Lichenoid Mucosal Reaction to Rituximab

Oral lichenoid reactions are clinically and histologically indistinguishable from oral lichen planus (OLP) but have a distinct etiology. In the case of oral lichenoid drug reactions (OLDRs), lesions arise in temporal association with exposure to certain medications, such as nonsteroidal anti-inflammatory, anti-hypertensive, and oral hypoglycemic agents [1, 2]. We present a case of rituximab-induced OLDR in a patient with follicular non-Hodgkin lymphoma.

A 43-year-old woman with stage IIIA follicular lymphoma presented with a 3-month history of bilateral tongue and buccal mucosa sores. As her first line of therapy, she had been enrolled in a clinical trial of high-dose rituximab monotherapy (750 mg/m²; Rituxan; Genentech, South San Francisco, CA, <http://www.gene.com>; Biogen Idec, Cambridge, MA, USA, <http://www.biogenidec.com>), with the last of four doses administered 3 months prior to her consultation—the time the oral sores appeared. The remainder of her past medical history was unremarkable and her only medication was vitamin C supplements. She had experienced no prior mouth sores. She denied any skin, genital, eye, or throat lesions or symptoms.

Extraoral examination was unremarkable. Intraoral examination showed multifocal white reticulations surrounding ulcers ranging from 0.5 to 4.0 cm in diameter, with white keratotic halos and peripheral erythema (Fig. 1A–1D). These lesions were distributed bilaterally and symmetrically on the buccal mucosa, upper labial mucosa, and dorsal and ventral tongue, as is typical for OLDP. With the clinical diagnosis of a rituximab-induced OLDR based on the chronology of lesions, a punch biopsy was obtained, and the histopathology was lichenoid mucositis consistent with OLDP. The patient was prescribed topical dexamethasone solution (5 mg per 5 mL), to swish and spit 5 mL twice daily, and 40 mg prednisone for 7 days with a 1-week rapid taper.

At 3-week follow-up, intraoral examination revealed marked improvement with decrease in pain symptoms and 50% decrease in ulcer size overall (Fig. 2A, 2B). However, because of continued ulcers, an intralesional injection of 12 mg of triamcinolone acetonide was administered into the left ventral tongue and each of the buccal mucosa—the most painful sites—and high-dose prednisone was reinstated at 40 mg daily for 3 weeks together with topical dexamethasone therapy. Two weeks later, the patient had only one ulcer <1 cm on the ventral tongue. Prednisone was tapered, and she continued with topical dexamethasone. Three weeks later, the patient presented with a flare-up. A second intralesional injection of 12 mg of triamcinolone acetonide was administered into the right and left buccal mucosa; prednisone was reinstated at 30 mg daily, and topical therapy with clobetasol 0.05% gel was added. The patient was gradually tapered off prednisone and maintained on topical steroids with one other

flare 7 months from the original presentation. At 9-month follow-up, 1 year from the start of ulcers, she presented with complete resolution of lesions (Fig. 2C, 2D). She has not been exposed to rituximab again and has not experienced a recurrence of these lesions. She is in clinical remission at 6-year follow-up.

The diagnosis of OLDR depends largely on the establishment of a temporal relationship between lesion onset and the use of the offending agent and the resolution of symptoms upon withdrawal of the agent. The resolution of symptoms may be immediate or may take several months, in which case treatment of the OLDR with topical corticosteroids in addition to the reduction in dose or discontinuation of the offending agent may be required [1, 2]. The ultimate proof of diagnosis is recurrence on rechallenge, but this is not always possible or desirable. What was unusual about this current case was the length of time it took for the lesions to resolve with systemic and topical corticosteroid therapy.

Rituximab, a chimeric monoclonal antibody that targets the B-cell CD20 antigen, was the first commercially available monoclonal antibody for the treatment of lymphoma and is well tolerated by the majority of patients. The majority of adverse events are infusion related, manifesting as flu-like symptoms that occur within hours of infusion [3, 4]. Other less common reactions include hypotension, bronchospasm, pruritus, rash, and, rarely, tumor lysis syndrome in patients with a high tumor burden. Recently, Bakkour and Coulson reported a case of a widespread cutaneous lichenoid eruption related to treatment with obinutuzumab, a novel anti-CD20 monoclonal antibody, in a patient with relapsed follicular lymphoma initially treated with rituximab without any cutaneous side effects [5]. To our knowledge, this is the first report of OLDR subsequent to treatment with high-dose rituximab in the English literature. In light of the wide use of rituximab for the treatment of lymphoma and the increasing use for autoimmune diseases such as rheumatoid arthritis, pemphigus vulgaris, and systemic lupus erythematosus [6, 7], awareness and recognition of this unusual side effect of treatment with rituximab is critical to allow for prompt management to reduce morbidity.

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Figure 1. Day of consultation. Extensive ulcers surrounded by white reticulation and erythema on the right buccal mucosa (A), left buccal mucosa (B), right lateral tongue (C), and left lateral tongue (D).

Figure 2. Three weeks later, right buccal mucosa (A) and left lateral tongue (B) after topical dexamethasone and prednisone therapy; 9 months later, right buccal mucosa (C) and left lateral tongue (D) showing complete healing.

Disclosures

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