mune disease. A conjunctival biopsy was also performed in the left inferior conjunctival fornix of the mother's eye to exclude ocular cicatricial pemphigoid. The biopsy specimen showed a nonspecific mononuclear infiltration and epithelial squamous metaplasia. Direct immunofluorescence results were negative for IgG, IgM, IgA, and complement factors (C3 and C4).

As expected, magnetic resonance imaging showed marked hyperplasia or agenesia of the lacrimal glands in the mother. A corneal impression cytology test was performed in both patients and periodic acid–Schiff staining (Sigma Diagnostics, St Louis, Mo) showed the presence of epithelial squamous metaplasia and goblet cells on their corneal surfaces. (Figure 1B) Immunohistochemistry demonstrated the absence of cytokeratin K3 positive cells and the presence of cytokeratin K19 positive cells in their corneas (Figure 1C and D).^4

Comment. In this report, we describe 2 cases of LADD syndrome associated with limbal stem cell deficiency and corneal hypoesthesia. Limbal stem cell deficiency was diagnosed on the basis of clinical features (corneal epithelial erosions and neovascularization) and cytological findings (presence of goblet cells and specific cytokeratins of the corneal epithelium). Clinical ocular features of LADD syndrome, described as corneal erosions, neovascularization, and ulceration, were thought by authors to be clinical manifestations of the underlying dry eye condition. Based on the literature, we hypothesized that dry eye may also induce the development of limbal deficiency as well as corneal anesthesia. This hypothesis was at first confirmed by the mother's condition. However, the daughter showed an initial partial limbal deficiency and a history of corneal ulceration with no deficiency of tear production and without the anatomical changes related to dry eye. Therefore, it is possible that limbal deficiency could represent a genetically determined, clinical characteristic of LADD syndrome, adding this syndrome to the ever-increasing list of conditions associated with limbal stem cell deficiency. The impairment of corneal sensitivity is a new characteristic of LADD syndrome and the pathogenetic mechanism is unclear. Indeed, corneal hypoesthesia was also present in the child, with no presence of dry eye. It is possible that limbal stem cell deficiency and corneal hypoesthesia could both be contributing factors toward corneal changes found in this syndrome.

Our study suggests 2 additional clinical features of LADD syndrome, other than dry eye. Indeed, we found the presence of limbal stem cell deficiency and corneal sensitivity impairment in the absence of dry eye. These results have important therapeutic implications. In fact, to date, the therapeutic approach for the ocular manifestations of LADD syndrome was the treatment of the dry eye condition, based on tear substitutes and lacrimal punctum occlusion. These novel observations of LADD syndrome may introduce new therapeutic options; it would be interesting to evaluate if a limbal transplantation could be effective in improving the clinical manifestations of the disease, such as corneal anesthesia.

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Aggressive Glioma of Adulthood Simulating Ischemic Optic Neuropathy

The acute onset of visual loss with optic disc edema in the absence of venous engorgement or retinal hemorrhages in an elderly patient is suggestive of anterior ischemic optic neuropathy (AION). Visual loss in nonarteritic AION is typically maximal at onset. In a subset of patients with AION, however, visual loss progresses during the first 4 weeks. In giant cell arteritis, visual loss may be due to AION or posterior ischemic optic neuropathy in which the optic disc is not swollen. Both conditions may progress rapidly, even to no light perception, in a matter of hours or days. Malignant or aggressive gliomas of the optic nerve are lesions that initially may be confused with nonarteritic AION or arteritic AION because they may have a similar clinical picture of deteriorating vision and a swollen optic disc. Awareness of the differentiating features between this condition and the more common arteritic or nonarteritic AION will assist in expeditious diagnosis, appropriate investigations, and timely treatment. In this report, we review the literature on aggressive gliomas of adulthood and describe 3 patients with optic nerve gliomas who had an appearance that could be confused with ischemic optic neuropathy.

Report of Cases. Patient 1. A 70-year-old woman developed blurred vision in her right eye in September 1999. At her initial assessment by the ophthalmologists, vision was 3/200 OD with a right relative afferent pupillary defect. Her optic disc was reported to be normal in appearance, and she was considered to have retrolubar optic neuritis. Each day during the subsequent 3 weeks, she described her vision as getting “darker and darker.” Subsequent examination revealed that vision had decreased to light perception OD but her optic disc remained normal. Magnetic resonance imaging (MRI) revealed the suggestion of enhancement of the retrolubar optic nerve.
A presumptive diagnosis of retrobulbar ischemic optic neuropathy from giant cell arteritis was made, and she was treated with systemic corticosteroids. She had no other signs or symptoms of giant cell arteritis. She underwent temporal artery biopsy, the results of which were negative. During continued treatment with corticosteroids, her vision subjectively deteriorated further. Automated static perimetry in the unaffected left eye showed scattered defects (Figure 1). Five years before she had experienced central retinal vein occlusion (CRVO) in the left eye.

Our initial examination of the patient approximately 4 weeks later revealed no light perception OD and 20/20 OS. She had no proptosis and normal globe retropulsion bilaterally. Her right pupil was amaurotic. Color vision and red Amsler grid test results in the left eye were normal. Applanation tensions were 13 mm Hg OD and 12 mm Hg OS. Ocular motility was full. Automated perimetry now showed a superior quadrantic defect in the left eye.
eye, which respected the vertical meridian (Figure 1B). Optic disc edema was now present in the right eye with venous overfilling and several dot intraretinal hemorrhages.

An additional MRI study showed extensive enlargement and enhancement of the right optic nerve (Figure 2A). A biopsy specimen of the optic nerve revealed a malignant glioma. Despite chemotherapy and 6000 rad (60 Gy) of conformal radiation to the chiasm and right optic nerve glioma, she developed involvement of the optic chiasm (Figure 2B) and progressive visual loss in the left eye with a superior temporal quadrantic defect, which progressed to a complete temporal hemianopia and nasal visual loss (Figure 1C). She subsequently developed distant metastasis (Figure 3) and died in August 2000. Postmortem examination was not performed.

Patient 2. A 60-year-old man noted decreased vision in his right eye in December 1992. The vision was stable for 7 weeks but began to deteriorate 2 weeks before our initial evaluation. At that time, vision was 20/200 OD with a right relative afferent papillary defect and a swollen optic disc. The venous vasculature was normal without peripheral retinal hemorrhages. The results of ophthalmologic examination in the left eye were normal. An MRI suggested possible enlargement and mild diffuse enhancement of the right optic nerve extending to but not involving the optic chiasm. Neuro-ophthalmic evaluation 10 weeks after his initial visual loss showed visual acuity of 20/100 OD and 20/20 OS. Color vision in the right eye was decreased but was normal in the left eye. A central scotoma in the right eye was plotted, but the visual field in the left eye was normal. The right optic disc was elevated with chorioretinal folds with circumpapillary exudates extending into the papillomacular area (Figure 4). The differential diagnosis was that of an inflammatory optic neuropathy or optic nerve tumor.

Despite treatment with intravenous corticosteroids followed by an oral taper, his vision did not improve. A subsequent MRI showed no change in the minimal enhancement of the optic nerve. An optic nerve sheath fenestration was performed with removal of cerebrospinal fluid for analysis. The fluid was negative for malignant cells, and the vision improved to 20/50 OD with detumescence of the disc swelling.

One month later the vision decreased to hand motions (HM) OD, and the fundus picture was that of a CRVO with optic disc edema and hemorrhages, venous tortuosity, and choroidal filling defects on fluorescein angiography. Two months later the vision in the previously normal left eye decreased to 20/40 OS, although the optic disc remained normal. Subsequent MRI revealed involvement of the optic chiasm and...
the left optic nerve by a mass. A biopsy specimen of the right optic nerve revealed an anaplastic astrocytoma (Figure 5). The patient received external beam radiation from right and left anterior oblique ports for a total of 5200 rad (52 Gy). Immediately after this, he underwent stereotactic radiosurgery for a total tumor dose of 1500 rad (15 Gy). In February 1993, he had a single radiosurgical boost dose to the optic nerve for a total of 5200 rad (52 Gy). Immediately after this, he underwent stereotactic radiosurgery for a total of 5200 rad (52 Gy).

Figure 6. Visual field shows a dense central scotoma in the right eye (A) and a superior altitudinal defect in the left eye (B) in patient 3. Abbreviations are given in the legend to Figure 1.

The patient was considered to have nonarteritic AION in the right eye. Visual field testing revealed superior and inferior arcuate defects in the left eye consistent with glaucoma.

A rheumatologist thought she had giant cell arteritis and requested temporal artery biopsies, the results of which were negative. Despite this, she was treated with systemic corticosteroids, which were tapered rapidly. An MRI study showed no abnormal optic nerve or chiasmal enhancement.

Her vision continued to decline, and 6 months following initial consultation, her vision was light perception OD and 20/30 OS. Ophthalmoscopic examination revealed that the right optic nerve was still edematous, but she now had scattered flame-shaped hemorrhages throughout the posterior pole and along the distribution of the vascular arcades. Cystoid macular edema was also
Gliomas that involve the optic nerve usually occur in children, many of whom have signs of neurofibromatosis type 1. These gliomas typically demonstrate slow or no growth for years, especially if they are limited to the optic nerve. An intracranial location of the same tumor may produce more serious signs and symptoms, not necessarily because of the more aggressive histopathologic features of the tumor but rather owing to its location, which often involves the postchiasmal visual pathways or hypothalamus.

Optic nerve gliomas are rare in adults. When they do occur, these gliomas tend to be highly aggressive, leading to blindness and death in a relatively short period. Hoyt et al. describe the clinical syndrome of the so-called malignant gliomas of adulthood in a landmark article that predated modern neuroimaging. They list 4 features of the syndrome: it involved predominantly middle-aged men, mimicked optic neuritis initially, progressed within 5 to 6 weeks to blindness, and ended in death within several months. They characterize the syndrome as due to the occurrence of a common type of brain tumor (glioblastoma) in an uncommon location (the optic nerve).

Malignant optic nerve gliomas may occur in isolation or as one of several intracranial gliomas of presumed multicentric origin. The diagnosis is more apparent when an initial imaging study shows that additional lesions accompany the optic nerve mass.

Review of the literature suggests that the average age at initial treatment for aggressive gliomas of adulthood is 52 years. All of the 35 patients identified had visual loss, 5 had associated proptosis, and 16 had associated neurologic symptoms (headache, hemiplegia, or dementia). In most patients both eyes become affected within 5 to 6 weeks, and the patient soon becomes blind. If the tumor originates in the anterior portion of the optic nerve, the symptoms start unilaterally, with a swollen optic nerve and subsequent progression to venous occlusion and then bilateral involvement. When the origin is in the distal portion of the optic nerve or the optic chiasm, the visual loss may be simultaneously bilateral or nearly so and is associated with a pale or normal-appearing optic disc (posterior ischemic optic neuropathy).

Since most patients with aggressive optic nerve gliomas are middle-aged or older, the process is readily distinguished from optic neuritis. However, AION is frequently encountered in the same age group as aggressive optic nerve gliomas, and the distinction between them is more problematic. Anterior ischemic optic neuropathy is characterized by a relatively sudden loss of vision in 1 eye accompanied by the ophthalmoscopic appearance of a swollen, sometimes pale, optic disc. The peripheral retina and the retinal vascular circulation are normal without venous congestion or peripheral hemorrhages. The visual loss in nonarteritic AION is stable and nonprogressive in approximately 70% of patients. Giant cell arteritis produces a form of AION that strikes an even older population, causes more severe visual loss that may progress more rapidly, and will often involve the second eye within days or weeks. The optic disc swelling in both these forms of AION subsides within 6 to 12 weeks and the disc becomes pale. Optic atrophy without cupping is the end stage of nonarteritic AION, but cupping, often indistinguishable from glaucoma, is seen after arteritic AION.

The optic disc swelling of adult gliomas, unlike that of AION, per-
sists. Usually there is progression to retinal venous occlusion and then to retinal arterial occlusion. The appearance of a congestive venous retinopathy in AION is distinctly unusual. Unlike incipient CRVO, where visual acuity is preserved, the initial visual loss associated with adult gliomas is severe and, as seen in our patients, may progress to no light perception before the appearance of a CRVO or central retinal artery occlusion (CRAO). A more detailed description of the characteristics of these 3 entities is found in the Table.

Most patients with AION have normal MRI studies. Enhancement of the optic nerve has been described in both arteritic20 and nonarteritic AION.21 However, the enhancement in both forms of AION is uncommon and much more subtle than in any of our patients. Therefore, any enhancement of the intracanalicular optic nerve must raise the probability of a process other than ischemia.

The initial clinical course of our 3 patients suggested nonarteritic or arteritic ischemic optic neuropathy as the cause of visual loss. The first patient was diagnosed as having posterior ischemic optic neuropathy because of the sudden onset of visual loss with a normal optic disc appearance. The atypical course of inexorable and rapid progression of visual loss and the subsequent development of disc edema led to imaging, which identified the lesion and suggested the correct diagnosis. The second patient was diagnosed as having an inflammatory optic neuropathy because of the presence of optic disc edema and retinal exudates. The optic neuropathy failed to respond to corticosteroid treatment. We then considered AION to be the cause of the visual loss, and an optic nerve sheath fenestration was performed. The optic disc edema eventually worsened, and the patient developed macular edema and venous obstruction and subsequently optic discial shunt vessels, all signs of progressive retinal venous obstruction. The third patient was initially diagnosed as having nonarteritic AION and subsequently arteritic AION because of her atypical progressive course. In her follow-up examination 5 months later, she had evidence of a CRVO. However, in all 3 patients there was a clear history of progressive visual loss for more than 1 month and persistent disc edema lasting more than 2 months, with the ultimate development of late retinal venous obstruction. Venous congestion or CRVO developed in all 3 patients within 5 months. We believe that if the initial appearance of the optic nerve seems consistent with that of ischemic optic neuropathy (swollen optic nerve without venous engorgement or retinal hemorrhages) but the subsequent course is not (prolonged disc edema for >6 weeks or development of combined CRAO/CRVO or CRVO several months after the initial onset of optic nerve swelling), the patient should undergo neuroimaging with consideration given to the diagnosis of aggressive gliomas of adulthood.

Patient 1 survived for 11 months, and her vision deteriorated slowly to a final level of no light perception OD and 20/30 OS with a temporal hemianopic defect. Patient 2 survived for 20 months, and the vision in her fellow eye decreased to HM. Patient 3 survived for 2½ years, and her visual function was preserved in the contralateral eye until her death. It cannot be stated with certainty if the preservation of vision in the fellow eyes of these 3 patients was due to the treatment. However, we believe that prompt diagnosis and institution of appropriate treatment provide these patients with the best chance for prolongation of life and retardation of their visual loss.

We recommend that any patient diagnosed as having ischemic optic neuropathy who experiences continued progression of visual loss, persistent optic disc swelling, or the late development of signs of CRVO or CRAO should undergo MRI to identify this unusually aggressive tumor.

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2. Listerick R, Charrow J, Greenland M, Met M. Natural history of optic pathway tumors in...

**Figure 1.** Sagittal (left) and axial (right) contrast-enhanced T1-weighted magnetic resonance images reveal focal leptomeningeal enhancement (arrows) in the occipital lobes and superior cerebellum, and an old right basal ganglia infarct.