Epibulbar Rosai-Dorfman Disease: Novel Manifestation and Treatment

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease [RDD]) is a benign, idiopathic, self-limiting lymphoproliferative disease, described by Rosai and Dorfman in 1969. Extra-nodal manifestations represent about 43% of cases. The disease is classically accompanied by fever, malaise, leukocytosis, increased erythrocyte sedimentation rate, and hypergammaglobulinemia. Rosai-Dorfman disease is diagnosed histopathologically, with abundant histiocytes often engulfing lymphocytes and lymphoid cells, known as emperipolesis. The histiocytes are characteristically reactive to CD68 and S-100 proteins.

Herein, we discuss the unique case and treatment of a woman who had RDD with bilateral epibulbar lesions concurrent with anterior uveitis.

Report of a Case. A 36-year-old woman with painful ocular erythema, photophobia, and decreased vision bilaterally for 8 months was referred to the Institute of Ophthalmology and Visual Science at New Jersey Medical School for sclerouveitis. She had no previous ocular history, but she had a medical history of hypertension and diabetes mellitus. On examination, her corrected visual acuities were 20/25 OD and 20/60 OS. Slitlamp examination showed trace cell and flare in the left anterior chamber and nontender, fixed erythematous nodules in the perilimbal sclera bilaterally. Systemic evaluation findings were normal, and laboratory results showed a Westergren erythrocyte sedimentation rate of 49 mm/h. Her sclera...
ouveitis had partially responded to prior treatment with topical and oral corticosteroids; however, this treatment was discontinued at her initial visit owing to her cushingoid appearance.

The well-circumscribed mass in the left eye (Figure 1A) was completely surgically excised. Histopathologically, it demonstrated large, periodic acid–Schiff–positive, CD68 protein– and S-100 protein–immunoreactive histiocytic cells with emperipolesis, characteristic of RDD (Figure 2).

Laboratory results 3 months after excision showed an elevated γ-globulin level (1.8 g/dL) and an increased erythrocyte sedimentation rate (36 mm/h). Chest and paranasal sinus radiographic findings were normal with no lymphadenopathy.

Four months after excision, the patient developed a rapidly growing, thick, 8 × 8-mm, vascularized mass on the right eye (Figure 1C). She refused a second surgery; oral cyclosporine was initiated. After 8 months of treatment (100 mg/d), the lesion regressed to 6 × 6 mm, appearing flatter and less erythematous (Figure 1D). She reported resolution of associated tenderness and redness. The left eye remains quiescent (Figure 1B), and neither eye shows uveitis.

Comment. The most common manifestation of RDD is painless cervical lymphadenopathy.1–2 Fewer than 10% of cases include ocular involvement, primarily in the orbit or adnexa.2 Around 20 cases with epibulbar involvement have been reported. Of the few with concurrent uveitis and scleritis, only ours involves bilateral epibulbar masses associated with uveitis as the sole manifestation.

Also, to our knowledge, this is the first reported case of RDD treated with systemic cyclosporine. Although cyclosporine inhibits T-lymphocyte interleukin 2 (IL-2) release, biopsy findings of the left epibulbar mass were negative for upregulated IL-2 receptors (CD25), contrasting with CD25 positivity reported in the literature.2 We postulate that the negative findings were a result of chronic steroid treatment. The histiocytes involved in RDD are immunophenotypically similar to recently differentiated, activated macrophages.3 Thus, we propose that the effectiveness of cyclosporine treatment may be due to cyclosporine’s inhibition of cyclophilin A, a potent monocytic chemoattractant.4

Most patients with RDD improve spontaneously.5 Treatments most commonly reported include surgery, corticosteroids, chemotherapy (alkylating agents, antimetabolites, vinca alkaloids), radiation, or a combination thereof.6 Surgical excision is often the first-line therapy in patients with ocular manifestation; however, outcomes of both surgical and medical therapy are inconsistent, frequently yielding no more than a partial response.6

In our case, surgical excision and cyclosporine treatment in the left eye showed complete symptom resolution after 1 year. Cyclosporine treatment led to shrinkage of the rapidly growing lesion in the right eye with decreased vascularity. The patient reported that she was comfortable and steroid independent. Although producing a limited response when used alone, cyclosporine may be a useful therapeutic tool as an adjunct to surgery or when surgery is refused.

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The pathogenesis of peripapillary choroidal thickening and caviation, a yellow-orange, dome-shaped lesion inferotemporal to the myopic cone, is unknown. Some investigators believe the anomaly is congenital in origin owing to the presence of a clef-like communication between the retina and choroid with vitreous prolapse and anomalous vessels. However, we observed a case that developed similar findings but due to a different cause, the gradual sinking of peripapillary retinal tissue into a sclerochoroidal cavity associated with retinal hole formation and posterior vitreous prolapse, newly termed myopic peripapillary sinkhole.

Report of a Case. A 63-year-old myopic man was first evaluated in 1984 for pigment dispersion syndrome and suspicious optic discs. Owing to the appearance of the disc and a visual field defect in his left eye, topical antiglaucoma therapy was initiated with betaxolol hydrochloride, 0.25%, twice daily and the intraocular pressure remained between 13 and 16 mm Hg over several decades. Serial disc photographs in the left eye between 1984 (baseline) and 1994 revealed the gradual collapse and ultimate disappearance of a peripapillary retinal vessel associated with an enlarging retinal hole, adjacent disc hemorhages, and the development of a yellow-orange peripapillary lesion (Figure 1).

Results of a 3-dimensional topographic analysis of the peripapillary tissue (Figure 2) were normal in the right eye. However, the left eye revealed a broad and deep inferotemporal peripapillary depression. Additional views showed collapsed retinal tissue with hole formation and an underlying optically empty space, likely representing vitreous prolapse into a sclerochoroidal cavity (video, http://www.archophthal.com).

Comment. We believe that prior to the development of myopia, the retinal nerve fiber layer is in contact with underlying sclera. We postulate that as the eye elongates, ectatic sclera pulls away from the overlying retina, creating a hollow or cavern. The roof of the cavern (the retinal nerve fiber layer) gradually collapses, possibly due to excessive overlying pressure, weakened underlying sclerochoroidal architecture, and/or malnutrition from absence of the choroid in the conus. As the retinal nerve fiber layer and accompanying vessels collapse (a telltale sign of the sinkhole), axons and retinal nerve fiber layer capillaries kink, with resulting visual field loss, disc hemorrhages, and retinal hole formation. At a crucial point, the retinal hole facilitates the escape of liquid vitreous into the underlying ectatic sclerochoroidal hollow, completing the sinkhole process. We observed 3 other cases of peripapillary thickening and caviation that manifested in patients older than 55 years. Although we were not able to witness the development of the sinkhole, we suspect that we missed the initial retinal prolapse phase and witnessed only the end of the sinkhole process.

The definition of a sinkhole is a depression in the ground communicating with a subterranean passage and formed by collapse of a cavern roof. Our patient’s series of events seems to resemble this natural phenomenon. The entity known as peripapillary thickening and caviation may be part of a constellation of acquired peripapillary findings as evidenced by the chance long-term observation of a series of events culminating in a find-