keratoconus. The published cases that developed haze either had stage III keratoconus or more advanced changes including thinner corneas, higher keratometry values, and prominent Vogt striae. Mazzotta et al reported that hyporeflective bands in a reticular pattern representing stromal microstriae prior to CXL could be a confocal sign of advanced keratoconus, predicting haze formation. This pattern was not seen in our cases, consistent with the milder clinical picture. Despite the lower risk profile of our patients, both developed dense, deep stromal scars that were morphologically different and more severe than the faint haze described by Mazzotta et al and Raiskup et al. The deep stromal scar also occurred at the junction between the treated and untreated cornea along the demarcation line, which has not been previously described. Mazzotta et al also described increased keratocyte density in the region of the scar, in contrast to the reduced keratocyte population in our cases. Riboflavin–UV-A exposure typically causes keratocyte apoptosis in the early postoperative period, and we speculate that a sublethal effect in the deep stroma where the UV-A irradiation dose is lower may lead instead to fibroblastic transformation and an aberrant scarring response. This would explain the delayed reaction seen and, if proven in subsequent study, may suggest that longer or higher-intensity UV-A irradiation is indicated. Performing a modification of the technique in which the epithelium is not removed may also help prevent this complication.

In conclusion, deep corneal stromal scarring may complicate CXL for mild keratoconus and, if severe, may lead to a significant increase in astigmatism.

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Submitted for Publication: February 2, 2010; final revision received April 23, 2010; accepted May 3, 2010.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by Singapore Eye Research Institute grant R573/61/2007.

Methods. This study reports all cases of TRB from 2000 to 2008 treated at The Hospital for Sick Children (Toronto, Ontario, Canada). All patients were treated during a prospective clinical trial that was approved by The Hospital for Sick Children research ethics board and that conforms to the principles of the Declaration of Helsinki.

Report of Cases. Case 1. A 4-month-old girl had hypothalamic overgrowth syndrome and central blindness from a large suprasellar tumor...
observed on computed tomographic (CT) and magnetic resonance imaging (MRI) scans (Figure, A). Her bilateral retinal tumors were initially diagnosed as astrocytic hamartoma.14 Cranioopharyngioma or germ cell tumor was suspected, but CSF α-fetoprotein and β-human chorionic gonadotropin levels were normal. Needle biopsy of the suprasellar region showed necrotic tumor, but open biopsy confirmed the diagnosis of TRB, with bilateral group B (T1b) eyes, staged according to the International Intraocular Retinoblastoma Classification (IIRC).15 Postoperative CSF sample was positive for tumor cells (M1e on TMN staging),16 but samples obtained prior to and during the needle biopsy were negative. There were no bone marrow or bone metastases. Her germline RB1 mutation was a deletion (g.59444 del196) affecting splicing of exon 8.

She responded to 6-cycle systemic CEV-CSA and to intraven-
tricular cytarabine-topotecan given via an Ommaya reservoir, with clearing of the CSF metastases, shrinkage of the suprasellar tumor, central blindness, and retinal tumors, and restoration of vision. She received a suprarenal dosage of carboplatin, etoposide, and cyclophosphamide as consolidation with autologous peripheral stem cells for bone marrow rescue. However, 19 months after diagnosis and 11 months after transplant, the tumor recurred along the needle biopsy tract, and she died 32 months after the diagnosis was given.

Autopsy revealed multiple subdural and subarachnoid nodular growths and widespread leptomeningeal and ventricular metastases, especially around the needle biopsy tract (data not shown). The suprasellar mass was calcified and nonviable. The eyes showed calcified tumor and retinal scarring, with one tiny focus of viable tumor in the right eye.

Case 2. A 6-month-old boy presented with leukocoria of the left eye, which was classified as IIRC group D (T3a) and enucleated. Two months later, he developed central blindness, and a large suprasellar tumor was found on CT and MRI scans (Figure, C); a small tumor in the right eye was classified as IIRC group A (T1a). He had CSF metastases (M1e stage) but no bone marrow or bone metastases. To avoid risk of tumor dissemination as observed in case 1, the suprasellar tumor was not biopsied. His germline RB1 mutation was a 1–base pair deletion (c.1951delT) in exon 19 causing a premature stop codon and nonfunctional pRB protein.

He responded to 6-cycle systemic CEV-CSA and to intraventricular cytarabine-topotecan, with clearing of CSF metastases, shrinkage of the suprasellar tumor (Figure, D) and retinal tumors, and restoration of vision. He received the autologous peripheral stem cell transplant regimen described for case 1 as consolidation. He remains in remission 3.4 years after diagnosis and the remaining 2 surviving for 14 and 32 months, respectively.

A possible advantage of our chemotherapy regime that may have contributed to the prolonged survival of patients with TRB may have been the addition of CSA, which not only reverses multidrug resistance in retinoblastoma tumor cells but also inhibits the p170-rich vascular endothelial cells that form the blood-brain barrier limiting the entry of chemotherapeutic drugs into the central nervous system. Toxicity has always been the dose-limiting factor for multidrug resistance–reversal chemotherapy. Published studies have used 5- to 7-day continuous CSA infusions to reverse tumor-cell p170, but prolonged exposure to CSA also circumvents normal-cell p170. This leads to increased toxicity to p170-expressing bone marrow, liver, kidney, gut, and other tissues and delays liver and renal excretion and metabolism of chemotherapy, thereby further increasing drug exposure to normal tissues. We have shown that 3-hour high-dose CSA infusions avoid enhancement of high-dose CEV toxicity (so our patients tolerate chemotherapy well) and are efficacious in modulating retinoblastoma chemotherapy.

Cytarabine, a pyrimidine antimetabolite antileukemic agent, generally has little anti–solid tumor activity but is not a substrate of p170 and can kill retinoblastoma cell lines in vitro. Used together with topotecan (a topoisomerase I inhibitor), which is less susceptible to multidrug resistance, we have successfully cleared CSF metastases, the most difficult type of retinoblastoma metastases to cure.

High-dose craniospinal radiation therapy is not an option for young children because it causes devastating long-term neurological effects (cognitive and learning problems) and hormonal complications (growth, thy-
Treatment of TRB using the Toronto Protocol and intrathecal topotecan combined with cytarabine, followed by consolidation with autologous peripheral stem cell transplant after supralethal chemotherapy avoids the need for radiation therapy and, in some instances, extends survival.

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Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grants to Dr Chan from The Ontario Institute for Cancer Research and to Dr Gallie from the Canadian Retinoblastoma Society and the Royal Arch Masons of Canada.


Acute macular neuroretinopathy (AMNR) is a rare retinal condition that features the sudden onset of bilateral central scotomata, which may be preceded by a viral prodrome in some patients. Acute macular neuroretinopathy may be difficult to diagnose because of the subtle or even absent findings on funduscopic examination and fluorescein angiography. Bos and Deutman initially described AMNR in 4 patients with paracentral scotomata, slightly decreased visual acuity, and reddish, wedge-shaped intraretinal lesions directed toward the fovea. Because of the acute onset of the symptoms and based on their theory that the more superficial layers of macular retina were involved, the term AMNR was adopted.

Herein, we describe 2 patients with features of AMNR in whom Amsler grid testing, infrared imaging, spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence, and multifocal electroretinogram (mERG) were useful in characterizing the precise structural and functional deficits of this condition. The localization of structural deficits to the outer retina and photoreceptor layer using SD-OCT and evidence of depressed cone amplitudes using mERG in both patients were more consistent with photoreceptor and outer retinal dysfunction. Hughes et al previously reported 2 cases of AMNR that featured outer retinal structural changes using SD-OCT. The functional and anatomic deficits observed in our patients using multimodality diagnostic testing, combined with the previous structural characterization of AMNR,2-3 are supportive of the proposed nomenclature acute macular outer retinopathy (AMOR) to more accurately describe this unique clinical entity.2