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No Increase in IgG4-positive Plasma Cells in Limbal Rosai–Dorfman Disease

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Abstract

Purpose—Extranodal Rosai–Dorfman disease is a rare benign condition recently reported to sometimes show features of IgG4-related disease. The purpose of this study was to describe the corneal–limbal manifestation of the entity and to investigate whether numerous IgG4-positive plasma cells are associated with the disease at this site.

Methods—This is an interventional retrospective small case series.

Results—Two patients presenting with painless limbal mass lesions underwent total excisional biopsy with anterior lamellar keratoplasty for diagnostic and therapeutic purposes. Histopathologic evaluation of the specimens revealed inflammatory lesions containing atypical S100-immunoreactive histiocytes diagnostic of Rosai–Dorfman disease, but not an increase in the IgG4-positive plasma cells. Point mutations (V600E) in the BRAF oncogene were absent.

Conclusions—Rosai–Dorfman disease should be considered in the differential diagnosis of limbal mass lesions. Involvement at this site was not associated with BRAF mutation or IgG4 abnormalities in the cases examined.

Keywords

Rosai–Dorfman disease; IgG4; BRAF; limbus; epibulbar

Rosai–Dorfman disease (RDD), also known as “sinus histiocytosis with massive lymphadenopathy,” is a rare condition and is more common in children and young adults.^{1,2} Clinical findings frequently encountered in patients with RDD include lymphadenopathy, fever, lymphocytosis, elevated ESR, and polyclonal gammopathy. The lesions comprise enlarged histiocytes with admixed chronic inflammatory cells. Phagocytosis of lymphocytes or other cells by the histiocytes (emperipolesis) represents a signature histopathologic change. The atypical histiocytes are immunopositive for CD68 and S100, but unlike cells in

Langerhan histiocytosis, they are negative for CD1a. Erdheim–Chester disease also features atypical histiocytes, but these are negative for both S100 and CD1a.

Cervical lymphadenopathy is the most common clinical RDD manifestation, but extranodal involvement is seen in up to 43% of patients, and may not be associated with lymphadenopathy.² The eye represents a relatively frequent extranodal site, and in 1 series, ophthalmic manifestations were seen in 11% of cases, with the involvement of the orbit, eyelid, naso-lacrimal system, conjunctiva, and uvea.³ Although ocular RDD manifests most commonly in the orbit, the bulbar conjunctiva and limbus are increasingly being recognized as potential sites, although the biology of lesions on the ocular surface remains poorly defined. Epibulbar RDD lesions generally present as discrete limbal tumor-like nodules with prominent associated blood vessels. The 16 cases described to date were rarely associated with lymphadenopathy, and generally occurred as solitary findings with no systemic involvement.^{4–12}

Extranodal RDD has recently been found to contain increased IgG4-positive plasma cells in a number of cases,¹³ but the presence of such cells has not been investigated in limbal and other epibulbar lesions. Although some IgG4-positive plasma cells can be found in a range of conditions, when greatly elevated, they can indicate the presence of IgG4-related disease. Another possible etiologic association of RDD is BRAFV600E mutation. These mutations constitutively activate the proto-oncogene and promote unregulated MEK-ERK signaling in tumors including melanoma and in some atypical histiocytoses.¹⁴ Although previous studies reported that neither extranodal nor nodal RDD has been associated with BRAF mutation, ocular lesions have never been examined. We describe 2 cases of limbal RDD and examine IgG4 and BRAF in these lesions.

RESULTS

Case 1

A 28-year-old white man presented with a “cloudy spot” on his right eye associated with blurred vision, redness, and foreign body sensation. The patient had previously experienced similar problems in the same eye and was treated with topical steroids with no clinical improvement. A previous conjunctival biopsy identified only nonspecific chronic inflammation with no atypical histiocytes. The visual acuity corrected to 20/20 in both eyes. Slit-lamp examination of the right eye revealed an inferonasal corneal limbal mass centered at the 5-o’ clock position measuring 3 mm × 7 mm with associated neovascularization and conjunctivalization but with no epithelial defect or thinning of the stroma (Figs. 1A, B). Anterior segment optical coherence tomography demonstrated that the lesion was confined to the corneal stroma and limbus. The patient underwent a total excisional biopsy for diagnostic and therapeutic purposes and anterior lamellar keratoplasty. The patient did well over the next 2 months, with rapid epithelization of the corneal graft and with no signs of local recurrence or systemic disease.

On microscopic examination, the lesion was characterized by an atypical histiocytic infiltrate in the substantia propria with associated chronic inflammation (Fig. 1C). The overlying epithelium was not involved. Histiocytes with engulfed lymphocytes

(emperipolesis) were present. Immunohistochemical stains for CD68 and S100 (Fig. 1D) were positive in the histiocytes, whereas immunostains for CD1A were negative. IgG immunostains (Fig. 1E) highlighted scattered plasma cells, but IgG4 immunostains were largely negative (Fig. 1F).

Case 2

A 14-year-old contact lens-wearing white girl presented with a 5-month history of a painless growth in the right eye. The visual acuity corrected to 20/20 in both eyes. Slit-lamp examination of the right eye revealed a pink, elevated, triangular mass lesion at the 5:30 position arising from the limbus and extending onto the clear cornea and adjacent conjunctiva (Fig. 2A). The overlying epithelium was intact without ulceration or any inflammatory infiltrate. Mid-stromal haze was noted at the leading edge of the lesion. The rest of the examination was within normal limits in both eyes. The patient underwent excisional biopsy, removing the 6-mm lesion in its entirety with anterior lamellar keratoplasty. The patient did well over the subsequent months, with rapid epithelization of the corneal graft. No local recurrence or systemic disease was noted at the last follow-up 4 years after the surgery.

Microscopic examination revealed subepithelial sheets of plump pale histiocytes (Fig. 2B) with admixed lymphocytes and plasma cells, some of which were noted within the cytoplasm of the histiocytes (Fig. 2C). The plump histiocytes were immunoreactive for S100 (Figs. 2D, E). No eosinophils were present, and CD1a was not expressed (Fig. 2F). IgG4 stains did not identify any positive plasma cells, but only limited lesional tissue remained for this analysis.

Molecular Studies

DNA was extracted from both lesions and the BRAF gene was evaluated for V600E mutations at the Johns Hopkins Hospital Molecular Laboratory by pyrosequencing using a standard CLIA-certified test. This mutation was not identified in either case.

DISCUSSION

RDD was first described as a distinct histiocytic disorder in 1969 by pathologists Juan Rosai and Ronald Dorfman.¹ Ocular or periocular involvement in extranodal disease is relatively common. Foucar et al³ reported that in their series of 113 cases with RDD, 13 were found to have ophthalmic manifestations. Ophthalmic lesions most commonly involve the orbit and eyelids, and present as painless, slowly progressive proptosis, often with associated lymphadenopathy. Predominantly limbal epibulbar RDD lesions are also increasingly being identified, generally in children or young adult patients who typically lack lymph node or other involvement.

The first such case was published by Zimmerman in 1988,⁴ and over the next 25 years a total of 16 patients have been reported in the literature.^{7,8,11,12} Both of the cases we report here represented local patients seen over the last 4 years at our hospital, and it is possible that RDD involving the ocular surface is underdiagnosed. Our cases can be differentiated from other atypical histiocytic lesions such as Erdheim-Chester disease and Langerhan cell

histiocytosis by the presence of emperipolesis and immunoreactivity for S100 but not CD1a. The age of patients with limbal/epibulbar RDD lesions reported to date ranges from 1 to 71 years, with males being affected more commonly than females.

Typically, such lesions present as painless, pinkish red raised growths arising from the limbus and sometimes extending onto the clear cornea. Intense vascularization, lack of overlying epithelial defects, lack of edema or thinning surrounding the whitish yellowish inflammatory infiltrate within the stroma, and lack of endothelial or anterior chamber inflammation are the common features, and can help to differentiate RDD from other inflammatory lesions. The presence of a smooth epithelium with no keratinization on lissamine green dye staining differentiates RDD from the squamous neoplastic lesions of the limbus. In their 2008 review of 9 published limbal cases with RDD, Fernandes et al found that only 2 patients presented with lymphadenopathy or other systemic findings.⁸

Although the pathogenesis of RDD is not well understood, it is thought to most likely represent an abnormal immune response. At least a subset of RDD has been recently found to contain increased numbers of IgG4-positive plasma cells, and an association with IgG4-related disease has been suggested. This was initially documented in the skin and lungs, including 8 cases of extrapulmonary adult RDD in which 6 had increased IgG4-positive cells.^{15,16} In a subsequent series of 26 nodal and extranodal cases with RDD, more than 10 IgG4-positive plasma cells per high-powered field were identified in 19 cases (73%), and more than 40% of IgG expressing plasma cells were IgG4-positive in 8 cases (31%).¹³

Complicating such analyses is the fact that a range of cutoffs for abnormal numbers of IgG4-positive cells per high-powered field and IgG4:IgG ratios have been proposed, and these may vary depending on the site being examined.¹⁷ In addition, increased numbers of IgG4-positive plasma cells are not necessarily sufficient for the diagnosis of IgG4-related disease, and other features such as storiform fibrosis and obliterative phlebitis have been proposed as requisite features. In the lacrimal gland, consensus guidelines suggest that as many as 100 positive cells per high-powered field can be normal,¹⁷ although others have questioned whether such stringent numerical criteria are appropriate at this site and whether ancillary histopathologic features should be required.¹⁸ No published series documenting the range of IgG4-positive plasma cells in normal and abnormal bulbar conjunctiva exist, making it difficult to assess lesions at this location. However, IgG4-positive plasma cells were very rare in our 2 limbal cases, suggesting that IgG4 alterations do not commonly play a role in RDD disease on the ocular surface.

Another potential molecular cause of atypical histiocytic proliferations is the mutation of the BRAF oncogene, most commonly BRAFV600E, which is particularly significant because of new pharmacological therapies targeting this pathway.^{19–21} These genetic alterations are often identified in Langerhan cell histiocytosis and Erdheim–Chester disease. Previous studies have shown no association between this genetic mutation and RDD at extraocular sites, and it was also lacking in our limbal cases.²²

In summary, we report 2 cases of limbal RDD in relatively young patients presenting as pink, elevated limbal lesions with neovascularization. Both patients underwent excisional

biopsy of the lesions with good results, and no lymphadenopathy or other signs of systemic involvement were noted in either case by their primary care physician. Because of the generally benign course for RDD at this site, in our cases, and in most previously published cases, the initial referral is to a primary care physician rather than to an oncologist. Although there can be an association between extranodal RDD and IgG4 disease, we did not identify this in our 2 limbal lesions. Although RDD does not commonly involve the ocular surface, it may be underdiagnosed and should be considered when epibulbar masses are encountered, particularly in younger patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

A and B, Slit-lamp photography shows an inferonasal corneal limbal mass with neovascularization and conjunctivalization. C, Histological examination revealed an atypical histiocytic infiltrate present in the substantia propria with associated chronic inflammation (H&E stain, original magnification $\times 100$). D, Immunohistochemistry for S100 protein showing cytoplasmic immunoreactivity in the histiocytes (original magnification $\times 400$). E and F, Although numerous IgG-positive plasma cells were noted, IgG4-positive plasma cells were very rare with none in this field (100 $\times$).

FIGURE 2.

A, A Pink elevated, well-defined limbal nodule with dilated blood vessels. B, Histological examination revealed an atypical histiocytic infiltrate in the substantia propria, with epithelium at the top of the field (H&E stain, original magnification $\times 100$). C, Engulfed lymphocytes (emperipolesis, arrow) could be found within the cytoplasm of some of the enlarged histiocytes (H&E, original magnification $\times 1000$). D and E, S100 Immunohistochemistry showing cytoplasmic immunoreactivity in the histiocytes, some with phagocytized lymphocytes (arrow). F, CD1a immunostains were negative (original magnification $\times 100$).