

Treatment of Benign Lymphoid Hyperplasia of the Orbit With Rituximab

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Abstract: Benign lymphoid hyperplasia is a disorder characterized by polyclonal lymphocytic infiltration of orbital tissues, predominantly with B-cells. Rituximab is a monoclonal antibody directed against CD20, a B-cell marker. Two patients with recurrent orbital masses involving the lacrimal glands were treated with rituximab. The diagnosis of benign lymphoid hyperplasia with predominance of CD20⁺ cells was confirmed in both cases based on a surgical biopsy. Both patients had been previously treated with standard therapies, including high-dose steroids, and one patient had failed external-beam radiation therapy. They both responded well to treatment with intravenous rituximab. Neither patient experienced any side effects associated with rituximab.

(*Ophthalmol Plast Reconstr Surg* 2010;26:11–13)

Benign lymphoid hyperplasia is a lymphoproliferative disorder consisting of tissue infiltration by small, predominantly B-lymphocytes and reactive follicles. Its presentation is very similar to that of lymphoma, and biopsy must be performed to rule out lymphoma and ensure accurate diagnosis. Current standard treatments for benign lymphoid hyperplasia are high-dose steroids and external-beam radiation therapy.

Rituximab is a monoclonal antibody that targets the CD20 marker on B-cells and is currently approved by the U.S. Food and Drug Administration for treatment of non-Hodgkin lymphoma and rheumatoid arthritis. We report successful treatment of 2 patients with benign lymphoid hyperplasia of the orbit with rituximab.

CASE REPORTS

Case 1. A 41-year-old woman with a history of benign lymphoid hyperplasia of the right orbit was evaluated by our orbital oncology service after the onset of periorbital swelling, ptosis, diplopia, and decreased vision. She had been treated with high-dose oral steroids for recurrent episodes of orbital congestion in the past but had been in remission for 2 years before this presentation. Ocular adnexal examination revealed significant fullness of the right upper eyelid. A firm, tender mass was palpable. MRI showed an increase in the size of the lacrimal gland mass (Fig. 1A). Biopsy

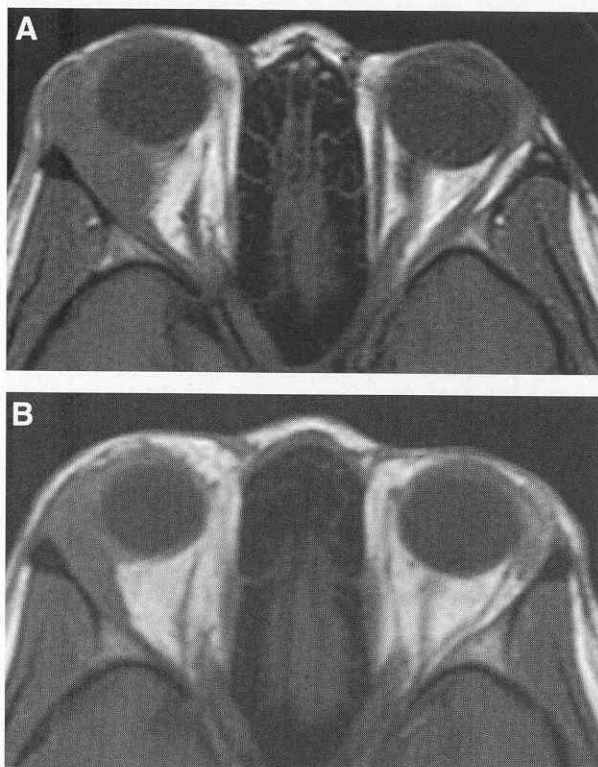


FIG. 1. Case 1. **A**, MRI shows an enlarged right lacrimal gland. **B**, MRI after treatment with one dose of rituximab shows more than 50% resolution of the lacrimal gland mass.

of the mass and pathologic examination of the biopsy specimen revealed lacrimal gland tissue with a chronic inflammatory infiltrate characterized by the presence of many reactive lymphoid follicles (Fig. 2A) and a mixed infiltrate of small lymphocytes, plasma cells, and some eosinophils in areas of the tissue between the follicles. Immunohistochemical staining of sections of the tissue were reviewed by an expert hematopathologist at M. D. Anderson Cancer Center (J.M.) and showed an overall predominance of CD20⁺ B-cells (Fig. 2B). By flow cytometry, there were 54% CD20⁺ B-lymphocytes in the biopsy specimen. On flow cytometry, the B-lymphocytes were shown to be polytypic for κ and λ chains.

Because of the patient's intolerance of steroids during past episodes and her refusal of radiation therapy as a treatment option, one dose of rituximab (375 mg/m²) was given intravenously. There were no adverse reactions to the medication. Subsequent examination and MRI, 3 months later, showed at

Accepted for publication May 27, 2009.

The authors have no financial interests to disclose.

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DOI: 10.1097/IOP.0b013e3181b8e056

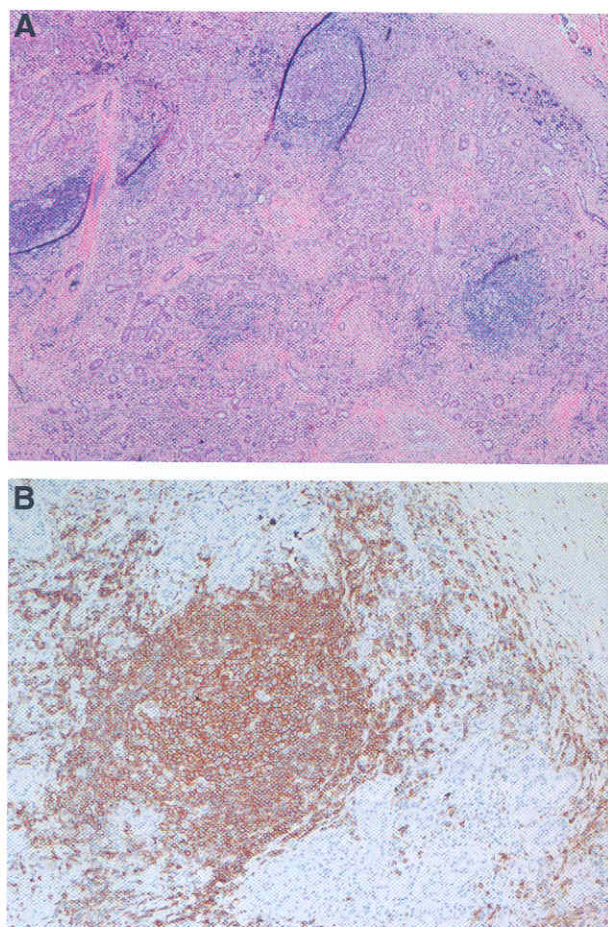


FIG. 2. Case 1. **A**, The lacrimal gland contains a chronic inflammatory infiltrate with a prominence of reactive lymphoid follicles. Immunohistochemical staining shows a marked predominance of CD20⁺ lymphocytes (**B**) in the lymphoid follicles and mixture of CD20⁺ and CD3⁺ lymphocytes (not shown) in areas of the tissue infiltrate outside of the follicles.

least 50% reduction in the eyelid edema and proptosis and the size of the lacrimal gland mass (Fig. 1B). There was resolution of the patient's symptoms. At last follow-up, 9 months after treatment with rituximab, the patient remained without evidence of recurrence of her orbital disease.

Case 2. A 23-year-old woman presented for a second opinion on treatment options for lymphoid hyperplasia of both orbits. This patient had a history of recurrent bilateral eyelid and orbital swelling. An orbital biopsy was reviewed by an expert hematopathologist (J.M.) and was consistent with benign lymphoid hyperplasia. Immunostaining revealed CD20⁺ lymphocytes. Based on flow cytometry, there were 43% CD20⁺ cells in the biopsy specimen, and the B-lymphocytes polytypic for κ and λ chains.

The patient had been treated with systemic steroids on several occasions with good initial response but with recurrence of symptoms on steroid withdrawal. The left orbital disease had subsequently been treated with radiation therapy (22.50 Gy in 15 fractions over 3 weeks) during one of the recurrent episodes. The radiation therapy was completed 6 months prior to presenting to our orbital oncology service with bilateral recurrent masses.

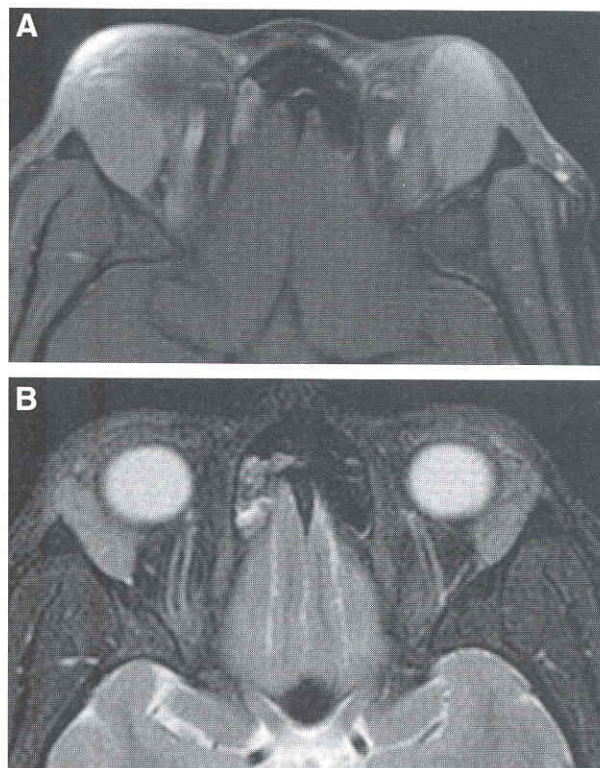


FIG. 3. Case 2. **A**, MRI shows bilateral enlargement of lacrimal glands. **B**, MRI after administration of 4 weekly doses of rituximab shows more than 50% decrease in the size of lacrimal gland infiltration bilaterally.

Findings on ocular adnexal examination were significant for large, mobile, firm masses bilaterally causing ptosis of both upper eyelids. Lymphadenopathy was noted in the left preauricular region. There was moderate symmetric proptosis bilaterally. MRI of the orbit revealed symmetric enlargement of the lacrimal glands (Fig. 3A).

Intravenous rituximab (375 mg/m²) was administered weekly for 4 weeks. There were no adverse reactions to the medication. At last follow-up, 3 months after treatment with rituximab, examination showed significant decrease in the orbital swelling bilaterally, and MRI showed more than 50% decrease in the size of the lacrimal gland masses (Fig. 3B). The patient remained without evidence of recurrence of her orbital disease.

DISCUSSION

The observations in the 2 patients presented in this report suggest that rituximab, administered either as a single dose or as multiple doses, may be a reasonable option for treatment of CD20⁺ benign lymphoid hyperplasia of the orbit, particularly in patients with disease that has recurred after standard treatments or proved refractory to standard treatments. Rituximab is approved by the U.S. Food and Drug Administration for the treatment of CD20⁺ B-cell lymphomas.

Benign lymphoid hyperplasia can be left untreated if the associated symptoms are minimal and tolerable. There is evidence, however, that benign lymphoid hyperplasia can undergo malignant transformation, especially in lesions involving the lacrimal gland.^{1,2} In a study by Polito and Leccisotti,² 5 patients with benign lymphoid hyperplasia of the orbit were left untreated, and 2 eventually developed lymphoma. Currently,

standard treatments for benign lymphoid hyperplasia of the orbit include the use of oral steroids, at least for the first episode, and for recurrent or refractory cases, external-beam radiation therapy, usually consisting of 20 to 30 Gy delivered in 10 to 15 fractions.^{2,3} Some authors have suggested that radiation therapy is more effective than systemic steroids in preventing malignant transformation of benign lymphoid hyperplasia of the orbit.²

Rituximab is a chimeric monoclonal antibody that selectively targets B-cells bearing the CD20 surface marker and causes complement-dependent and antibody-dependent cellular cytotoxicity and apoptosis.^{4,5} Since benign lymphoid hyperplasia of the orbit predominantly consists of B-cells bearing the CD20 surface marker,^{1,6} rituximab is an intuitive treatment alternative for recurrent or refractory benign lymphoid hyperplasia of the orbit. To our knowledge, there has been only one other report of this approach, by Witzig et al., who reported a high-response rate to rituximab in 11 patients with "pseudolymphomas of the orbit." All 11 patients reportedly received 4 weekly doses of rituximab (375 mg/m²). Only 1 of the 11 cases was refractory to treatment with rituximab. The other 10 showed sustained responses for at least 4 months.⁷

Rituximab is generally well tolerated and has fewer side effects than steroids. The most common side effects include infusion-related side effects (tingling sensation and itching immediately after the infusion of drug), nausea, fever, and chills.⁸ There have been rare cases of progressive multifocal leukoencephalopathy reported in association with rituximab

use in patients with lupus and also in patients with a diagnosis of lymphoma.⁸

In addition to its generally good side-effect profile, other potential advantages of rituximab include the fact that treatment can be repeated and that rituximab, unlike radiation therapy, is not associated with any known ocular side effects.

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