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 monocytic 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 hypoplasia or agenesis 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). 1

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. 2 3 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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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 repulsion 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 quadrant 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 quadrant 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 relative afferent pupillary 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 and chiasm for a total of 1250 rad (12.5 Gy). Despite this radiation therapy, vision decreased to HM OS, and he developed MRI evidence of subependymal spread of the tumor and died approximately 20 months after the onset of the visual loss.

Patient 3. A 77-year-old woman sought treatment in November 1995 for decreased vision in her right eye for 3 weeks. She saw an ophthalmologist who made a diagnosis of nonarteritic AION. Her medical history revealed hypertension, a positive purified protein derivative test result, hypoglycemia, and mononucleosis. She had been diagnosed as having low-tension glaucoma 7 years before. Her medications included 0.5% timolol maleate, 2% pilocarpine hydrochloride, and 2% dorzolamide hydrochloride.

Visual acuity was counting fingers at 6 ft OD and 20/30 OS. External examination results were normal. She was unable to identify any of the Ishihara pseudoisochromatic color plates or the red Amsler grid using the right eye but identified them correctly with the left. Slitlamp examination results were unremarkable. Applanation tensions were 24 mm Hg OD and 23 mm Hg OS. She had a prominent relative afferent pupillary defect in the right eye. Automated static perimetry revealed a dense central scotoma in the right eye and superior and inferior arcuate visual field defects in the left (Figure 6). Fundus examination showed a swollen right optic disc with venous engorgement and glaucomatous cupping in the left eye.

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 20/40 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
noted. The left optic disc remained unchanged. A diagnosis of CRVO was made, and she was referred back for neuro-ophthalmologic examination.

These findings were confirmed, and because they were not consistent with AION, subsequent MRI showed that the entire right optic nerve was enlarged from the papilla to the optic chiasm with diffuse enhancement following contrast administration (Figure 7). The initial MRI study was not available for review. A clinical diagnosis of possible malignant glioma of the optic nerve was made, and biopsy of the optic nerve was performed. The biopsy specimen was interpreted as an anaplastic astrocytic neoplasm because of the degree of nuclear pleomorphism and a high Ki67 labeling index.

She underwent radiation to the right optic nerve by 3-field conformal radiotherapy technique for 40 days, completed at a total of 5940 rad (59.4 Gy). Neuro-ophthalmologic evaluation 18 months following initial treatment revealed no light perception OD and 20/40 OS. The right optic disc was flat and pale, and there was sclerosis of the retinal vessels. She ultimately developed neovascular glaucoma in the right eye. The patient died 2½ years after her initial visit. An autopsy was not performed.

Comment. 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 predates 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.6 The appearance of a congestive venous retinopathy in AION is distinctly unusual.17 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 arteritic and nonarteritic AION.20 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 intracranial or intracranial 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 optociliary 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 his fellow eye decreased to HM. Patient 3 survived for 20 months, and her vision deteriorated slowly to 20/300 OD and 20/30 OS with a temporal hemianopic defect. Patient 3 died 20 months after his initial examination. Her vision deteriorated to no light perception and her visual field was reduced to 20/300 OS. 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 his 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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Abbreviations: CRAO, central retinal artery occlusion; CRVO, central retinal vein occlusion; ION, ischemic optic neuropathy; MRI, magnetic resonance imaging.

### Table. Clinical Characteristics of Ischemic Optic Neuropathy and Aggressive Gliomas

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonarteritic ION</th>
<th>Arteritic ION</th>
<th>Aggressive Glioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual loss</td>
<td>Sudden</td>
<td>Sudden</td>
<td>More slowly</td>
</tr>
<tr>
<td>Progression</td>
<td>Approximately one third</td>
<td>Occasionally</td>
<td>The rule</td>
</tr>
<tr>
<td>Second eye involvement</td>
<td>24% with a mean interval of 2.9 y</td>
<td>Days to weeks later</td>
<td>Progressive involvement of the second eye</td>
</tr>
<tr>
<td>Disc appearance</td>
<td>Swollen, usually sectorial</td>
<td>Swollen, usually chalk white</td>
<td>Swollen or normal, not particularly pale initially</td>
</tr>
<tr>
<td>Remainder of fundus</td>
<td>Normal</td>
<td>May have retinal infarcts</td>
<td>Evolves into combined CRAO and CRVO picture</td>
</tr>
<tr>
<td>Spontaneous recovery of vision</td>
<td>42% (≥3 lines)</td>
<td>Usually not</td>
<td>No</td>
</tr>
<tr>
<td>MRI</td>
<td>Normal</td>
<td>Normal</td>
<td>Enhancement of retrobulbar optic nerve</td>
</tr>
<tr>
<td>Visual field</td>
<td>Optic nerve defect</td>
<td>Optic nerve defect</td>
<td>Optic nerve or chiasmal defect</td>
</tr>
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Transient Cortical Blindness With Leptomeningeal Enhancement After Attempted Peripherally Inserted Central Venous Catheter Placement

Transient cortical blindness is an infrequent complication of endovascular procedures.1-3 We describe a patient who developed transient cortical blindness associated with focal leptomeningeal enhancement on contrast-enhanced T1-weighted magnetic resonance imaging (MRI) following attempted placement of a peripherally inserted central venous catheter (PICC).

Report of a Case. A 57-year-old woman with metastatic carcinoma of the colon, which had spread to the liver and peritoneum, was hospitalized for partial small-bowel obstruction. Placement of a PICC for total parenteral nutrition (TPN) was attempted with inadvertent cannulation of the brachial artery and infusion of 10 mL of nonheparinized normal saline. The catheter was promptly removed; however, the patient began to complain of blurring vision in each eye approximately 15 minutes after the attempted PICC placement. During the procedure, the patient was hypertensive and tachycardic with a blood pressure of 170/120 mm Hg and a heart rate of 120 beats per minute. The patient’s blood pressure was controlled with low-dose oral metoprolol.

After the procedure, the patient complained of progressive visual loss, headache, and malaise, which progressed to complete binocular visual loss during the ensuing 4 hours. Ophthalmic examination revealed no light perception vision bilaterally and briskly reactive pupils, without a relative afferent pupillary defect. The anterior segment, extracocular motility, and dilated funduscopic findings were normal in each eye. Findings from the remainder of the neurologic examination were otherwise normal.

Contrast-enhanced MRI obtained 4 hours after the onset of visual loss revealed focal leptomeningeal enhancement in the occipital lobes and superior cerebellum (Figure 1). Diffusion-weighted images showed no evidence of ischemia, and magnetic resonance angiography demonstrated normal cerebral vasculature.

Lumbar puncture showed an elevated protein level of 119 mg/dL and a normal glucose level of 81 mg/dL with a normal opening pressure. No atypical cells or white blood cells were seen. The results for cerebrospinal fluid cultures and blood cultures were negative. Twenty-four hours after the onset of visual loss, the patient experienced 2 generalized seizures, which were controlled with intravenous dexamethasone and phenytoin.

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.