Sclerosing Inflammatory Pseudotumor of the Eye

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We report the clinical course and pathologic findings in a case of intraocular sclerosing inflammatory pseudotumor in a 21-year-old man. The patient initially had a unilateral right interstitial keratitis, scleritis, uveitis, ciliary body mass, and retinal detachment. Scleral and vitreous biopsy specimens revealed an inflammatory process. The eye was eventually enucleated despite therapy with high doses of prednisone and ciprofloxacin hydrochloride. Histologic examination of the globe showed nongranulomatous, acute (neutrophils) and chronic (lymphocytes and histiocytes) inflammation with proliferation of fibrous tissue within the vitreous cavity, uvea, sclera, and contiguous orbital fibroadipose tissue. The contralateral eye later developed a similar mass that resolved following aggressive and prolonged immunosuppressive therapy with retention of 20/16 visual acuity.

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Inflammatory pseudotumors compose a group of rare, poorly understood, idiopathic, inflammatory mass lesions. They may be classified as sclerosing or nonsclerosing according to the presence or absence of a dense fibrotic stroma. The nonsclerosing type is more common and has been reported to occur in almost every part of the body, including orbital tissues and the uveal tract. Sclerosing inflammatory pseudotumors have been described in the orbit and lacrimal glands. We report herein a case of bilateral intraocular sclerosing inflammatory pseudotumor with eventual extraocular extension, presenting as a ciliochoroidal and vitreous mass with scleritis, keratitis, uveitis, and retinal detachment in one eye. To the best of our knowledge, this is the first such case reported in the literature with successful treatment and preservation of vision in one eye.

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OD and 12 mm Hg OS. External examination of the right eye revealed a swollen, tender, erythematous sclera with overlying episcleral and conjunctival injection located in the inferior half of the globe extending from the perilimbal area to the fornix (Figure 1). An arcuate zone of interstitial keratitis was observed that involved the peripheral cornea manifesting as epithelial bullae and stromal haziness. The anterior chamber and vitreous cavity contained 3+ inflammatory cells and 2+ flare. Fundus examination disclosed a large, white-yellow mass in the ciliary body extending from the 3- to 9-o’clock position with posterior extension but without macular involvement (Figure 2 and Figure 3). A few scattered hemorrhages and a shallow serous retinal detachment were seen on the surface of this mass. The optic disc was hyperemic but had distinct borders. The left eye was completely normal at the time of initial presentation. B-scan ultrasonography revealed a low to medium reflectivity with irregular internal structure (Figure 4). Magnetic resonance imaging demonstrated no extraocular extension.

A review of symptoms was unremarkable except for a history of an ordinary childhood case of chickenpox. The differential diagnoses of sclerouveitis with associated ciliochoroidal mass includes granulomatous inflammatory conditions (sarcoidosis, Wegener granulomatosis, and foreign body reaction), infectious causes (bacteria, herpesviruses, and fungi), and neoplastic masquerade syndrome (leukemia, lymphoma, melanoma, metastatic carcinoma). Findings from an extensive diagnostic evaluation were negative except for an elevated varicella zoster virus (VZV) IgG titer that was elevated to 156 enzyme immunoassay units (reference range, 0-15 enzyme immunoassay units).

Specimens obtained from vitreous and scleral biopsies performed on September 1, 1997, revealed acute (neutrophils) and chronic (lymphocytes and histiocytes) nongranulomatous inflammation. Microbial cultures were negative for bacteria, fungi, and acanthamoeba. Neither malignant cells nor microorganisms were observed on pathologic examination. Immunoperoxidase stains performed on the scleral
tissue and polymerase chain reaction analysis of vitreous samples failed to detect gene sequences for acid-fast bacilli, herpesvirus 1 and 2, cytomegalovirus, VZV, Borrelia burgdorferi, and Toxoplasma.

The working diagnosis at this time was idiopathic sclerouveitis. The patient was already taking famcyclovir, 500 mg orally 3 times a day, and oral prednisone, 60 mg daily, and was reluctant to alter these medications. We prescribed intravenous cyclophosphamide infusions at a dose of 1 g every 3 to 4 weeks and hourly 1% prednisolone acetate eyedrops, in the belief that the problem was primarily immunologic/inflammatory in nature. Postoperatively, the visual acuity improved to 20/400 OD with marked reduction of pain and eye redness.

One month later, however, the patient returned with an increase in the size of the ciliochoroidal mass, progression of retinal detachment up to the macula, and visual acuity reduced to hand motions. Findings from B-scan ultrasonography were suggestive of extrascleral extension of the process. On October 8, the patient underwent repeated vitrectomy, 3 retinal biopsies, 1 large debulking choroidal biopsy, and successful retinal detachment repair using silicone oil. The biopsy specimens revealed an intact retina and nongranulomatous inflammation with abundant plasma cells and neutrophils associated with increased collagen and vascularity of the choroid. Malignant cells were not found in the vitreous. Immunohistochemical staining of the ciliary body disclosed a large number of cells bearing IgA, IgG, IgM, IgE, IgD, and C4. The retina was uninvolved histologically. Malignant cells were not found in the vitreous. Flow cytometry of vitreous cells disclosed CD4+ and CD8+ T lymphocytes, as well as polyclonal κ and λ immunoglobulin light chain–positive B lymphocytes. The patient's immunosuppressive regimen was continued postoperatively, with the addition of diltiazem, 1000 mg by mouth daily. The patient's eye pain decreased and his visual acuity improved to 20/200 OD on November 4, 1997.

Six weeks postoperatively, the cultures from the vitreous samples yielded growth of coral pink negative rods interpreted as Methylobacterium extorquens, sensitive to ciprofloxacin and amikacin. The subretinal mass had continued to enlarge, prompting cessation of intravenous cyclophosphamide treatment and reduction in the prednisone dosage since the concern now was that of infection. Treatment with intravenous ciprofloxacin hydrochloride was begun. Despite these measures, the patient returned 2 weeks later with further enlargement of the mass that now involved the entire macula. Visual acuity was reduced to light perception and the patient's eye pain had recurred. Computed tomography revealed a soft tissue density along the inferior and lateral aspect of the right globe similar to that seen on magnetic resonance imaging. The left globe was normal. A transscleral biopsy was performed, the results of which revealed acute and chronic inflammation only. Because of the lack of response to antimicrobial treatment and the opinion of the infectious disease consultant that the finding of M extorquens in the culture yield was most likely a contaminant, the concern about an infectious origin was abandoned. The prednisone regimen was increased to 50 mg daily.

Two weeks later, the patient returned with a white mass in the superotemporal ciliary body of the opposite eye at the 2-o’clock position with adjacent scleritis. Repeated systemic evaluation was not contributive. Because of the poor prognosis for recovery of the right eye and the probability for progression of the disease in the left eye, diagnostic enucleation of the right eye was offered to the patient; this was accomplished on January 27, 1998. Histopathologic examination findings of the enucleated globe revealed an inferior vitreous mass, obliteration of the uvea, and scleral thickening; the process extended through the sclera to involve the inferior orbital fat (Figure 5 and Figure 4. Preoperative B-scan ultrasonogram showing the anteriorly located right intraocular mass. Figure 5. Gross view of enucleated right globe showing an inferior vitreous mass and fibrous tissue adherent to the inferior wall of the globe. The inferior sclera was replaced by a mass of inflamed sclerotic tissue, which had destroyed the inferior choroid.)
Within the mass were nonspecific acute (neutrophilic, Figure 7) and chronic inflammation characterized by mononuclear, lymphocytic, and plasmacytic infiltration, together with proliferation of collagenous tissue and absence of granulomatous inflammation (Figure 8). Specific stains for microorganisms (acid-fast, methenamine silver, Brown-Hopps) and electron microscopic studies failed to disclose any organisms. Several ocular and general pathologists reviewed the pathology slides, and the consensus was that of a sclerosing inflammatory pseudotumor of the eye with scleritis probably of autoimmune origin.

The patient was started on therapy with intravenous cyclophosphamide and high-dose oral prednisone once more in an effort to salvage his remaining eye. Over the next 4 weeks, the mass in the left eye remained the same size and the scleritis persisted. However, on the eighth week of immunosuppression, there was reduction in mass size and by the 14th week, the mass had disappeared and the scleritis resolved, leaving an anterior staphyloma. The prednisone was slowly tapered over a period of 8 weeks without relapse. Pulse intravenous cyclophosphamide therapy was maintained together with oral diflunisal, 1000 mg daily. The final visual acuity OS was 20/16, in October 1999, 10 months after cessation of intravenous cyclophosphamide and prednisone therapy.

COMMENT

Intraocular sclerosing inflammatory pseudotumor is a rare condition that can present as a ciliochoroidal mass, sclerouveitis, and interstitial keratitis. This case appears to be clinically and histologically different from the hypercellular and nonfibrotic reactive lymphoid hyperplasias described by Ryan, Jakobiec, and others.8-10 Intraocular inflammatory pseudotumors appear to arise from uveal tissues and are associated with uveitis.2,11,12 This case is clinically distinguished from previous reports of intraocular pseudotumors by the presence of scleritis with orbital ex-
tension and interstitial keratitis, and it is histologically distinguished by the presence of dense fibrotic stroma in the presence of an intense plasmacytic and neutrophilic infiltrate. It is believed by some authors that the sclerosing variant may represent a more aggressive or more recalcitrant form of the disease. However, other authors have found no differences in duration of illness and response to corticosteroids between the sclerosing and nonsclerosing variants.

The origin of intraocular pseudotumor is unknown but is widely believed to be either infectious or autoimmune. The autoimmune theory is supported by the observation of concomitant autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus, and associated drug therapy and by the response to corticosteroids and, in this case, to cyclophosphamide. The proposed pathogenesis of sclerosing pseudotumor is exaggerated proliferation of fibroblasts and deposition of extracellular matrix caused by the aberrant immune-mediated production of fibrogenic cytokines (platelet-derived growth factor, transforming growth factor β). Previous reports have described ciliary body masses, uveitis, iris infiltration, narrow-angle glaucoma, and retinal detachment as manifestations of inflammatory pseudotumor. This case adds scleritis, interstitial keratitis, and extraocular orbital extension to that list. Our approach to management involved a thorough review of systems and an initially noninvasive diagnostic search for systemic diseases associated with inflammatory intraocular masses. Strong support for the diagnosis of inflammatory pseudotumor is obtained by histopathologic means, which must rule out neoplasm and infection. We recommend immediate institution of immunosuppressive therapy once the disease is recognized. As this case illustrates, treatment may require a combination of high-dose corticosteroids and cyclophosphamide to effect resolution, although response to treatment may be delayed by several weeks. It is difficult to assess the prognosis of intraocular pseudotumors given the small number of reported cases in the literature. In our studied case, one eye was enucleated for diagnostic reasons once all vision was lost, while the eventually affected contralateral eye retains 20/16 visual acuity.

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REFERENCES