A rare case of oral tumor presenting as first sign of immunoglobulin G4–related disease

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Immunoglobulin G4 (IgG4)–related disease is an idiopathic autoimmune disease characterized by elevated serum and tissue IgG4 levels, organ enlargement, and a clinical response to immunosuppressants. We present such a case in a 39-year-old female, whose lesion was located in the right buccal space involving the minor salivary gland. After the tumorlike growth was removed, diagnosis was confirmed with histopathologic slides showing lymphoid cell infiltration, dense fibrotic stroma, and IgG4-positive plasma cells. The patient underwent steroid therapy, and there has been no recurrence since. Rarely do we see IgG4-related sclerosing disease involve the buccal minor salivary gland in its early stages. Thus, it is important to include IgG4-related disease in the differential diagnosis when considering autoimmune diseases with oral manifestations. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:e187–e190)

CASE PRESENTATION

A 39-year-old female patient visited our outpatient clinic, complaining of a hard mass that persisted for the past 3 months on her right cheek. She denied any past medical history, and clinical findings included a slightly dome-shaped, palpable, indurated mass, about 2×2 cm in size, on the right buccal mucosa. No change in color was noted in the overlying oral mucosa, as shown in Figure 1. Magnetic resonance imaging (MRI) showed diffuse soft tissue thickening and hyperemic change of the right buccal mucosa, extending to the buccomasseteric space (Figures 2 and 3). A frozen-section specimen was obtained under general anesthesia to rule out malignancy before the right buccal tumor was completely removed. The lesion was densely fibrotic and whitish when sectioned in half. Histopathologic findings at $\times$ 100 (Figure 4) and $\times$ 400 (Figure 5) magnifications included fibroadipose and minor salivary glandular tissues with lymphoid cell infiltration or lymphoid follicle formation in dense fibrotic stroma. Because of the immunologic characteristics, CD20 antibodies were used to show neoplasms of B-cell derivation, and CD30 antibodies were used to detect lymphoproliferative disease. Immunoglobulin G4 (IgG4) immunostaining yielded positive for plasma cells (Figure 6; Table I). Postoperative treatment consisted of glucocorticoid therapy, starting with prednisolone 30 mg/day, which was later tapered and eventually discontinued 4 months after initial consultation. The patient is still under follow-up 5 years later, and there has since been no relapse.

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DISCUSSION

IgG4-related disease is an idiopathic, fibroinflammatory, autoimmune disease with a wide spectrum of symptoms, depending on the organ(s) involved. It is predominantly seen in middle-aged to elderly male patients, but symptoms in the head and neck region show no gender predilection. The general clinical pattern of the affected organ is diffuse enlargement and sclerosis of a tumefactive lesion, resulting in irreversible damage and organ dysfunction, such as impaired salivary secretion in Mikulicz syndrome.

Imaging

Imaging characteristics of IgG4-related disease are usually nonspecific, but the general pattern ranges from inflammation to sclerosis,[1] depending on progression of the disease. On computed tomography, the organ involved usually appears enlarged, with decreased yet homogeneous attenuation. On T2-weighted MRI, the lesion shows a low signal, reflecting increased cellularity and fibrosis.[2] Regional lymph nodes are enlarged in 80% of the cases; however, this does not represent lymphatic spread but, rather, a disturbance in the immune system.[1]

IgG4-related disease has a tendency to involve multiple organs, hence full-body radiographic examination, such as with positron emission tomography, is essential to detect involvement of other organs. In a multifocal image, malignancy may also be suspected but can be differentiated with biopsy and histopathologic analysis, in addition to other diagnostic criteria of IgG4-related disease.

Histopathology

Biopsy is essential in establishing a pathologic diagnosis, but for IgG4-related disease, the correlation of all findings—the sum of all parts—is more important than individual findings because IgG4-related disease does not display any pathognomonic characteristics. Thus, histopathologic features may be determined to be “highly suggestive” or “having

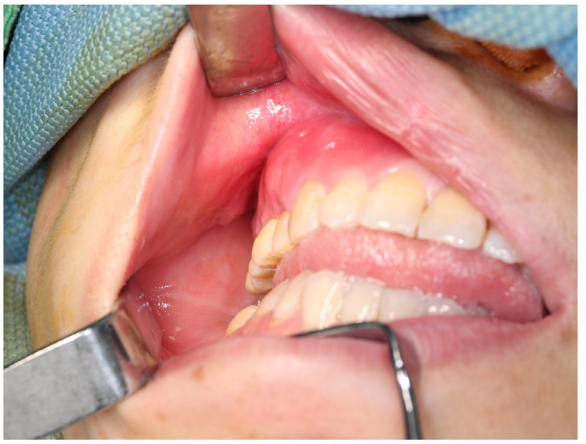

Fig. 1. Preoperative clinical photo of the right buccal lesion. The lesion has a slight dome shape, and is dense and firm upon palpation.

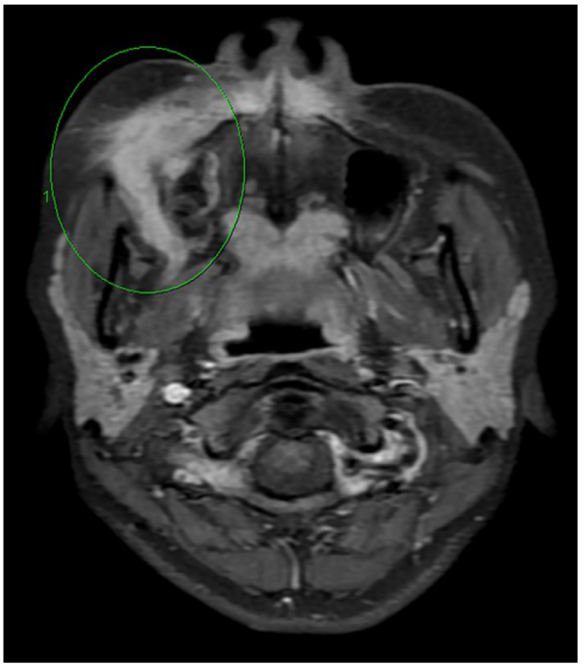

Fig. 2. Axial magnetic resonance imaging (MRI) shows a hyperdense lesion over the right buccal region, with diffuse, fibrotic borders, as indicated within the green circle.

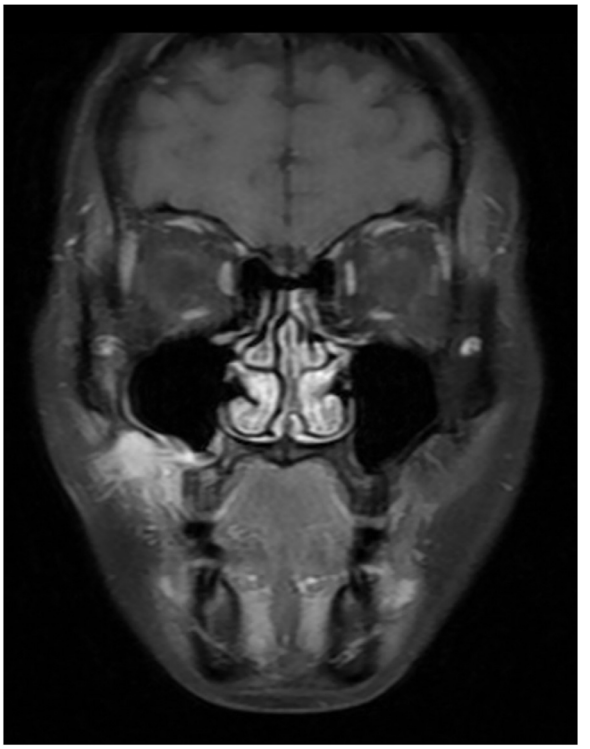

Fig. 3. Coronal magnetic resonance imaging (MRI) shows the same hyperdense lesion over the right buccal region adjacent to the posterior molars, about 2 × 2 cm in size, extending to the buccomasseteric region.

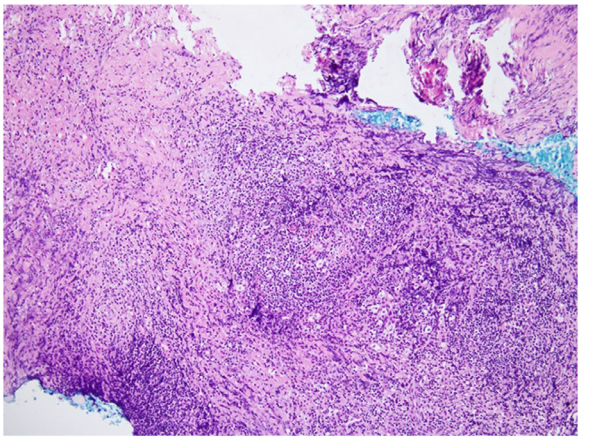

Fig. 4. Hematoxylin and eosin staining of the right buccal lesion at low-power field shows fibroadipose and minor salivary glandular tissues, with lymphoid cell infiltration in dense fibrotic stroma (original magnification × 100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlides: VM05633.*

probable histopathologic features," rather than resulting in a definitive pathologic diagnosis. At the other end of spectrum, those categorized as "having insufficient histopathologic evidence" are not necessarily excluded because the finding may be a result of sampling error, previous therapy, and/or progression to fibrosis. Nevertheless, the 3 major histopathologic characteristics associated with IgG4-related disease are (1) dense lymphoplasmacytic infiltrate, often consisting of T cells and plasma cells; (2) fibrosis, consisting of spindle cells, either fibroblasts or myofibroblasts, arranged at least focally in a storiform pattern; and (3) obliterative phlebitis, with the same lymphoplasmacytic infiltrate invading the walls and lumens of veins and sometimes arteries. Diagnosis may be established if 2 of the 3 characteristics are observed, usually the former 2, except in certain

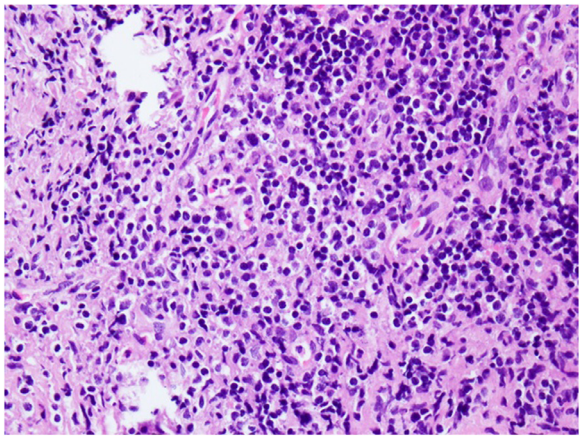

Fig. 5. Hematoxylin and eosin staining of the same right buccal lesion at high-power field shows lymphoid cell infiltration in dense fibrotic stroma (original magnification × 400). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlides: VM05634.*

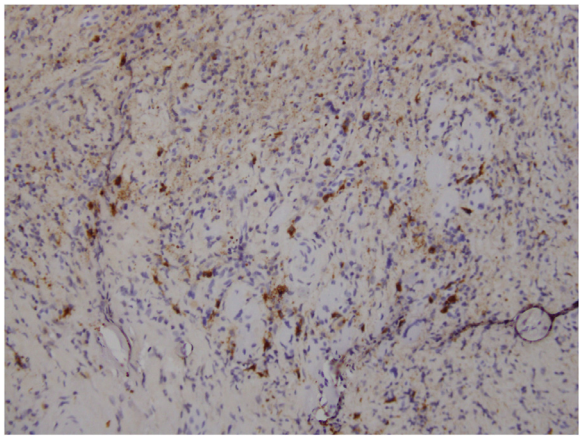

Fig. 6. Immunoglobulin G4 (IgG4) immunostaining at the same magnification (x 400) yields positive result for plasma cells. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05635.*

Table I. Immunostains used during differential diagnosis of the buccal lesion

Antibody	*Dilution*	*Clone*	*Company*
Anti-Human CD20 cy	IC:1:200	L26	Dako, Santa Clara, CA
Anti-Human CD30	IC:1:40	Ber-H2	Dako, Santa Clara, CA
IgG4 stain	IC:1:800	HP6069	Invitrogen, Carlsbad, CA

organs, such as the lymph node, lung, minor salivary gland, and lacrimal glands, where only the first trait is usually observed.[3]

To examine the dense lymphoplasmacytic infiltrate, IgG4 immunostaining is paramount, especially in cases where serum IgG4 level is not elevated or clinical signs are not evident. The appropriate cutoff point for the number of IgG4+ plasma cells in a high-power field (HPF) is different for each organ because of the varying extent of fibrosis, although in some studies, the general consensus is greater than 10 cell/ HPF.[4] Nevertheless, more important than the number of IgG4+ plasma cells is the ratio between IgG4+ and IgG+ plasma cells. Most literature accept a ratio of greater than 40% as the appropriate cutoff value,[3] but not in the absence of other findings.

Counting of IgG4+ plasma cells is tricky, first because of the presence of focal dense IgG4+ distribution (namely, "hot spots") despite most sites having a diffuse, increased number of IgG4+ plasma cells. Second, the high-IgG4 background makes counting difficult. Thus, there is no gold standard in measuring the number of IgG4 plasma cells, but the recommendation has been to first choose 3 "hot spots" as representative fields; second, to observe them under × 40 objective lens directly or using photographs; and last, to count the IgG4+ plasma cells using the "gestalt" method before averaging the cell count.[3]

Pathogenesis and Mechanism

Of all the subclasses of IgGs, IgG1 is the most abundant type, at 5 to 11 mg mL^{-1}, and IgG4 is the least abundant, ranging from 0.35 to 0.51 mg mL^{-1}.

It is currently unclear whether an increase in IgG4 production is more closely correlated with innate immunity or acquired immunity because there is evidence supporting either possibility. On the one hand, T helper cell type 2−dominated cytokine production resulting in an increase in regulatory T cells and IgG4 indicate an anomaly in acquired immunity, whereas certain pathogens, such as *Helicobacter pylori* may also induce IgG4 production, preventing innate immunity and allowing low-grade infection to persist. Cells of innate immunity, such as monocytes and basophils, may function abnormally, leading to the pathogenesis of IgG4-related disease through overactivation of toll-like receptors. Macrophages may also overexpress cytokines, such as transforming growth factor-β, resulting in fibrosis that is commonly noted in patients with IgG4-related disease.[5]

Diagnosis

There are currently no universal criteria for the diagnosis of IgG4-related disease. However, an IgG4 team organized by the Ministry of Health, Labor, and Welfare in Japan, has established comprehensive diagnostic criteria for IgG4-related disease in 2011, comprising 3 major parts: (1) diffuse or localized swelling in one or multiple organs, (2) elevated serum IgG4 level of 135 mg/dL or greater, and (3) lymphocytic infiltration and fibrosis, with IgG4+/IgG+ ratio greater than 40% and greater than 10 cells/HPF. If all 3 criteria are fulfilled, the possibility of IgG4-related disease is high; if only the first and third are fulfilled, the diagnosis is probable; if only the first 2 are

fulfilled, it is only possible. Recent studies have proven serum IgG4 levels to be neither specific nor sensitive for IgG4-related disease because malignant tumors and autoimmune diseases may also induce elevated serum IgG4 levels.[6] Other malignant tumors, such as adenocarcinoma and squamous cell carcinoma, may also mimic IgG4-related disease clinically and histopathologically[7] or even exist concurrently. Thus, correlation is of paramount importance in differential diagnosis, especially when the mandatory biopsy analysis does not yield clear results. Unfortunately, biopsy specimens may be difficult to obtain from certain organs, such as the pancreas. Therefore, additional organ-specific criteria were established to improve the differential diagnosis. Other laboratory biomarkers that may aid in diagnosis include elevated serum plasmablasts, which also correlate with disease activity.[7] However, plasmablasts assays are not widely available, and further studies are needed before it is routinely used for clinical diagnosis.

Treatment

Eventual fibrosis of the involved organ may result in severe and irreversible obstruction and damage, so treatment is necessary in patients with active and symptomatic IgG-related disease, especially those with multiorgan involvement, significantly elevated IgG4 levels, and a history of relapse. Patients who display only asymptomatic lymphadenopathy or mild submandibular gland enlargement may be kept under watchful observation instead.[7] Treatment comprises chemotherapy for active disease and surgery to remove already fibrotic regions that are unresponsive to chemotherapy. Surgical intervention, that is, stenting of the biliary tract, may be used for debulking to improve cosmetic results and/or to minimize dysfunction. Glucocorticoids are the first-line chemotherapy agents, with prednisone at 30 to 40 mg/day being a common choice, and the dose is dependent on the aggressiveness of disease and on patient weight. The dose should be maintained for 2 to 4 weeks before being tapered within 3 to 6 months. However, many clinicians in Japan recommend low-dose glucocorticoids for up to 3 years as maintenance dose,[7] the most common dose being 5 mg/day, followed by 2.5 mg/day. When glucocorticoids are contraindicated or there are persistent and/or recurrent symptoms, rituximab,[7] a steroid-sparing drug with B-lymphocyte depletion, is a good alternative, at 3-weekly doses of 375 mg/m^2. Improvement is defined as fulfillment of at least 2 of the 3 following criteria: (1) improvement of clinical status, (2) decrease in serum IgG4 level, and (3) reduction in radiologic abnormalities.[7] IgG4-related disease may be synchronous or metachronous, so long-term follow-up is important to detect possible recurrences at a different site.

CONCLUSION

IgG4-related disease is an autoimmune disease with potential multiorgan involvement. Fibroinflammatory lesions may be observed on various imaging modalities, with fibrosis being the dominant finding in later stages. Diagnosis is based on the correlation of all characteristic findings, such as organ enlargement, elevated serum IgG4 level, and lymphocytic infiltration and fibrosis, with IgG4+/IgG+ ratio greater than 40% and greater than 10 cells/HPF. Treatment is dependent on the extent of fibrosis, with immunosuppressant therapy being key to diffusing active disease.

PRESENTATION

This abstract was previously presented as an e-poster at the 23rd Congress of the European Association for Cranio-Maxillo-Facial Surgery (EACMFS) in 2016 at London, UK.

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