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Khurram, S.A., Fernando, M., Smith, A.T. et al. (1 more author) (2013) IgG4-related sclerosing disease clinically mimicking oral squamous cell carcinoma. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, 115 (2). e48 - e51. ISSN 2212-4403

https://doi.org/10.1016/j.oooo.2012.04.011

Vol. xx No. x Month 2012

IgG4-related sclerosing disease clinically mimicking oral squamous cell carcinoma

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IgG4-related sclerosing disease is a distinct clinicopathologic entity known to involve the maxillofacial region, particularly the salivary, lacrimal, and pituitary glands. We report a case with lesions involving the tongue and palatine tonsil with associated skin lesions. A 45-year-old female patient presented with a history of soreness, dysphagia, and an asymptomatic rash involving the upper trunk. The initial clinical diagnosis of her oral lesions was squamous cell carcinoma. The diagnosis of an IgG4-related lesion was confirmed by histologic examination of the oral and skin lesions as well as confirmation of raised serum IgG4 levels. Tapering systemic corticosteroid therapy resulted in complete resolution of the lesions. This is the first report of IgG4-related sclerosing disease presenting as concurrent oral and skin lesions, with the oral lesion clinically resembling oral squamous cell carcinoma. Such lesions present a diagnostic challenge, but the outcome is very favorable. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;xx:xxx)

CASE REPORT

A 45-year-old female patient was referred by her medical practitioner to the local maxillofacial surgery unit because of a 4-month history of gradually worsening pain and soreness involving the left side of the tongue with associated dysphagia. She also had a widespread skin rash which presented at the same time as her oral symptoms. The patient had a history of poorly controlled type II diabetes, which was being managed with metformin as well as insulin. She also suffered from hypertension and asthma and was allergic to penicillin. The patient was a heavy smoker but reported minimal alcohol intake.

On examination, a 3.0 × 1.5 cm tender, indurated, speckled patch with a nodular surface and raised margins involving the left lateral border and dorsum of tongue was seen (Figure 1). In addition, a similar lesion involving the right tonsillar region and palpable lymph nodes bilaterally involving level II of the neck were also noted. Extraoral examination showed an asymptomatic psoriatic rash of the same vintage as the oral lesions involving the patient's chest, arms, and legs, which had not been treated previously.

INVESTIGATIONS

Initial hematologic investigations showed slightly raised white cell, neutrophil, and platelet counts of 17.8 × 10^9/L, 11.7 × 10^9/L, and 511 × 10^9/L, respectively (normal ranges 4-11 × 10^9/L, 2.5-7.5 × 10^9/L, and 150-400 × 10^9/L, respectively) with a low mean corpuscular volume of 72.7 fL (normal range 76-96 fL) and a ferritin level of 12 ng/mL (normal range 15-200 ng/mL). Magnetic resonance imaging (MRI), an orthopantomogram, and a chest x-ray were ordered for clinical staging, and incisional biopsies of the tongue and tonsillar lesions were scheduled to obtain a tissue diagnosis.

The orthopantomogram and the chest x-ray did not reveal any abnormality. No obvious tongue or tonsillar lesions were identified on the MRI study, and the clinically enlarged bilateral neck lymph nodes were judged to be reactive rather than suggestive of a malignant process.

Incisional biopsies of the tongue and tonsillar lesions showed similar features with a nodular surface architecture (Figure 2). The epithelium was markedly hyperplastic and focally hyperparakeratinized with extensive neutrophil infiltration but no evidence of fungal infection (Figures 2 and 3, *A*). Long and narrow epithelial rete processes extended into the lamina propria, the latter containing a dense inflammatory infiltrate dominated by plasma cells, but also containing macrophages and lymphocytes. The initial impression was that of plasma cell mucositis, and further investigations were carried out to characterize the inflammatory infiltrate and distinguish whether the lesion was neoplastic (i.e., multiple myeloma, extramedullary plasmacytoma) or reactive.[1] In situ hybridization confirmed the polyclonal nature of the infiltrate, and immunohistochemistry demonstrated expression of CD3 (Figure 3, *B*), CD79a (Figure 3, *C*), CD138, and MUM1 (results not shown), with no expression of CD56 and cyclin-D1

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Received for publication Dec 2, 2011; returned for revision Apr 19, 2012; accepted for publication Apr 19, 2012.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2012.04.011

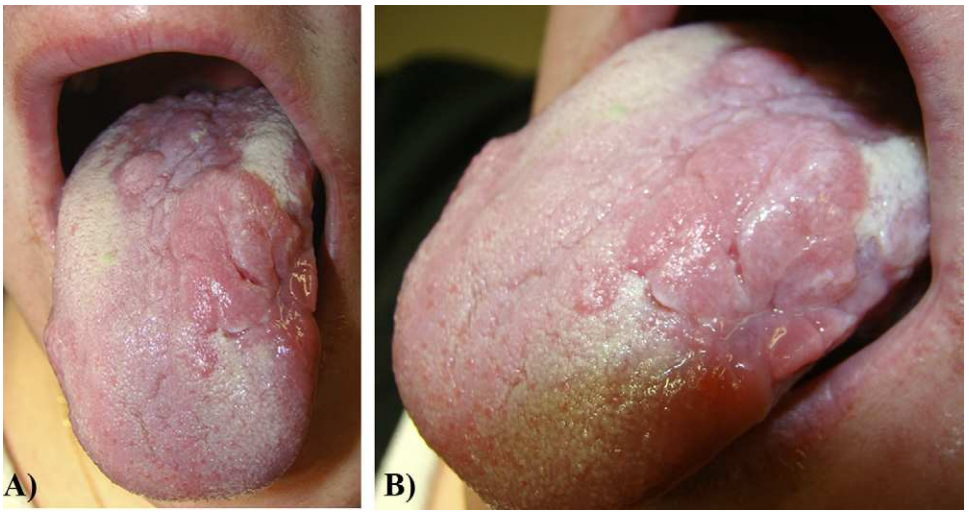

Fig. 1. **A,** An erythematous, indurated, and irregular lesion involving the midline and left dorsum of the tongue extending posteriorly, as seen on clinical examination. **B,** Lateral view of the tongue, showing the lesion extending into the left lateral tongue border and encroaching on the ventral surface.

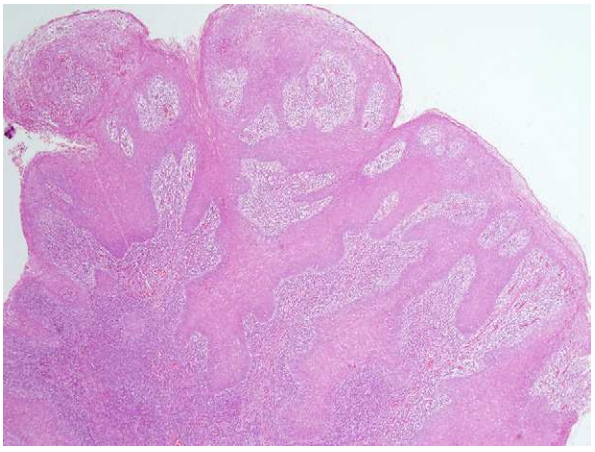

Fig. 2. Hematoxylin and eosin staining of the tongue lesion, showing a nodular surface architecture with hyperplastic epithelium overlying heavily inflamed connective tissue.

(results not shown). The Ki-67 proliferation fraction exceeded 10% (Figure 3, *D*). These results confirmed the predominantly plasmacytic and reactive nature of the lesion. However, the site of the lesion, the lack of symptoms involving other oral sites, and the coincident skin lesions excluded plasma cell gingivitis, indicating a consideration for IgG4-related sclerosing disease.

Immunohistochemistry revealed a ratio of IgG4- (Figure 3, *E*) to total IgG (Figure 3, *F*)–expressing cells of 65%. A literature search indicated varying degrees of fibrosis associated with IgG4-related sclerosing disease ranging from mild to severe depending on the stage of the lesion, with long standing lesions tending to show more fibrosis than the early ones.[2] Based on these findings and the diagnostic criteria recommended by Cheuk and Chan,[3] a histologic diagnosis of IgG4-related disease was made, which was later confirmed by raised serum IgG4 levels of 3.52 g/L (normal range 0.08-1.40 g/L). Biopsy of one of the cutaneous lesions showed a prominent and predominantly plasmacytic infiltrate within the dermis with no evidence of vasculitis, in keeping with the oral diagnosis.

MANAGEMENT

Tapering steroid therapy was commenced in liaison with the patient's diabetes management team in consideration of the medical history of diabetes. The patient was started on 10 mg daily dexamethasone which was reduced to 6 mg after a week. After 2 weeks, the dexamethasone was replaced by 5 mg prednisolone for a month followed by hydrocortisone pellets as the symptoms gradually resolved.

The treatment resulted in complete resolution of the oral and tonsillar lesions and associated symptoms within 2 months, with a marked reduction in skin lesions. The complaint of dysphagia was also resolved, and serum IgG4 levels returned to normal. The patient has been undergoing regular clinical reviews and so far has not experienced any recurrences.

DISCUSSION

IgG4-related sclerosing disease was first described in the context of pancreatitis by Sarles et al. in 1961,[4] and the autoimmune nature of the disease was proposed by Yoshida et al. in 1995.[5] Most of the initial studies focused on pancreatic manifestations, with the multiorgan involvement discovered later.[6] Furthermore, the diagnostic levels for serum IgG4 concentration were

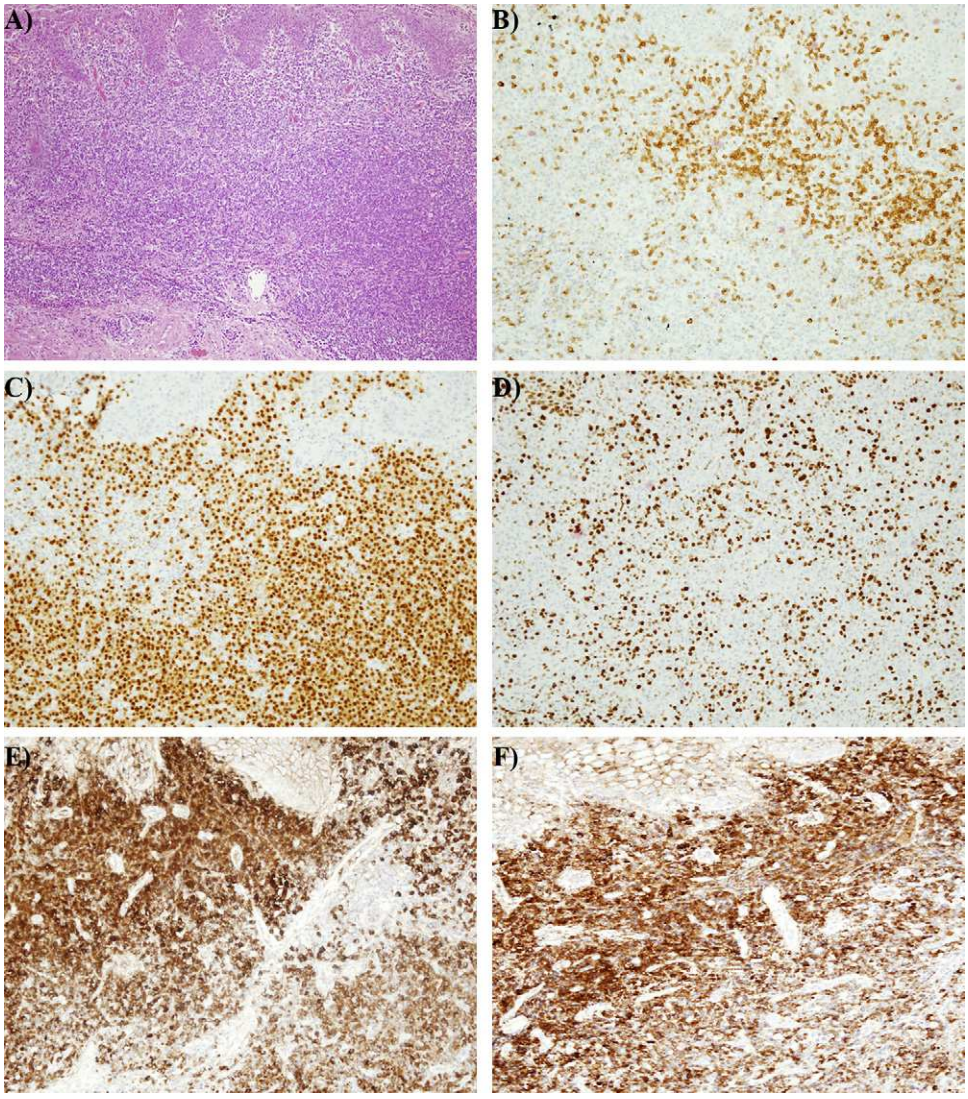

Fig. 3. Histologic sections from incisional biopsy of tongue lesion showing hematoxylin and eosin and immunohistochemical staining. **A,** A dense inflammatory infiltrate was seen in the connective tissue. Immunohistochemical analysis of the infiltrate with positive staining for **(B)** CD3 and **(C)** CD138. **D,** The Ki-67 proliferation fraction was >10%. The ratio of **(E)** IgG4- to **(F)** total IgG-expressing cells was 65%.

not fully established until 2001.[7] In the head and neck region, IgG4-related sclerosing disease has been referred to as "Kuttner tumor" (chronic sclerosing sialoadenitis) and has been known to involve salivary, lacrimal, and pituitary glands with a variable degree of fibrosis or sclerosis depending on the stage of the disease.[8] In addition to simultaneous involvement of multiple organs, the disease is characterized by fibrosis and sclerosis in association with a distinct and extensive IgG4-secreting lymphoplasmacytic cell infiltrate. In normal conditions, IgG4 is the least abundant member of the IgG family and in the normal population accounts for <6% of the total serum IgG. The current diagnostic criteria include elevated serum IgG4 level coupled with increased IgG4-expressing cells within the involved tissues (>50 positive cells per high-power field, with an IgG4/IgG ratio of >40%), in addition to variable sclerosis with possible degeneration of the associated structures.[3] IgG4-relared sclerosing disease typically involves men from 50 to 70 years of age.

Pancreatic malignancy arising in a background of IgG4-related disease has been reported by multiple groups.[9-11] Recent reports have shown destructive IgG4 lesions involving the maxillary sinus[12] and nasal septum,[13] both of which resolved after treatment with systemic corticosteroids. Gill et al. reported salivary duct carcinoma arising in IgG4-related fibrosclerosis involving the parotid gland.[14] In bullous pemphigoid,

IgG4 has been shown to be the most abundant IgG subclass within the oral lesions as well as circulating within the serum and urine.[15-17] In addition, IgG4 is the predominant serum antibody in pemphigus,[16] epidermolysis bullosa acquisita,[18] and herpes/pemphigoides gestationis,[19] with serum levels reflecting disease activity. The precise cause of IgG4 overexpression in these conditions is not known, with genetic factors, continued antigenic stimulation, and an isotype shift from the inflammatory IgG1 subclass to a noninflammatory IgG4 subclass being suggested as possible factors.[15,20] However, other than the increased IgG4 production, the disease process in these pathologic entities markedly differs from IgG4-related sclerosing disease, with no evidence of fibrosis or sclerosis and the lack of a plasma cell–dominated tissue infiltrate.

To our knowledge, there have been no previous reports of IgG4-related sclerosing disease presenting as concurrent oral and skin lesions with clinical resemblance to oral squamous cell carcinoma (OSCC). Inclusion of IgG4-related sclerosing disease in the differential diagnosis of any atypical inflammatory oral lesions that clinically resemble OSCC should be considered to reduce the need for surgical intervention. Histologic interpretation can be difficult, because features similar to plasma cell mucositis are seen in a number of neoplastic and reactive conditions, including multiple myeloma, extramedullary plasmacytoma, and plasma cell gingivitis.[1] Diagnosis requires thorough hematoxylin and eosin examination, an appropriate panel of immunohistochemistry markers, and consideration of associated clinical features. Once diagnosed, the clinical outcomes can be quite favorable, with complete resolution following steroid therapy. However, surgery might be inevitable in patients with long-standing lesions and resulting extensive fibrosis.

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