


Primary Orbital Peripheral T-Cell Lymphoma: Histologic, Immunophenotypic, and Genotypic Features

Primary orbital peripheral T-cell lymphoma is an exceedingly rare neoplastic disorder. Advances in laboratory methods and molecular pathology have greatly improved our ability to accurately diagnose this lymphoid malignant neoplasm. We report a case of primary extranodal peripheral T-cell lymphoma arising within the orbit. Atypical features of the clinical course are described.

Report of a Case. A 44-year-old man developed progressive diplopia and retro-orbital pain. Uncorrected visual acuity was 20/20 in both eyes. Examination findings included hypertropia in the left eye, esotropia, and proptosis in the right eye (Figure 1). Orbital magnetic resonance imaging showed bilateral enlargement of the extraocular muscles, more pronounced on the right. Thyroid ultrasonography disclosed mild thyromegaly, but results of serum thyroid functions tests were normal. The patient was diagnosed as having thyroid-related immune orbitopathy and high-dose oral prednisone was prescribed, with prompt resolution of symptoms and proptosis. However, prednisone was poorly tolerated and its use was discontinued, leading to a recurrence of symptoms.

Neuro-ophthalmology consultation noted mild hypertropia and 2 mm of proptosis in the right eye. A second round of thyroid function testing, erythrocyte sedimentation rate, rapid plasma reagin, antinuclear antigen, and rheumatoid factor findings were all normal. Mag-
Hypotropia in the right eye, and exo-sparing oculomotor nerve palsy with proptosis in the right eye, a pupil-later, the patient again developed temporary resolution of the proptosis with low-dose prednisone led to parenteral methotrexate sodium showed a slightly elevated anti-thyroid-related immune orbitopathy yielded clinical improvement.

Six months later, the patient developed edema in the right lower eyelid and conjunctival injection with chemosis, retro-orbital pain, and proptosis due to recurrent enlargement of extraocular muscles, all in the right eye. A biopsy specimen of the lateral rectus muscle from that eye demonstrated a polymorphous lymphocytic infiltrate composed of small T and B lymphocytes with clumped chromatin, round to irregular nuclear contours, and scant cytoplasm admixed with occasional larger, atypical lymphocytes with complex nuclei and moderately abundant clear cytoplasm (Figure 2). The larger, atypical lymphocytes were marked as T cells by using CD2, surface CD3, CD45RO but demonstrated loss of other T-cell markers CD5 and CD7, indicative of an aberrant T-cell population. CD4 and CD8 staining were both present on small lymphocytes, but a specific pattern on the large atypical lymphocytes was difficult to interpret. Immunostains for Epstein-Barr virus latent membrane protein and CD56 were negative. There was insufficient tissue for additional stains such as CD30 or cytotoxic markers TIA-1 and granzyme B. These findings were consistent with a diagnosis of peripheral T-cell lymphoma, not otherwise specified. Polymerase chain reaction gene rearrangement studies with T-cell receptor γ-primers showed a monoclonal peak corresponding to a Vγ-11 gene rearrangement, thus confirming a clonal T-cell process.

The patient declined additional treatment and did not return for follow-up until 8 additional months had elapsed (20 months after he was first evaluated). Marked proptosis and orbital congestion were present in the right eye (Figure 3A). Another systemic workup was performed, and a computed tomographic scan of the head showed a mass at the base of the tongue (Figure 3B). A biopsy specimen showed an infiltrate of large atypical lymphoid cells similar in appearance to the previous orbital biopsy specimens. T-cell immunophenotype and polymerase chain reac-
tion gene rearrangement confirmed a clonal T-cell process similar to that found earlier in the orbit. Bone marrow biopsy was performed, and the specimen was free of tumor involvement. Computed tomographic imaging of the chest, abdomen, and pelvis was negative for adenopathy. Mild splenomegaly at 16 mm was palpated and, combined with biopsy-proved orbital and sublingual disease, led to a clinical diagnosis of stage IIIB peripheral T-cell lymphoma. The patient successfully completed 8 cycles of chemotherapy with cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone. Three years after his initial visit, all tumor masses had resolved. Apart from mild vertical diplopia and postchemotherapy epiphora, all ophthalmic symptoms had cleared at the last follow-up examination.

Comment. Orbital and ocular adnexal lymphoid neoplasms are not uncommon, representing 6% to 8% of all orbital tumors and up to 15% of all ocular adnexal tumors. On the basis of published data from multiple large clinical series, most orbital lymphoproliferative disorders are (1) peripheral extranodal B-cell non-Hodgkin malignant lymphoma, (2) atypical lymphoid hyperplasia, or (3) benign reactive lymphoid hyperplasia. Primary orbital/ocular adnexal T-cell lymphoma is rare and most often represents malignancy or secondary involvement by systemic malignant non-Hodgkin lymphoma. In 1999, Coupland et al described the first case of primary T-cell orbital lymphoma confirmed both immunophenotypically and genotypically. Woog and coworkers recently analyzed the diagnostic features and clinical course of 8 patients with orbital and adnexal involvement by natural killer/T-cell lymphoma, an Epstein-Barr virus–associated neoplasm of noncytotoxic T lymphocytes. Our case of primary orbital peripheral T-cell lymphoma, not otherwise specified, was discovered in a 44-year-old man. Nearly 2 years elapsed before a confirmatory diagnosis was established. Several unusual clinical features in this challenging case contributed to the delay in diagnosis. Diplopia was the initial symptom for which the patient sought treatment. Orbital imaging studies identified bilateral, asymmetric enlargement of the extraocular muscles, not the diffuse, molded soft-tissue density ordinarily encountered in a lymphoid infiltrate. Proptosis slowly developed during a period of months. Orbital external beam radiotherapy offered temporary improvement. Furthermore, the patient experienced retrobulbar pain and multiple cranial nerve pareses. Taken as a whole, this constellation of clinical findings is usually not associated with orbital lymphoid infiltrates.

Interpretation of tissue specimens in this case was equally challenging. The first of 3 biopsy specimens showed chronic inflammation localized to extraocular muscle tissue. A second biopsy specimen exhibited histopathologic findings and immunohistochimical staining strongly suggestive of peripheral T-cell lymphoma; however, confirmatory gene rearrangement studies were inconclusive. The third biopsy specimen, taken from the inferior part of the orbit, established the definitive diagnosis. A subsequent mass at the base of the tongue exhibited identical immunophenotype and genotype.

The diagnosis of primary orbital adnexal T-cell lymphoma was approached with caution. The eye and orbit harbor no native lymphoid tissue. Previously published reviews have claimed that the entity does not exist; however, such statements predated contemporary advances in molecular pathology. It remains unclear why the overwhelming preponderance of orbital lymphoid neoplasms originate from B lymphocytes. Saga and coworkers observed that most extranodal lymphomas arise in extranodal lymphoid tissue, although some extranodal lymphomas involve extralymphatic sites such as the orbit. Bardenstein posulates that orbital adnexal lymphoma arises from transformed lymphocytes that were replicating as part of an ongoing reactive inflammatory process such as orbital pseudotumor (idiopathic orbital inflammation). This explanation mirrors the clinical course observed in our patient. Papalkar et al reported a fatal case of rapidly progressive orbital T-cell lymphoma that was originally diagnosed as idiopathic orbital inflammation.

Most cases of orbital peripheral T-cell lymphoma represent secondary orbital involvement by distant spread of systemic disease. Although biopsy-proved T-cell lymphoma was confirmed in a nearby extranodal site (oral cavity), we believe this second mass represents regional spread of primary orbital disease. Its appearance was first noted.
nearly 2 years after the initial orbital symptoms. Our experience shows that clinicians must be persistent when orbital disorders exhibit unusual examination findings or paradoxical clinical behavior. Anecdotal case reports describe clinical scenarios involving orbital T-cell lymphomas that were initially diagnosed as idiopathic orbital inflammation or orbital cellulitis.14,15

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Postoperative Vancomycin-Resistant Enterococcus faecium Endophthalmitis

Enterococci are normal flora in the human gastrointestinal tract. They are intrinsically resistant to many antibiotic agents and may acquire resistance to almost all available antibiotics, including vancomycin. Vancomycin-resistant enterococci (VRE) have emerged as serious nosocomial pathogens. More than 28% of enterococcal infections in US intensive care units are resistant to vancomycin and many more patients become colonized than infected with these organisms.4 Despite the increasing incidence of infection with this organism, ophthalmologic infections are rare. We report the first case, to our knowledge, of postoperative VRE endophthalmitis. The infection occurred as a result of colonized donor corneal tissue.

Report of a Case. A 73-year-old woman with a history of Fuchs dystrophy underwent penetrating keratoplasty. On the first postoperative morning, she reported eye pain. Visual acuity was light perception. There was moderate conjunctival hyperemia. Fibrin and a small hypopyon were present in the anterior chamber. The patient underwent immediate pars plana vitrectomy and intravitreal injections of 1 mg of vancomycin hydrochloride and 400 µg of amikacin sulfate. Frequent topical fortified vancomycin and gentamicin sulfate, as well as topical and oral steroid agents, were used during the early postoperative period. Cultures of the aqueous, the vitreous, and the donor corneal rim yielded vancomycin-resistant (minimum inhibitory concentration >64 µg/mL) Enterococcus faecium. Restriction endonuclease analysis of genomic DNA confirmed that the isolates from the 3 sources were genetically identical. The organism was susceptible to linezolid (minimum inhibitory concentration 1 µg/mL), and 600 mg of linezolid was administered intravenously twice daily. Additional intravitreal injections of 1 mg of vancomycin and 500 µg of ampicillin sodium were given. Signs and symptoms of infection improved steadily. The patient received a 2-week course of oral linezolid after discharge from the hospital. Two years after surgery, visual acuity was 20/80. The graft was thin and clear. There was pallor of the optic nerve and attenuation of the retinal vessels.

Comment. A case of endogenous endophthalmitis caused by VRE in an immunocompromised patient has been reported; the outcome was poor, resulting in enucleation.2 Postoperative enterococcal endophthalmitis is relatively rare but associated with a poor prognosis. In 2 large series of postcataract endophthalmitis, only 2% to 4% of positive isolates yielded enterococcal organisms; all were susceptible to vancomycin.3,4 In addition, vancomycin-susceptible enterococcal endophthalmitis has been reported after penetrating keratoplasty.3 A MEDLINE search of the literature from January 1966 to October 2005 revealed no cases of postoperative VRE endophthalmitis. Genetic analysis of specimens identified the corneal donor tissue as the source of infection.

The organism was resistant to vancomycin and to all other antibiotics on the panel with known intraocular safety. The patient was reinjected with intravitreal vancomycin in an attempt to achieve levels in excess of the minimum inhibitory concentration. Systemic treatment with linezolid, an oxazolidinone with potent activity against VRE,6 was added to intravitreal and topical antibiotic therapy. At the time we treated our patient, the ocular penetration of linezolid was unknown. Subsequent investigation has