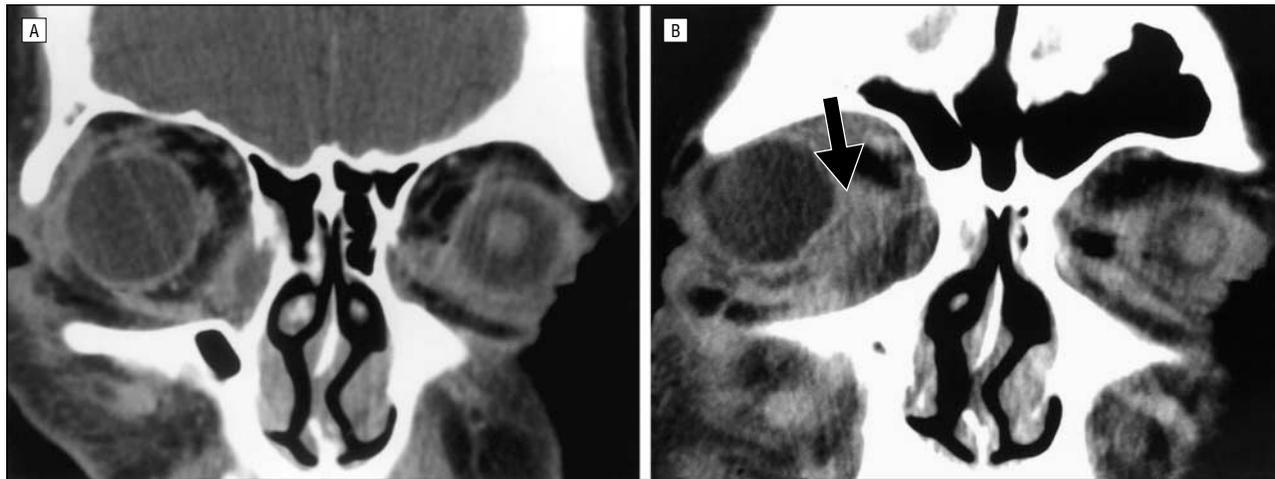
Case 3. A 62-year-old woman sought care from her ophthalmologist with a 5-day history of tearing and swelling of the left upper and lower eyelids. Her ocular history included nasolacrimal obstructive symptoms for many years and prior episodes of dacryocystitis. Oral cephalexin monohydrate (250 mg, 4 times daily) was prescribed. During the next 2 days, she developed proptosis and chemosis of the left eye and was referred for consultation.

Her visual acuity with correction was 20/20 OD and 20/60 OS. A trace left afferent pupillary defect was noted. Marked chemosis and ery-

Table 1. Orbital Cellulitis and Abscesses Secondary to Dacryocystitis in 4 Patients

Patient No./ Age, y	Location of Orbital Abscess	Degree of Proptosis	Chemosis	Motility	Conjunctival Hyperemia	Length of Follow-up, mo	DCR Patent at Last Visit
1/38	Extraconal	Marked	Yes	Severely restricted	4+	19	Yes
2/64	Intraconal	Marked	Yes	Severely restricted	4+	2	Yes
3/62	Intraconal	Marked	Yes	Severely restricted	4+	2	Yes
4/51	Intraconal	Moderate	No	Restricted	2+	6	Yes

*DCR indicates dacryocystorhinostomy.



A, Coronal computed tomographic scan of a 51-year-old, otherwise healthy man shows dacryocystitis before orbital cellulitis and abscess formation. Note the proximity of the lacrimal sac to the intraconal space. B, Coronal computed tomographic scan shows progression to orbital abscess (arrow), indenting the globe.

thema were noted, and 13 mm of relative proptosis was measured. A motility examination showed severely restricted ductions of the left globe. Her intraocular pressure was 19 mm Hg OD and 46 mm Hg OS. Dilated fundus examination showed slight hyperemia of the left nerve. The patient was afebrile but had a white blood cell count of $11.6 \times 10^3/\mu\text{L}$ with leukocytosis. An orbital computed tomographic scan showed a large medial orbital mass contiguous with the lacrimal sac, suggestive of an abscess. The paranasal sinuses were clear. The patient was hospitalized, and intravenous cefazolin and gentamicin were initiated. Urgent medial orbitotomy through a Lynch incision was performed. The lacrimal sac and the superior aspect of the nasolacrimal duct were found to be grossly dilated and tense. The sac was opened, and copious purulent material was removed and cultured. Three large dark-gray dacryoliths were extracted from the sac. Examination of the sac revealed a fistulous communication extending from the sac into the medial intraconal space. A dacryocystorhinostomy was performed with silicone stents.

During the next several days, the patient showed gradual improvement. Cultures grew *S viridans*, *S intermedius*, and *Veillonella parvula*. Infectious disease consultation recommended 3 weeks of intravenous cefazolin and 1 week of oral cephalexin. Follow-up at 8 weeks after the operation revealed complete resolution of the proptosis, edema, and

chemosis. Adduction was nearly full. Visual acuity measured 20/25 OS. A residual left afferent pupillary defect was present with slight pallor of the left optic nerve.

Case 4. A 51-year-old, otherwise healthy man sought care because of a 2-day history of right-sided medial canthal swelling, pain, redness, and tearing. He was previously seen by his internist, who prescribed oral erythromycin stearate. For several weeks before seeking care, he noted intermittent epiphora and swelling that could be relieved with digital massage. His medical history was unremarkable except for a penicillin allergy.

On examination, his visual acuity was 20/20 OU. Medial canthal and lower-eyelid edema and erythema were present. His motility was full, and there was no proptosis. Initial computed tomographic scanning showed an enlarged lacrimal sac and surrounding soft tissue inflammation (**Figure, A**). Intravenous vancomycin and gentamicin were initiated. During the next 2 days, improvement was noted; however, on the third day, when the patient complained of increased pain, his examination showed 3 mm of proptosis, increased resistance to retro-pulsion, diminished extraocular movements, and marked induration of the medial canthal region. His vision remained 20/20 OU, and no afferent pupillary defect was present. A repeated computed tomographic scan showed marked orbital soft tissue inflammation and a

medial orbital abscess (**Figure, B**). Intravenous trovafloxacin mesylate was initiated for improved anaerobic coverage. When no clinical improvement was noted 24 hours later, the patient underwent an endoscopic dacryocystorhinostomy with evacuation of copious purulent material from the lacrimal sac. Silicone stents were also placed. The results of cultures were negative. A lacrimal sac biopsy specimen showed acute and chronic inflammation. Follow-up at 1 week showed intact vision, resolution of edema, full ocular motility, and no proptosis. His stents were removed at 6 months, and his dacryocystorhinostomy was patent.

Comment. Patients with nasolacrimal duct obstruction seek treatment primarily to relieve symptoms of epiphora, irritation, and mucoid discharge. If obstruction progresses to acute dacryocystitis, pain and swelling of the lacrimal sac region occur, necessitating systemic antibiotics and definitive surgical treatment. In chronic dacryocystitis, patients often obtain temporary relief of symptoms with external decompression of the lacrimal sac. If dacryocystitis is untreated, orbital extension has been reported.¹⁻⁹ These cases are summarized in **Table 2**.

This study describes our series of 4 patients who developed orbital cellulitis and orbital abscesses arising from dacryocystitis. Of 4 patients, 3 had intraconal spread of the

Table 2. Orbital Extension in Patients With Dacryocystitis*

Source	Age of Patient	Final Visual Acuity	Previous Dacryocystitis	Dacryoliths Present	Bacterial Isolates	Sinus Disease
Ahrens-Palumbo and Ballen, 1982 ¹	60 y	20/20	Yes	No	<i>Staphylococcus epidermidis</i>	Ethmoidal
Allen et al, 1985 ²	57 y	6/6	No	...	<i>Eikenella corrodens</i> and <i>Enterobacter aerogenes</i>	Ethmoidal
Campolattaro et al, 1997 ³	3 mo	...	No	...	<i>Staphylococcus aureus</i>	No
	3 y	...	Yes	...	Alpha streptococcus	No
	19 y	...	No	...	<i>S epidermidis</i>	No
Kikkawa et al, 2002 (present study)	38 y	NLP	Yes	Yes	<i>S aureus</i>	No
	64 y	NLP	No	Yes	Nonenterococcal group, group D streptococci, <i>Streptococcus viridans</i> , and <i>S intermedius</i>	No
	62 y	20/25	Yes	Yes	<i>S viridans</i> , <i>Staphylococcus intermedius</i> , and <i>Veillonella parvula</i>	No
Lawless and Martin, 1986 ⁴	51 y	20/20	Yes	No	None	No
	3 y	...	No, but probing age 1 y	...	<i>Haemophilus influenza</i> and <i>S aureus</i>	Bilateral maxillary
Mauriello and Wasserman, 1996 ⁵	84 y	20/70	No	No	<i>S aureus</i>	Ethmoidal
Molgat and Hurwitz, 1993 ⁶	40 y	6/6	Yes	Yes	<i>S viridans</i>	Ethmoidal and maxillary
Ntountas et al, 1997 ⁷	38 y	20/20	No	Yes	<i>Streptococcus angiosus</i> , <i>Peptrostreptococcus</i> , and "anaerobic gram-negative rod"	No
Warrak and Khoury, 1996 ⁸	62 y	...	No	No	<i>Morganella morganii</i>	No
Weiss and Leib, 1993 ⁹	17 y	...	No	No	<i>S aureus</i>	No

*NLP indicates no light perception; ellipses, not available.

orbital abscess and culture-proven bacterial infections; 3 patients also had prior episodes of dacryocystitis. Each of these findings deserves further discussion.

Most patients with dacryocystitis develop preseptal cellulitis and not orbital extension. This has been attributed to the orbital septum by its insertion on the posterior lacrimal crest, limiting spread to the orbit.⁵ Several other barriers exist posteriorly, including the lacrimal fascia, the posterior limb of the medial canthal ligament, and deep heads of the pretarsal and preseptal orbicularis muscles (Horner muscle). Because the orbital septum and the medial canthal ligament insert on both the anterior and posterior lacrimal crests, we postulate that the main barrier to posterior extension is the deep heads of the preseptal and pretarsal orbicularis muscles. Hence, the anatomic barriers to prevent egress from the lacrimal sac are greater posteriorly than anteriorly.

Once the posterior barriers of the lacrimal sac have been breached, access to the intraconal space is essentially unimpeded, except for the Tenon fascia and the intermuscular septum. Because of the anterior and inferior location of the nasolacrimal sac in relation to the globe, a chan-

nel of communication can form between the medial and inferior rectus muscles directly to the intraconal space. Intraconal abscess formation can lead to rapid vision loss, necessitating urgent surgical intervention.

Although intravenous antibiotics were initiated immediately in all patients, surgical drainage is the definitive treatment. Surgical intervention in all 4 cases consisted of dacryocystorhinostomy with placement of silicone stents and orbital abscess drainage. Of 4 cases, 3 had an external approach, and 1 case had an endoscopic intranasal approach. All patients had a patent dacryocystorhinostomy at the last follow-up visit (range, 2-19 months).

The clinical bacteriological characteristics of dacryocystitis in adults have been studied previously.¹⁰ In our series, 2 of 4 patients had polymicrobial infections, 1 patient had a single organism, and 1 had no isolates. When examining the isolates from our series and the previously reported cases from Table 2, we find that, in general, younger patients (<3 years) tended to have single isolates, and older patients tended to have polymicrobial infections. These findings parallel those seen in orbital abscesses secondary to sinus disease.¹¹

In our series, 3 of 4 patients had a prior history of dacryocystitis. In fact, of the reported cases in Table 2, 6 (40%) of 15 had prior dacryocystitis. In addition, 5 (33%) of 15 had dacryoliths, including 2 patients who did not have a prior history of dacryocystitis but had dacryoliths found intraoperatively. We believe that prior dacryocystitis is a risk factor for orbital extension. Distension of the lacrimal sac during episodes of dacryocystitis can stretch the lacrimal sac walls and its posterior barriers (posterior limb of the medial canthal ligament, Horner muscle, and septum). These barriers weaken from distension and cause breaches and rarefaction, increasing the likelihood of posterior spread.

Other causes of orbital cellulitis secondary to dacryocystitis have been postulated.^{1,2} In 1 case report, the authors speculated that postoperative soft tissue swelling from blepharoplasty might have contributed to the obstruction of an already compromised lacrimal outflow system.² Other authors have theorized that orbital involvement could have resulted from spread of infection from the lacrimal sac to the ethmoid sinus through the lamina papyracea, with subsequent exten-

sion from the sinus to the orbit.¹ None of our cases had any evidence of sinus disease, and it is more likely that any sinus opacification seen is secondary to adjacent inflammation from the dacryocystitis or unrelated sinus disease. Other possible causes include hematogenous spread from other systemic sources and, in some cases, a primary orbital cellulitis that can extend into the lacrimal sac without the dacryocystitis necessarily being causal.

In summary, our series of orbital cellulitis and abscess secondary to dacryocystitis has been presented. Orbital cellulitis and abscess can rapidly progress to an intraconal abscess and can cause severe visual sequelae if untreated. Prompt recognition and appropriate surgical management of this condition are necessary to prevent vision loss. Prior dacryocystitis is a risk factor for developing orbital extension, and patients with prior episodes of dacryocystitis who elect not to have a

lacrimal bypass operation should be warned of these potential consequences.

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Correction

Error in Reference. In the article titled "Goblet Cell Numbers and Epithelial Proliferation in the Conjunctiva of Patients With Dry Eye Syndrome Treated With Cyclosporine," published in the March issue of the ARCHIVES (2002;120:330-337), on page 337, in the first reference, the editors of *Principles and Practice of Ophthalmology: Clinical Practice* are Daniel M. Albert and Frederick A. Jakobiec.