Juvenile Xanthogranuloma of the Limbus in an Adult

Juvenile xanthogranuloma (JXG) is a cutaneous granulomatous disease rarely seen in adults and has only been reported to occur at the limbus in very few cases. We describe a patient with an unusual corneal limbal mass and a skin rash, who was diagnosed histologically as having JXG. The clinical features and management of this rare entity are discussed.

Report of a Case. A 39-year-old man came to our department with a painless limbal mass on his right eye that had enlarged during 3 months. His visual acuity was 20/40 OU and on slitlamp examination, a yellowish, well-circumscribed, vascularized, round nodule was evident at the 6-o’clock position of the right limbus, measuring 6 mm in diameter.

The visual axis was clear, and on gonioscopy, neither the trabecular meshwork nor the iris was involved. Further ocular and orbital examination results were unremarkable. Systemic examination revealed an orange-red maculopapular rash involving the trunk, axillae, groin, and face (Figure 1). No associated lymphadenopathy, joint swelling, or oral ulceration were present. Examination of cardiorespiratory and abdominal systems disclosed normal results. Complete blood cell count with differential white cell count, serum lipid and urea levels, creatinine estimation, plasma viscosity, liver function test results, and chest x-ray film were all normal. Sarcoidosis and tuberculosis were excluded on examination by a pulmonologist. Before a diagnosis could be made, we performed biopsies of the ocular and skin lesions.

The histopathologic report of the limbal lesion showed early keratinization over a disorganized spindle cell lesion with scattered lymphocytes and plasma cells. Occasional giant cells were also noted. Histopathologic examination of the skin lesion identified a well-circumscribed lesion composed of histiocytic-looking cells with abundant, occasionally vacuolated cytoplasm, spindle-shaped cells, foci of lymphocytes, and bands of collagen. Multinucleated cells were also found and these occasionally showed the characteristic features of a Touton giant cell. Based on the histopathologic findings, a diagnosis of adult-onset JXG was made.

We initially opted for conservative management since the patient was reluctant to undergo surgery. However, 18 months following the initial examination, the lesion had grown to 9 mm × 5.7 mm (Figure 2) and was causing some discomfort. Surgical excision was carried out and the lesion was sent for histologic examination. This showed a granulomatous lesion rich in Touton-type giant cells, with occasional...
solitary tumors seem to be comparatively rare. Orbital lesions frequently, with epibulbar lesions being approximately 10% of patients. Iris lesions are the most common and sometimes cause spontaneous hypHEMA and secondary glaucoma. In the series by Zimmerman, eyelid lesions were the next highest in frequency, with epibulbar lesions being comparatively rare. Orbital lesions have also been reported infrequently. Solitary tumors seem to be more common in adult- and adolescent-onset disease. To our knowledge, there have been 4 reported cases of JXG occurring at the limbus in an adult. None of these cases had coexistent skin lesions. All were treated by surgical excision and no recurrences were reported; the longest follow-up, however, was only 2 years.

Our case had a 5-year history of cutaneous involvement before the onset of the limbal mass. The cause for this delay is unknown but it has been suggested that a form of local irritation is the stimulus for the accumulation of histiocytes that characterize the lesion histopathologically. However, there was nothing in our patient’s history to suggest that this was case. The diagnosis was based on the clinical signs and symptoms and the histopathologic appearance of biopsy specimens taken from the eye and skin. The typical appearance is a mixture of foamy and epithelioid histiocytes with a scattering of lymphocytes, eosinophils, and occasional plasma cells. The classic Touton giant cell, with its wreath of histiocytes, is often seen, especially in mature lesions.

Juvenile xanthogranuloma runs a benign course and therefore must be differentiated from the more serious group of histiocytic disorders—namely, the Langerhans cell histiocytosis X. Typically, JXG lesions are distinguished by the lack of staining for S100 protein. However, in a recent series, 6 of 100 cases were positive for monoclonal markers of S100 protein. Juvenile xanthogranuloma lesions also show positivity for macrophage markers, such as CD68 and HAM56 but lack Birbeck granules on electron microscopy. Fibrous histiocytomas can appear histologically similar to JXG but typically have a storiform pattern of fibrocytes and lack the cosinophilic infiltration. The other main differential diagnoses are dermoli-poma, dermoid, neurofibroma, and other xanthomas.

Previously reported cases have been treated with surgical excision or without lamellar keratoplasty. Iris lesions, which are difficult to treat surgically because of their vascularity, have been successfully treated with topical and systemic steroids, radiotherapy, and in one case, low-dose methotrexate.

In summary, to our knowledge, this is the first case report of skin involvement in an adult patient with limbal JXG. The skin lesions, when present, appear to persist, whereas in infants, they are usually self-limiting. Peribulbar lesions appear to be slow-growing and painless. This diagnosis should be made on histopathologic grounds and after exclusion of systemic granulomatous and histiocytic disorders.

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Figure 3. Histopathologic results showing the limbal lesion with multiple Touton giant cells (hematoxylin-eosin; original magnification ×20).
Bilateral Sequential Orbital Involvement by Eosinophilic Granuloma

Langerhans cell histiocytosis is an uncommon, multisystem disease with a clinical spectrum that includes benign unifocal disease (eosinophilic granuloma), chronic multifocal disease (Hand-Schüller-Christian disease), and acute or subacute fatal disseminated disease (Letterer-Siwe disease). It accounts for 1% to 7% of biopsied orbital tumors. Eosinophilic granuloma is the most common variant of Langerhans cell histiocytosis, with approximately 20% of cases affecting the orbital area. When it occurs in the orbit, it is usually unilateral and localized. We are unaware of a previously reported case of eosinophilic granuloma with bilateral orbital involvement, and a computerized literature search using Medline disclosed no other examples. We herein report a case of eosinophilic granuloma that exhibited sequential bilateral orbital involvement.

Report of a Case. In November 1988, a 5-year-old otherwise healthy boy was referred to us for evaluation of left eyelid swelling and proptosis (Figure 1A). He had been diagnosed elsewhere as having allergic eyelid edema, and he had been treated with topical corticosteroids with no response. There was a history of head trauma 3 months earlier that caused bilateral eyelid ecchymoses, and spontaneous healing occurred. Ocular examination disclosed visual acuity of 20/20 OU. There was 5 mm of left axial proptosis without palpable mass. Computed tomography (CT) showed an orbital mass with a heterogeneous internal structure in the lateral wall of the left orbit, and time-sensitive images showed extension into the brain and temporal fossa. Histopathologic examination showed clotted blood that contained eosinophils, histiocytes, and multinucleated giant cells (Figure 1B). Incisional biopsy findings revealed a dark brown mass consistent with degenerated blood. Histopathologic examination showed clotted blood that contained eosinophils, histiocytes, and multinucleated giant cells (Figure 1C). These findings suggested the diagnosis of either giant cell reparative granuloma or Langerhans cell histiocytosis. The bone defect closed spontaneously without treatment in 8 months.

In June 1990, 18 months after initial examination, the boy developed painful, nonerythematous swelling of his right upper eyelid. The CT findings disclosed a similar lesion in the superolateral aspect of the right orbit with destruction of the frontal bone and extension into the brain and temporal fossa. The mass contained densities consistent with fragments of bone. The previously affected left orbit appeared normal (Figure 2). Incisional biopsy of the right orbital mass was performed, and dark black tissue consistent with degenerated blood was observed intraoperatively. Histopathologic examination showed hemorrhagic tissue with small multinucleated giant cells, large histiocytes with folded nuclei, eosinophils, and fibrosis. The histiocytic cells showed intense positive immunoreactivity for S-100 protein, supporting the diagnosis of eosinophilic granuloma in the right orbit. After 6 months’ follow-up, the second lesion healed spontaneously without further therapy. At 93 months’ follow-up, the patient remains healthy without systemic problems.

Figure 1. A, A 5-year-old boy developed eyelid swelling and proptosis of the left eye. B, Axial computed tomography reveals a left orbital mass eroding the frontal bone with extension into the temporal fossa. C, Histopathologic examination showed admixture of histiocytes with nuclear folds, eosinophils, and multinucleated giant cells (hematoxylin-eosin, original magnification ×250).

Figure 2. Axial computed tomography demonstrated a similar mass in the superolateral aspect of the right orbit with destruction of the frontal bone into the brain and temporal fossa. The left orbit showed a healed lesion and bone defect.
Comment. Eosinophilic granuloma is a rare disease that is classified as a variant of Langerhans cell histiocytosis. It is generally diagnosed in children or young adults and shows a predilection for males. In the orbit, it typically manifests as a painful, tender, erythematous swelling near the superolateral part of the orbit anteriorly. In more posteriorly located tumors, eyelid swelling or proptosis can be the first sign. Computed tomography is the most helpful diagnostic test and shows an irregular, serrated osteolytic lesion with sclerotic margins. Histopathologic evaluation displays a proliferation of large histiocytic cells with folded nuclei consistent with Langerhans cells with interspersed eosinophils and small multinucleated giant cells. The histiocytic cells show a positive immunoreactivity for S-100 protein, CD1 (OKT6) antigen, and α-1 antichymotrypsin. Electron microscopy demonstrates intracytoplasmic Birbeck granules corroborating the diagnosis of Langerhans cell histiocytosis. In the orbit, the differential diagnosis in children includes dermoid cyst, lacrimal gland tumor, primary bone tumors such as osteosarcoma, aneurysmal bone cyst, ossifying fibroma, fibrous dysplasia, and metastatic tumors, such as neuroblastoma and Ewing sarcoma.

In the orbit, in contrast to eosinophilic granuloma, dermoid cyst is a round to ovoid lesion with a well-defined, enhancing thin wall and nonenhancing contents on CT evaluation. Epithelial tumors of the lacrimal gland (except adenoid cystic carcinoma) rarely affect young children and generally cause bone fossa formation rather than a large bone defect that reflects an epicenter of the lesion in the bone. Primary bone tumors do not exhibit the characteristic lytic lesion with sclerotic margin of eosinophilic granuloma on CT scan. Metastatic orbital tumors show the irregularly shaped bony defects, usually occurring late in the course of neuroblastoma or Ewing sarcoma, and systemic evaluation almost invariably reveals the primary tumor.

In a recent study, Lieberman et al suggested using the term Langerhans cell (eosinophilic) granuloma instead of Langerhans cell histiocytosis and classified it further into unicentric and multifocal eosinophilic granuloma. In a survey of 238 cases of eosinophilic granuloma from the general pathology laboratory in a cancer center, multifocal eosinophilic granuloma was found in 85 cases (36%) at the time of diagnosis. Some of these cases, 63% involved only bones (n=53), 24% involved both bone and soft tissue (n=20), and 14% involved only soft tissue (n=12). The involved bone included skull (52%), femur (29%), and rib (22%). Soft tissue involvement included skin (14%), lymph node (13%), and lung (11%). Another review of 348 cases treated in multiple pediatric hematology/oncology departments revealed that isolated bone lesions were mostly unifocal or bifocal in 39% of cases and multifocal in 19% of cases. Different from unifocal eosinophilic granuloma, multifocal eosinophilic granuloma usually has bimodal distribution and one peak between the ages of 0 to 10 years and the other between the ages of 20 to 30 years. Bilateral sequential orbital involvement, as seen in our case, is highly unusual, if not unique.

The treatment of eosinophilic granuloma may include surgical curettage, low dose irradiation, administration of cytotoxic agents, systemic corticosteroids, or intrascleral corticosteroids. In some cases, initial biopsy followed solely by observation is curative, leading to spontaneous resolution of the inflammatory mass as occurred in our case. The systemic prognosis of patients with unifocal eosinophilic granuloma and multifocal eosinophilic granuloma limited to bone is excellent. In a review of 348 cases treated in pediatric hematology/oncology departments, the survival rate was 96% to 100% at 7 years in patients with eosinophilic granuloma limited to bone. However, in some cases, local recurrence of the lesion is observed between 6 and 18 months. In our case, there has been no recurrence or progression to disseminated disease after 8 years. The multivariate prognostic analysis in 348 cases showed that organ involvement, age younger than 1 year, and failure responding to therapy were associated with a bad prognosis. In our case, none of these factors were present.

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Hereditary X-Linked Juvenile Retinoschisis: A Review of the Role of Müller Cells

Hereditary X-linked retinoschisis (RS) is the most common cause of juvenile macular degeneration in males and may lead to vitreoretinal degeneration characterized by cystic spoke-wheel maculopathy, peripheral retinoschisis, alterations of the vitreous body, and a reduced b wave on the electroretinogram. Its prevalence ranges from 1:5000 to 1:25000. The condition is usually bilateral and affects males only.
Males with juvenile RS usually seek treatment because of diminished vision at school age, followed by progressive visual deterioration later in life. Peripheral retinoschisis is found in 50% of patients and may be limited to the inferior temporal quadrant. Breaking of the inner schisis layer may lead to unsupported retinal vessels in the vitreous cavity, called a “congenital vascular veil.”

There have been few reports on the histopathologic characteristics of RS. The principal feature in all these cases was a large schisis cavity originating from the nerve fiber layer (NFL). Several theories concerning the pathogenesis of RS have been postulated. First, findings on fluorescein angiography led to a vascular theory of RS development because of delayed development of the retinal and choroidal vasculature in which the retina outgrows its blood supply infratemporally. Vascular changes might play a role in the evolution of the schisis, and RS may be complicated by neovascular glaucoma.

Second, Scheepen believed that the primary abnormality was vitreous traction on the inner retinal surface caused by inadequate growth or shrinkage of the cortical vitreous. The histologic characteristics of RS in a male infant with congenital retinal detachment and splitting in the inner retina but no schisis and in 2 male infants with congenital hereditary RS supported the theory of a vitreoretinal developmental anomaly. Third, based on pathological findings, several authors postulated that juvenile RS arises from a basic inherited defect in probably the innermost portion of the cytoplasm of Muller cells. Current molecular genetic and immunohistochemical findings contradict the theory of a primary defect in the Muller cells and suggest an abnormality that interacts with a Muller cell receptor or components of the extracellular matrix. Based on immunohistochemical analysis with a RS1-specific antibody applied to the enucleated eye of a relatively young patient with RS, we support the theory that photoreceptors appear to be the cells primarily involved in the pathologic characteristics of RS.

**Patient, Materials, and Methods.** At age 5 months, our patient was diagnosed as having X-linked juvenile RS. At age 19 years, his right eye was enucleated. The enucleated eye was fixed in 5% formaldehyde solution in a 0.1M phosphate buffer. After horizontal sectioning, the eye was embedded in paraffin. Sections (5-µm) were incubated with polyclonal antibody glial fibrillary acid protein (DAKO, Glostrup, Denmark) (dilution, 1:1200; incubation, 30 min at room temperature; peroxidase-antiperoxidase method). The monoclonal antibodies vimentin (Biogenex, San Ramon, Calif), and fibronectin (DAKO) and neurofilaments (Sanbio, Uden, the Netherlands) were applied using the avidin-biotin complex method (dilution, 1:3200, 1:1200, and 1:300, respectively; incubation, 10 min). Prior to incubation with vimentin and neurofilaments, slides were pretreated for 15 minutes in citrate buffer (microwave); prior to fibronectin incubation, slides were pretreated with pronase for 10 minutes. The RS1 antibody was provided by one of us (B.H.F.W.) and is identical to the RS1 antibody described in Molday et al. In short, the amino peptide LSSTEDEGFYWQKAC, corresponding to aa22-39 of the human RS1 precursor protein, was conjugated to keyhole limpet hemocyanin and used to immunize New Zealand White rabbits. For immunolabeling, a 1:1000 dilution of rabbit serum was used. Prior to incubation, slides were pretreated for 10 minutes in citrate buffer (microwave). A formalin-fixed paraffin-embedded eye with a healthy human retina was used as a control.

Material was sampled from the formalin-fixed retina and embedded in epoxy resin after dehydration with grading acetone. Semithin sections (1 µm) for light microscopy were made with a glass knife and stained with toluidine blue (1% weight-volume ratio). Ultrathin sections (70-80 nm) were cut with a diamond knife and mounted on unfilmed 300-mesh copper grids. After staining for 30 minutes with uranyl acetate and 2 minutes with lead citrate, the ultrathin sections were examined with a Zeiss EM 902 transmission electron microscope (Carl Zeiss, Oberkochen, Germany) with an acceleration voltage of 80 kV.

Our patient was also enrolled in a large study by the Retinoschisis Consortium on screening for mutations of the gene involved in RS (RS1).

**Results.** The family pedigree revealed an X-linked mode of RS inheritance with several males affected (Figure 1). In our patient, pursuit movements, a convergent strabismus of his right eye, and remnants of persistent pupillary membranes were recorded on early examination. At age 5 years, a cataract developed in his right eye. Visual acuity was light perception OD and 20/200.
At age 8 years, his right eye showed a mature cataract with posterior synechiae. Recurrent granulomatous uveitis with large iris nodules occurred in the right eye from age 18 years onward (Figure 2A) and initially responded to topical steroids and cycloplegia. Laboratory testing did not reveal a cause for the

Figure 2. Cataract and large iris nodules in the right eye (A). Funduscopy of the left eye (B) of a patient with juvenile retinoschisis shows delicate retinal cysts. In the enucleated eye, a depigmented area is noted macroscopically in the posterior pole (C) with some vascular veils extending anteriorly. Microscopically, the cysts originated from schisis in the nerve fiber layer in the inferotemporal part of the retina (asterisks) (D). The underlying retina and the nasal retina were detached (arrows), and the retina was folded at the base of the schisis cavities (hematoxylin-eosin, original magnification ×1.7). In the nasal-posterior part of the retina (E), there is splitting in the inner and outer plexiform layers (arrows) (hematoxylin-eosin, original magnification ×100). In the central retina (F) multiple PAS (periodic acid–Schiff)–positive globules are present in all retinal layers (original magnification ×400). In the anterior segment (G), occlusion of the pupil is present. The lens shows a hypermature cataract with posterior synechiae and rupture of the anterior lens capsule with a reactive inflammatory infiltrate (hematoxylin-eosin, original magnification ×25). Glial fibrillary acid protein stains strongly positive throughout the retina (H) (original magnification ×400). The nerve fiber layer (I) stains strongly positive with S100 (original magnification ×250). A healthy human retina (J) with strong RS1 antibody immunostaining in the inner segments of the photoreceptors, strong membranous staining in the outer nuclear layer, moderate immunostaining in the inner nuclear layer and the plexiform layers, and negative staining in the ganglion cell layer and the nerve fiber layer (original magnification ×250). The retinoschisis-affected eye with negative RS1 antibody staining in the atrophic central retina (K) and markedly reduced staining in the relatively well-preserved peripheral retina (L) (original magnification ×250).
uveitis. The patient was treated with 200 mg hydroxychloroquine sulfate per day. Electoretinography and visual evoked potential were almost nonrecordable in the right eye. At age 19 years, iris neovascularization developed in the right eye with secondary glaucoma; it was treated with acetazolamide and local therapy. Eventually, the right eye was emulated. The visual acuity of the left eye was counting fingers at the most recent examination (Figure 2B).

The eye was fixed in formalin and transported to the pathology department. Macroscopically, occlusion of the pupil, a mature cataract, and posterior synechiae were noted in the anterior segment. In the posterior pole, a depigmented area was found, with some vascular veins extending anteriorly (Figure 2C). The retina was partly detached, with delicate cysts inferiorly in the eye. On microscopic examination, the cysts were seen to have originated from schisis in the NFL in the inferotemporal part of the retina and were covered by a glial membrane. The underlying retina and the nasal retina were detached (Figure 2D). There was marked splitting in the NFL of the nasal retina along the plane of the ganglion cell layer and detachment of the inner limiting membrane (ILM). Alcian blue/hyaluronidase staining was negative. The retina was folded at the base of the schisis cavities with marked hyalinization of intraretinal vessels and degenerative calcification. In the nasal posterior part of the retina, there was splitting in the inner and outer plexiform layers (Figure 2E). In the depigmented posterior pole, the retinal pigment epithelium showed proliferative and degenerative changes with atrophy of the photoreceptors and the outer nuclear layer. In the pupillary block, the retina was partly detached without obvious schisis cavities. The inner retina showed splitting in the NFL and detachment of the ILM. In the central retina, multiple PAS (periodic acid-Schiff)–positive globules were present in all retinal layers, sometimes with lumens (Figure 2F). In the macular area, degenerative changes were found in the outer plexiform and nuclear layers. In the anterior segment, iris, neovascularization, occlusion of the pupil, and iris bombé were present. The lens showed a hypermature cataract with posterior synechiae and rupture of the anterior lens capsule (Figure 2G). A reactive mixed inflammatory infiltrate was present, with histiocytes and giant cells within the lens capsule. Foamy cells surrounded the lens and were present in the anterior chamber. Granulomas were noted along the pigment epithelium of the iris and ciliary body and focally at the retinal pigment epithelium, with associated uveitis.

On immunohistochemical examination, glial fibrillary acid protein (Figure 2H) and vimentin stained strongly positive throughout the retina and the inner and outer layer of the schisis cavities. The NFL (Figure 2I) and the inner and outer layers of the schisis cavities stained strongly positive with S100. The roof of the schisis cavity and the NFL stained focally positive with neurofilaments. The PAS-positive globules stained strongly positive with fibronectin. In the healthy human retina, immunostaining with the RS1 antibody revealed intense staining of the inner segments of the photoreceptors, strong membranous staining in the outer nuclear layer, moderate staining in the inner nuclear layer and the plexiform layers, and negative staining in the ganglion cell layer and the NFL (Figure 2J). The RS-affected eye showed negative staining in the atrophic central retina (Figure 2K) and markedly reduced staining in the relatively well-preserved peripheral retina (Figure 2L).

On electron microscopic examination, splitting had occurred in the NFL in the semithin sections. Intraretinal globules were present in the inner nuclear layer and the inner part of the outer plexiform layer and were composed of basement membrane–like material in the ultrathin sections (Figure 3A). A glial membrane was present at the vitreal side of the ILM. The retinal surface of the ILM was attached to footplates of degenerated Müller cells. The plasma membrane of some Müller cells was focally deficient with intraretinal deposits of intermediate filaments (Figure 3B).

In our patient and his family, the missense mutation Arg102Trp was found in exon 4 containing part of the conserved discoidin domain of the RS1 gene.20

Comment. The histological findings in our patient are characteristic of juvenile RS with an unusual complication of phacoantigenic endophthalmitis, which explains the clinical findings of granulomatous anterior uveitis. Immunostaining with the RS1-specific antibody was markedly reduced in the RS-affected eye. The healthy human retina stained strongly positive in the inner segments of the photoreceptors and the outer nuclear layer, moderately positive throughout the inner nuclear layer and the plexiform layers, and negative in the inner retina. This is consistent with findings for the same antibody applied in mouse and monkey retinas and a normal human retina.18 Similarly, a retina-specific polyclonal antibody, designated retinoschisin, has been described in mouse and human retinas.19 Although messenger RNA of the causative RS1 gene was detected only in the photoreceptor layer, the protein product of the gene (retinoschisin) was present both in the photoreceptors and within the inner portions of the peripheral human retina, and there was patchy immunoreactivity in the inner and outer nuclear layers at the macula.

By genetic linkage analysis, RS was first mapped to the distal region of Xp, and subsequent refinement eventually localized the RS gene in Xp22.22 The RS1 gene has 6 exons and encodes a 224 amino acid protein, which contains a highly conserved discoidin domain. The RS1 mRNA encodes a secretable adhesion protein.20,21 Its role is implicated in cell-cell adhesion and phospholipid binding, indicating that RS1 is important in cell adhesion processes during retinal development.20,21 It was postulated that the protein product RS1 is expressed and assembled in photoreceptors of the outer retina and bipolar cells of the inner retina as a disulfide-linked oligomeric protein complex.18,19 Recently, it has been demonstrated in vitro that retinoschisin is selectively taken up and


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transported by Muller cells into the inner retina in a direction-specific manner.\textsuperscript{24} Juvenile RS may therefore be caused by abnormalities in the secreted photoreceptor protein at some distance from the site of RS pathologic characteristics.\textsuperscript{19} Discoidin domains are present in extracellular or transmembrane proteins in cell adhesion or cell-cell interactions.\textsuperscript{25} The interaction of RS1 protein with a Muller cell surface receptor or the extracellular matrix would be in keeping with its discoidin domain.\textsuperscript{19}

We found no expression of RS1 protein in the central atrophic retina and markedly reduced staining in the relatively well-preserved peripheral retina in the RS-affected eye. This is consistent with a recent study showing reduced antibody staining in chimera mice with a targeted RS1 knockout.\textsuperscript{26} The reduced staining in the human RS-affected eye may be explained by the missense DNA mutation found in our patient, which may have resulted in a dysfunctional protein with a reduced half-life and defective cellular adhesive function. Many missense and protein-truncated mutations of the causative RS1 gene have now been identified and are thought to be inactivating.\textsuperscript{19} Such a defective adhesive protein may still be transported by the Muller cells into the inner retina, eventually leading to schisis formation. The basement membrane of the Muller cells forms part of the ILM. The Muller cell is the principal glial cell of the retina and is in intimate contact with the inner segments of the photoreceptors and the cells of the middle retinal layers, surrounding large areas of retinal vessels. The dysfunctional protein or abnormalities in the interaction of the protein with a Muller cell receptor or extracellular matrix may therefore be expected to affect the middle and inner retinal layers and to produce structural defects in the ILM and the NFL. This could account for the schisis, which was present not only in the inner retinal layers but also nasal-posteriorly in the inner and outer plexiform layers. The cone-shaped zone of Muller cells in the central and inner part of the fovea centralis plays an important role in the structural integrity of the macula, and defective cell-cell interaction may explain the characteristic foveomacular schisis, later replaced by atrophic changes.\textsuperscript{25} Similarly, Muller cells may also be involved in the extracellular deposits of amorphous PAS-positive dots in the retina and, possibly, walls of small vessels. The PAS-positive deposits were noted in all retinal layers in the atrophic central retina and were not restricted to the schisis cavities.\textsuperscript{10,11} In our patient, the immunohistochemical (glial fibrillary acid protein, S100, and neurofilament) and electron microscopic findings (presence of degenerative Muller cells and deposits of intermediate filaments) are consistent with earlier findings. However, glial fibrillary acid protein and S100 positivity were not restricted to the retina adjacent to the schisis.\textsuperscript{10,11} These differences may be explained by the age at the time of enucleation (age, 19 years vs 55, 53, and 83 years\textsuperscript{10,11}); our case probably represents an earlier stage of the disease. We support the hypothesis that the basement membrane–like material and filaments that accumulate extracellularly within the atrophic central retina may be caused by abnormalities in the interaction of the (defective) RS protein and a Muller cell receptor or extracellular matrix.\textsuperscript{19}

In summary, earlier studies\textsuperscript{18,19} have established through immunohistochemical analysis the cellular distribution localization of RS protein in mammalian and healthy human retinas. The photoreceptors and bipolar cells appeared to be the cell types primarily involved in maintaining the integrity of the central and peripheral retina, secreting a cell adhesion protein taken up and transported by Muller cells into the

Figure 3. Electron microscopic examination shows intraretinal globules composed of basement membrane–like material (A). The plasma membrane of some Muller cells was focally deficient with intraretinal deposits of intermediate filaments (B) (original magnification ×7000).
inner retina. In our study of an RS-affected human eye, a mutation of the RS1 gene appears to give rise to a dysfunctional adhesive protein, resulting in defective cellular retinal adhesion that eventually leads to schisis formation.

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Presumed Iris Hemangioma Associated With Multiple Central Nervous System Cavernous Hemangiomas

We present the unique case of a patient with a vascular iris lesion consistent with a cavernous hemangioma and central nervous system (CNS) cavernous hemangiomas demonstrated by magnetic resonance imaging (MRI). Clinical reports of iris vascular tumors are rare and cases with histopathologic abnormalities are even more uncommon.

Hemangiomas of the eye are most often associated with posterior segment structures. We could find no previously described association between vascular tumors of the iris and CNS in adults. Most of the modern reports of iris vascular tumors occur in isolation.2-3 There is one case of diffuse congenital hemangiomatosis with a unilateral iris cavernous hemangioma; however, this syndrome appears to be uniformly fatal by age 1 year.4

Report of a Case. A 48-year-old white woman was referred for evaluation after her local ophthalmologist noted an unusual iris mass in her right eye. The patient’s medical history was significant for schizophrenia for which she had been treated with thioridazine hydrochloride for many years. She was diagnosed with multiple cavernous hemangiomas of the brain and brachisthm 7 years earlier after a seizure-like episode prompted brain imaging (Figure 1). The brain lesions have since been followed with serial MRI studies and found to be stable. Examinations by her neurosurgeon showed no neurologic deficit. Recent laboratory studies revealed normal liver and kidney function. Her other medications were lorazepam, carisoprodol, and famotidine. Her ocular history is significant for myopia with astigmatism.

On examination, we found her best-corrected visual acuity was 20/25 OU. The right inferior iris had a lobulated blood-filled mass that appeared to be vascular in nature and did not extend into the angle on gonioscopy (Figure 2). Anterior segment echography showed this lesion to be 2.1 mm thick with an irregular internal structural and entirely contained within the iris. Iris angiography did not detect flow through the lesion. Golden brown deposits in the subepithelial layers and superficial stroma of her cornea and anterior stellate golden brown deposits in her lenses were thought to be secondary side effects of her thioridazine regimen. Her fundi were normal. She had no cutaneous vascular lesions.

Comment. We describe a patient with a vascular iris lesion and CNS cavernous hemangiomas that may represent a single disease process. Al
giomas, no mass effect, hyperintensity of benign cavernous hemangiomas. 3 Her CNS lesions have the MRI characteristics of cavernous hemangiomas. 4 Her clinical appearance seems consistent with findings from her iris lesion, its clinical syndrome may represent a new type of disseminated hamartoma distinctly different from other phakomatoses.

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Retrobulbar Optic Neuritis Associated With Infliximab

Tumor necrosis factor (TNF) α is a cytokine derived chiefly from macrophages. 5 The liberation of TNF-α is thought to stimulate the inflammatory process by binding to cell surface receptors. Infliximab is a chimeric antibody of the IgG class, which binds TNF-α, inhibiting its activity. 6 The Food and Drug Administration has approved infliximab, as an intravenous infusion, for the treatment of rheumatoid arthritis and Crohn disease. 7

Cytokine-targeted therapy in patients with rheumatoid arthritis has been increasing and has generally been reported to be safe, although headache and respiratory congestion may occur. Review of the package insert for infliximab lists "neurologic events" as possible adverse affects and adds that "infliximab and other agents that inhibit TNF have been associated in rare cases with exacerbation of clinical symptoms and/or radiographic evidence of de-myelinating disease." 8

Inhibition of TNF-α has also been studied in multiple sclerosis (MS), in which high TNF-α levels have been noted in MS plaques and mononuclear cells of patients with demyelinating disease. 9 In animal models of MS, the infusion of TNF-α is associated with worsening symptoms. 10 However, a randomized, controlled study of lenerecept, another TNF-α inhibitor that also inhibits the cytokine lymphotoxin, found no benefit in patients with MS. 11 Furthermore, patients treated with lenerecept had a significant increase in the rate of relapses and a trend toward more severe relapses.

One report of an exacerbation of preexisting demyelinating disease in 2 patients with rapidly progressive MS has suggested a possible link between infliximab and demyelination. 12 In these 2 patients, TNF-α infusion was associated with increased disease activity on magnetic resonance imaging (MRI). The number of lesions observed with contrast-enhanced MRI remitted and then increased again after rechallenge with the TNF-α inhibitor.

To our knowledge, there have been no reports of optic neuritis associated with infliximab. We describe a 55-year-old woman with rheumatoid arthritis who developed retrobulbar optic neuritis of the left eye after the infusion of infliximab.
imab. Although the optic neuritis may have been coincidental to the use of infliximab, we believe that this case report should heighten awareness of a possible link between loss of vision from demyelination and TNF-\(\alpha\) inhibition.

**Report of a Case.** A 55-year-old woman with a 2-year history of rheumatoid arthritis chiefly affecting the hands sought treatment with a 5-day history of decreased vision in the left eye accompanied by pain with eye movement. She had no paresthesia, weakness, or bowel and bladder dysfunction and no history of neurologic disease. She had initially been treated with methotrexate (one 12-mg subcutaneous injection per week) for 1 year; however, because of persistent stiffness of the hands, infliximab was added. Initially, she received 240 mg (3 mg/kg) of infliximab every 2 weeks for 3 doses, followed by an infusion of the same dose every 8 weeks, for a total of 9 infusions. Her loss of vision and pain with eye movement began 3 days after her last infusion of infliximab. She reported improvement in the stiffness in her hands within weeks of beginning the infliximab. She was also taking conjugated estrogens (Premarin; Wyeth Pharmaceuticals, St David’s, Pa) and folic acid. There was no family history of demyelinating disease.

Best-corrected visual acuity was 20/25 OD and 20/50 OS. She identified 14 of 14 Ishihara pseudoisochromatic color plates with the right eye and 6 of 14 with the left eye, and she had a left relative afferent pupillary defect. Findings from automated perimetry were normal in the right eye (Figure 1). Her optic discs were normal. The left eye (B) shows gray scale (right) and pattern deviation (left) of the right eye (A) are normal. The left eye (B) shows a superior altitudinal defect.

![Figure 1](image)

**Figure 1.** Findings from automated perimetry (Humphrey 24-2 threshold program [Zeiss Humphrey Systems, Dublin, Calif]) shows gray scale [right] and pattern deviation [left] of the right eye (A) are normal. The left eye (B) shows a superior altitudinal defect.

Comment. The patient’s clinical course was consistent with retrobulbar optic neuritis. Although optic neuritis associated with central nervous system demyelination is well known to occur after age 50 years, most cases occur between the ages of 20 and 50 years. In a study of the incidence of monosymptomatic optic neuritis in Stockholm, Sweden, only 1 (0.7%) of 147 patients was aged 55 years or older. Hence, our patient’s age of 55 years is somewhat atypical for an initial episode of demyelinating optic neuritis.

Although the relationship between the onset of visual symptoms and the infusion of infliximab may have been coincidental, this association is similar to that seen in the prior report of the exacerbation of rapidly progressive MS in 2 patients treated with this TNF-\(\alpha\) inhibitor. In both patients, an increase in the number of gadolinium-enhancing lesions on MRI was noted between 3 and 10 days after the initial infusion. A second infusion, given 2 weeks after the first dose, caused a second, smaller spike of lesions on MRI, which decreased over the ensuing 3 weeks. In addition, the number of lymphocytes and the IgG index in the cerebrospinal fluid, both indicative of MS activity, increased after the initial infusion. The authors speculated that the inability of infliximab to penetrate the blood-brain barrier, as documented by the failure to detect the cytokine in the cerebrospinal fluid, may have rendered the TNF-\(\alpha\) inhibitor ineffective.

A randomized, placebo-controlled study of 168 patients with MS (excluding patients with rapidly progressive MS) treated with lenenercept, another TNF-\(\alpha\) antagonist, found an increase in the frequency of exacerbations and a trend toward more severe exacerbations when compared with the placebo. The increased rate of exacerbations was noted both 24 and 48 weeks after the onset of treatment. In addition, there was a statistically significant dose-dependent decrease in the time to first exacerbation in patients treated with lenenercept.
Demyelination. Robinson et al.1 have suggested a role for an alteration in adhesion molecule expression.12 Other investigators have noted a possible link between TNFα and the need for further study of this cytokine inhibitor.2

Although this patient’s retrobulbar optic neuritis may have been coincidental to the infusion of infliximab, we believe that this case report underscores both the clinical awareness of the possible association and the need for further study of the possible link between TNF-α antagonism and demyelination, especially in light of the increasing use of this cytokine inhibitor.

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Central Retinal Vein Occlusion in Bird-Shot Retinochoroidopathy

Visual loss in bird-shot retinochoroidopathy is caused by cystoid macular edema, optic neuropathy and atrophy, vitreous opacities, epiretinal membranes, and subretinal neovascularization. We describe a patient with this syndrome whose visual loss was caused by a central retinal vein occlusion. This may occur as a rare vascular complication of bird-shot retinochoroidopathy.

Report of a Case. A 62-year-old woman was evaluated for a 2-day history of blurred vision and floaters in both eyes. Her ocular history was unremarkable, and her medical history was notable for systemic hypertension. Blood pressure was well...
controlled during treatment. On initial ocular examination, visual acuity was 20/25 OU. Slitlamp examination findings revealed no evidence of anterior chamber inflammation in either eye. Intraocular pressure was 14 mm Hg OU. Fundus examination results revealed bilateral mild vitreitis, retinal periphlebitis, and disc edema in association with depigmented cream-colored spots located predominantly in the nasal area of the fundus (Figure 1). These findings in association with the presence of HLA-A29 led to the diagnosis of birdshot retinochoroidopathy. Fluorescein angiography demonstrated diffuse retinal vasculitis with disc edema (Figure 2). As no visual loss occurred, the patient received no treatment and was put under medical control. Spontaneous remission was noted 2 years after onset, and visual acuity improved to 20/20 OU. Peripheral retinal periphlebitis and disc edema decreased.

After 4 months, the patient experienced a recurrence of uveitis. Disc edema and periphlebitis were exacerbated, and central retinal vein occlusion developed (Figure 3). Visual acuity decreased to 20/100 OD. Afferent pupillary defect was present. No etiologic factor, except very mild systemic hypertension, was found during the follow-up evaluation. A regimen of 60 mg daily of prednisone was administered, with no amelioration in the right eye. Capillary closure occurred. A panretinal laser photocoagulation was performed. Despite this treatment, preretal and prepapillary neovascularization occurred 4 years after the onset of the vein occlusion. When last seen, 6 years after the first examination, visual acuity was reduced in the right eye to hand motions.

Comment. Diffuse and bilateral retinal vasculitis, particularly along the major retinal vessels, and retinal vascular leakage are frequent in birdshot retinochoroidopathy. Vasculopathy leads to cystoid macular edema and papilloedema.1,2 Vascular occlusion is known to occur in the presence of vasculitis (up to 5% of branch vein occlusion is owing to vasculitis),3 and vascular occlusion has been described in systemic disease associated with vasculitis.4,5 However, cross-referencing “central retinal vein occlusion” and “bird-shot retinochoroidopathy” on the MEDLINE database brings up no items. A 1988 study by Priem and Oosterhuis2 of 102 patients with bird-shot retinochoroidopathy reports such an association: 1 central retinal vein occlusion and 2 branch retinal vein occlusions. The authors note that this incidence is...
higher than that found in a healthy population of the same age. Two hypotheses may be advanced concerning central retinal vein occlusion associated with birdshot retinochoroidopathy. The obstruction of a small peripheral retinal venule is well documented in vasculitis. Although less common, larger retinal vessels may also become inflamed and subsequently occluded, as occurred in our reported clinical case. Furthermore, in bird-shot retinochoroidopathy, pathological features include granulomatous inflammation in the retina around and under retinal veins and in the underlying choroid.1

Priem and Oosterhuis have developed another hypothesis: patients with bird-shot retinochoroidopathy have a high incidence of cardiovascular disease (systemic hypertension, coronary artery disease, strokes). Central retinal vein occlusion would then be one of the manifestations of cardiovascular risk.2 The risk for this patient of developing vein occlusion was increased by the association of disc edema and absence of an optic cup, which is known to be a risk factor for nonarteritic optic neuropathy.

In conclusion, we believe that as observed in our clinical case, central retinal vein occlusion may occur as a rare vascular complication of bird-shot retinochoroidopathy.

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Necrotizing Herpetic Retinopathy Associated With Ramsay Hunt Syndrome

Ramsay Hunt syndrome is a herpes zoster infection of cranial nerve VII, causing facial paralysis, and may also involve cranial nerves VIII, IX, V, X, and VI, in order of decreasing frequency.1 Necrotizing herpetic retinopathy refers to the spectrum of disease encompassing acute retinal necrosis and progressive outer retinal necrosis, and consists of peripheral necrotizing retinitis, vitritis, and retinal arteritis caused by a herpes virus.2 To our knowledge, we describe the first case of bilateral necrotizing herpetic retinopathy in an immunosuppressed patient with Ramsay Hunt syndrome.

Report of a Case. A 38-year-old woman with acquired immunodeficiency syndrome (CD4 cell count 2 months prior was 214/µL) had vascular lesions in the distribution of left cranial nerve V3, left-sided hearing loss, left facial weakness, and decreased vision in the left eye. Visual acuity with pinhole was 20/25 OD and 20/30 OS. Slitlamp examination revealed anterior vitreous cells in the left eye. Results of dilated fundus examination of the right eye were unremarkable and in the left eye revealed focal and confluent retinitis inferiorly and temporally. Necrotizing herpetic retinopathy in the left eye was diagnosed, the retinitis was demarcated with laser treatment, and intravenous ganciclovir and foscarnet were initiated. Intravitreal ganciclovir sodium (2000 µg/0.05 mL) and foscarnet sodium (1200 µg/0.05 mL) were administered in the right eye 3 times per week for a total of 5 injections. Audiography demonstrated left-sided neural hearing loss.

Five days later, the patient reported decreased vision in the right eye and right-sided hearing loss. Visual acuity was 20/40 OD and 20/50 OS. Dilated fundus examination revealed focal areas of peripheral retinitis in the right eye and stable retinitis in the left eye. Intravitreal ganciclovir sodium (2000 µg/0.05 mL) and foscarnet sodium (1200 µg/0.05 mL) were administered in the right eye 3 times per week for a total of 5 injections. Audiography demonstrated bilateral hearing loss, and magnetic resonance imaging revealed neuritis in bilateral cranial nerve VIII. On serial dilated fundus examinations, the confluent retinitis did not break through the laser demarcation in the right eye, and the focal lesions did not become confluent in the left eye. After 2 weeks of intravenous and intravitreal therapy, the retinitis was healed in both eyes and visual acuity stabilized at 20/50 OD and 20/100 OS. Two months later, after discontinuing systemic medication against medical advice, the patient developed recurrent necrotizing herpetic retinopathy with retinal detachments in both eyes. After intravenous and intravitreal antiviral therapy and retinal detachment repair with vitrectomy and silicone oil tamponade in both eyes, visual acuity was 20/70 OD and 20/40 OS. Nine months after initial examination, visual acuity was stable at 20/300 OD and 20/80 OS, with bilateral posterior subcapsular cataracts.

Comment. In 1907, Ramsay Hunt described facial nerve palsy associated with ipsilateral hearing loss and vascular lesions on the pinna or in the auditory canal.3 Facial weakness with associated vesicles establishes the diagnosis of Ramsay Hunt syndrome.4 The benefit of systemic steroids is equivocal; intravenous acyclovir sodium is indicated in patients with immunosuppression or encephalitis.5 Most patients regain function of cranial nerves VII and VIII.6 To our knowledge, 1 case of necrotizing herpetic retinopathy associated with Ramsay Hunt syndrome has been reported.4 In contrast to our case, the previously described patient was immunocompetent and developed unilateral necrotizing herpetic retinopathy. Systemic ganciclovir and foscarnet were administered to our patient because it has been reported that,
among patients with acquired immunodeficiency syndrome who develop necrotizing herpetic retinopathy, combination therapy with intravenous ganciclovir and foscarnet is associated with better visual outcomes than treatment with intravenous acyclovir or intravenous foscarnet alone.3 Ophthalmologists should monitor the fundus for retinitis in any patient with Ramsay Hunt syndrome and decreased vision.

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Chronic Lymphocytic Leukemia of the Orbit

Report of a Case. A 78-year-old man was referred to our clinic for evaluation of bilateral ptosis that developed over the previous 2 months. His ocular history was remarkable for cataract extraction and intraocular lens implantation in both eyes 1 year prior to initial examination. His medical history was significant for chronic lymphocytic leukemia (CLL) diagnosed 7 years earlier during a laboratory workup for anemia (hematocrit, 22.1%) and lymphocytosis (white blood cell count, 150 × 10³/µL), which was detected on results of routine blood work. There was no lymphadenopathy or splenic enlargement at the time of diagnosis, consistent with stage 0 CLL. He did not require treatment.

At initial examination, his visual acuity was 20/30 OU. The examination findings were notable for normal pupils, severely limited ductions in all directions in both eyes, and bilateral ptosis (Figure 1). Levator function was 2 mm OU. Pupillary revealed marked resistance to retropulsion in both eyes.

Computed tomography demonstrated enlargement of all extraocular muscles in both eyes, with mild enlargement of the lacrimal glands and soft tissues of both upper and lower eyelids (Figure 2).

The patient underwent anterior orbitotomy with biopsy specimens obtained from the anterior orbital fat. Histologic examination revealed a dense infiltrate of small lymphocytes that stained positive for IgD kappa, CD5, CD19, CD20, and CD23, consistent with B-cell CLL. These marker studies were identical to the pattern observed at the time of initial diagnosis of CLL.

He was treated with local radiation to both orbits consisting of 200 rad (200 cGy) per fraction over 10 fractions. This resulted in complete resolution of his ptosis and restoration of normal motility in both eyes at 1 month after initiating treatment (Figure 3). A computed tomography scan obtained 3 months after beginning radiation treatment demonstrated reduction in the size of the extraocular muscles.

When the diagnosis of orbital CLL was made, he was referred to his hematologist/oncologist for systemic evaluation. Blood work results revealed a white blood cell count of 8.3 × 10³/µL and hematocrit of 30%. There was no lymphadenopathy or splenomegaly. These findings suggested that the orbital recurrence of the CLL was not associated with systemic recurrence. He remained unchanged at last follow-up 14 months after initial examination and had no evidence of recurrence, either within the orbit or systemically.

Comment. Chronic lymphocytic leukemia is the most common type of leukemia in the United States. It is usually B cell in origin and is characterized by the proliferation of lymphocytes that accumulate within the blood, bone marrow, lymph nodes, and extranodal tissues. Patients are typically older than 50 years, and the disease is more common in men.

Leukemia, in general, has been reported in tissues throughout the eye, as well as in the orbit and adnexal structures. Clinically, these structures are more involved in acute leukemias, with retinal findings most frequently observed. Acute leukemia is well known for its ability to manifest within the orbit as a granulocytic sarcoma, or chloroma, usually in children.

Autopsy studies have shown ocular and periocular involvement of chronic leukemia in 75% of patients.1,2 Clinically, CLL may be observed in structures throughout the eye.3 Several manifestations of CLL have been reported in and around the orbit, including infiltration of the lacrimal structures resulting in epiphora and dacryocystitis,4,5 lacrimal gland swelling,6 sicca syndrome (without lacrimal gland enlargement),7 optic nerve infiltration,8 proptosis,9,10 orbital apex syndrome,11 and orbital apex syndrome.11

Figure 1. External appearance at initial examination demonstrating profound ptosis OU.
The patient in this report differs from previous reports of CLL involving the orbit in several ways. First, previously reported manifestations of orbital CLL infiltration include a diffuse orbital mass and unilateral extraocular muscle enlargement. Radiographically, our patient had findings suggestive of thyroid-associated orbitopathy, namely, enlargement of the extraocular muscles bilaterally. We are unaware of this manifestation of CLL having been reported previously.

Clinically, his near total ophthalmoplegia and ptosis suggested a disease entity other than thyroid-associated orbitopathy. However, the radiographic findings shown here suggest that CLL should be included in the differential diagnosis of bilateral extraocular muscle enlargement.

Second, CLL seen within the orbit has been described as the initial manifestation of the disease or occurring in patients with active and, in some cases, worsening systemic disease. Our patient had no evidence of systemic disease activity at the time of diagnosis and, in fact, his blood cell counts at the time of diagnosis of his orbital CLL were at their best since his initial CLL diagnosis. To our knowledge, there have been no reports of periorcular or orbital manifestation of CLL in the setting of systemic remission. While secondary lymphoepithelial tumors have been reported in association with CLL (Richter syndrome), the identical tumor markers in specimens from the orbit and from initial diagnosis suggest that the orbital manifestation was part of the same disease process. Our observation suggests that the possibility of local orbital recurrence should be considered despite a seemingly indolent disease course.

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Figure 2. Computed tomography scans in the coronal (A) and axial (B) planes demonstrating enlargement of the extraocular muscles in both eyes.

Figure 3. External appearance 1 month after completing radiation treatment, demonstrating improved upper eyelid position in both eyes.
necrosis is a retinal infection. In the mouse system, BALB/c mice that receive an anterior chamber injection of an antigen acquire an unusual systematic immune response, termed “anterior chamber–associated immune deviation” (ACAID).19,20 In this system, impaired antigen-specific DH coexists with high serum titers of antigen-specific antibodies. The results presented in this article serve to support our hypothesis that anterior chamber–associated immune deviation may be the immunologic mechanism that is triggered in the eyes of some patients undergoing idiopathic reactivation of VZV in the trigeminal ganglion. For reasons yet to be revealed, zosteriform spread of antigenic VZV particles to the anterior chamber leads to suppression of virus-specific T cells that mediate DH, and by so doing, rob the eye of the protection afforded by these CD4+ T cells. Acute viral infection of sensitive intraocular tissues ranging from iris to retina is the inevitable consequence. If we could understand how to abort anterior chamber-associated immune deviation in this situation, intraocular complications of ophthalmic herpes zoster might be eliminated from clinical ophthalmology.

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