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## RARE DIAGNOSIS OF IGG4-RELATED SYSTEMIC DISEASE BY LIP BIOPSY IN AN INTERNATIONAL SJÖGREN SYNDROME REGISTRY

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### Abstract

IgG4-related disease has been recently defined as a distinct clinic-pathologic entity, characterized by dense IgG-4 plasmacytic infiltration of diverse organs, fibrosis, and tumefactive lesions. Salivary and lacrimal glands are a target of this disease and, when affected, may clinically resemble Küttner tumor, Mikulicz disease, or orbital inflammatory pseudotumor. In some patients, the disease is systemic, with metachronous involvement of multiple organs, including the pancreas, aorta, kidneys, and biliary tract. We report a 66-year old man who presented with salivary gland enlargement and severe salivary hypofunction and was diagnosed with IgG4-related disease on the basis of a labial salivary gland biopsy. Additional features of his illness included a marked peripheral eosinophilia, obstructive pulmonary disease, and lymphoplasmacytic aortitis. He was evaluated in the context of a research registry for Sjögren syndrome and was the only one of 2594 registrants with minor salivary gland histopathologic findings supportive of this diagnosis.

### Introduction

Chronic bilateral enlargement of the lacrimal and/or salivary glands can have an inflammatory, infectious or neoplastic etiology. In 1892, Mikulicz provided a detailed description of the acinar atrophy and massive small cell infiltration of the glandular

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interstitium in a man with this clinical presentation (1). “Mikulicz syndrome” was subsequently found to have a variety of etiologies, including lymphoma, Sjögren syndrome (SS), and the newly described group of IgG4-related diseases (2-4). In SS, persistent swelling of the salivary glands occurs in a minority of patients and raises concern for lymphomatous transformation (5). Within the past decade, IgG4 plasmacytic infiltration has been recognized as a pathologic feature of several forms of salivary and lacrimal gland disease, including chronic sclerosing sialadenitis (Küttner tumor), orbital inflammatory pseudotumor, and “Mikulicz disease” (6-8). Patients with these forms of IgG4-related plasmacytic salivary and lacrimal gland disease may have systemic disease (known variably as IgG4-related systemic disease, IgG4-related sclerosing disease, and IgG4-positive multiorgan lymphoproliferative syndrome), manifested by contemporaneous or past involvement of other organs with a pathologic process marked by IgG4 plasmacytic infiltration, extensive fibrosis, and obliterative phlebitis (9-11). Elevated serum IgG4 levels and eosinophilia are often present. The most common is sclerosing pancreatitis; others include lymphoplasmacytic aortitis, retroperitoneal fibrosis, sclerosing cholangitis, and inflammatory pseudotumors of the lung, breast or liver.

Kitagawa et al were the first to identify IgG4-plasmacytic infiltration as a pathologic feature of chronic sclerosing sialadenitis (Küttner tumor), a tumor-like condition affecting most often the submandibular glands (6). Their study was based on a retrospective review of pathologic material. Following their report in 2005, other Japanese investigators reported patients with severe and persistent swelling of the lacrimal and salivary glands in whom IgG4 plasmacytic infiltration of the affected glands and/or elevation of serum IgG4 levels was present (12,13). In some of these patients, the diagnosis was established or supported by minor labial salivary gland biopsy (6,14-16). These patients were different from those affected by SS, having a more equal gender ratio, normal sialography, and excellent response to corticosteroids (16,17). Reports of IgG4 related sialadenitis are rare in the United States, although a recent retrospective case series from the Massachusetts General Hospital has confirmed the frequent presence of IgG4 plasmacytic infiltration in cases of Küttner tumor (18).

We report herein a patient with IgG4-related systemic disease who presented with salivary gland swelling and severe xerostomia. His diagnosis was established within the context of the Sjögren’s International Collaborative Clinical Alliance (SICCA) research registry (19).

## Materials and Methods

**SICCA** is an ongoing longitudinal multi-site observational study that is developing and studying a large and growing cohort of uniformly evaluated individuals from ethnically diverse populations (19). Enrollment criteria are broad to create a cohort reflecting a wide range of symptoms and signs, from possible early SS to well established disease. SICCA participants must be at least 21 years of age and have at least one of the following: a complaint of dry eyes or dry mouth; a previous diagnosis of SS; elevated titers of antinuclear antibodies (ANA), rheumatoid factor, and/or anti-SS-A or SS-B antibodies; bilateral parotid enlargement; a recent increase in dental caries; or a possible diagnosis of secondary SS. Enrollment began in fall 2004 at six international SICCA Research Groups that recruit, enroll and examine participants, and collect and ship biospecimens to the central repository in San Francisco. The Groups are located at University of Buenos Aires and German Hospitals, Buenos Aires, Argentina; Peking Union Medical College Hospital, Beijing, China; Copenhagen University Hospital Glostrup, Denmark; Kanazawa Medical University, Japan; Kings College London, UK (added in 2007); and University of California, San Francisco, USA. In 2009, additional research groups were established at the Johns Hopkins

University and the University of Pennsylvania, both in the United States, and in Aravind, India.

All SICCA groups use the same protocol-directed methods to provide uniform evaluations, data records from ocular, oral and rheumatologic examinations, and biospecimen collections. Labial salivary gland biopsy samples are obtained at the time of the SICCA baseline evaluation on all participants, or a previous biopsy specimen is accepted if it was obtained no more than 3 years previously and the microscopic slides are available for examination. Labial salivary gland biopsies are performed, after local anesthetic infiltration, to harvest 5–10 glands, some of which are fixed in neutral buffered formalin while others are quickly frozen in liquid nitrogen. Three to five formalin-fixed labial salivary glands are processed by the local pathology departments (paraffin embedding, sectioning, and hematoxylin and eosin [H&E] staining) and remaining glands are frozen and stored in liquid nitrogen. H&E-stained sections of each specimen are evaluated independently by 2 of 3 pathologists calibrated in this assessment (TED, DC, and JG), who are blinded with regard to the participants' demographic, clinical, and serologic characteristics and who assign 1 of 6 possible diagnoses: focal lymphocytic sialadenitis, non-specific chronic sialadenitis, sclerosing chronic sialadenitis, granulomatous inflammation, marginal-zone (mucosa-associated lymphoid tissue [MALT]) lymphoma, or within normal limits (20).

Informed consent was obtained from all participants in the SICCA research registry in compliance with the Helsinki Declaration, and the study was approved by the UCSF Committee on Human Research, the Johns Hopkins University School of Medicine Institutional Review Board, and the local institutional review boards at the other participating institutions.

### Case Report

A 66 year-old man presented with a 6-month history of parotid and submandibular gland enlargement, severe xerostomia, dry eyes, 25-pound weight loss, and night sweats. His current illness began 9 months earlier with two episodes of pneumonia, followed by a productive cough and dyspnea. On CT imaging, there was enlargement of the left parotid and right submandibular glands (Figure 1). A needle biopsy of the left parotid gland one month earlier had shown a polymorphous lymphocytic infiltrate, but no evidence of neoplasm. On his initial evaluation at our institution, he had diffuse enlargement and induration of his parotid (left greater than right) and submandibular glands. The oral cavity was dry and minimal saliva could be expressed through Wharton or Stensen ducts. There was no palpable lymphadenopathy. He underwent an evaluation for possible SS as a participant of SICCA. On an unanesthetized Schirmer test, there was 5 mm of wetting over 5 minutes in both eyes. Ocular surface staining with lissamine green and fluorescein was abnormal, with scores of 8 in both eyes, using a quantitative scoring method devised by the SICCA investigators (21). No saliva was collected with either stimulated (parotid saliva) or unstimulated (whole saliva) methods. Anti-SS-A and SS-B antibodies were negative. WBC was 13040/mm<sup>3</sup> with 53% eosinophils. Labial salivary gland biopsy showed diffuse fibrosis of the glands with loss of all acini and most ducts, presence of lymphoid follicles with germinal centers, and diffuse plasmacytic infiltration, more than half of which stain positively with anti-IgG4 (Figure 1). Serum IgG4 level was 348 mg/dl. An ascending thoracic aortic aneurysm and mediastinal adenopathy were evident on CT imaging. Bronchial lavage fluid contained 275 WBC (44% eosinophils). Transbronchial lymph node biopsy showed polytypic lymphocytes and increased eosinophils. The eosinophilia and salivary gland swelling resolved with prednisone therapy, initially at a daily dose of 40 mg. His course over the next year was marked by persistent salivary hypofunction, weight stabilization, recurrent bronchitis, and panlobar pneumonia necessitating hospitalization. Pulmonary function testing showed a forced vital capacity of 3.17 Liters (77% predicted),

forced expiratory volume in 1 second of 2.09 Liters (65% predicted), and total lung capacity of 6.48 Liters (97% predicted). A serum IgE level was 115 kU/L. He underwent surgical repair of the thoracic aortic aneurysm one year after initial presentation to our institution. A surgical biopsy of the aortic aneurysm showed lymphoplasmacytic aortitis with an IgG4 plasmacytic infiltrate. Treatment with rituximab was then initiated.

## Discussion

IgG4-related systemic disease is emerging as a distinct clinico-pathologic entity with multisystem involvement. It predominantly affects middle-aged and elderly men as a chronic illness with metachronous involvement of various organ systems, including the pancreas, salivary and lacrimal glands, thyroid, aorta, retroperitoneum, and lungs. The pathology is typically one of sclerosis and IgG4 plasmacytic infiltration, and underlies the entities of chronic sclerosing sialadenitis (Küttner tumor), lymphoplasmacytic aortitis, sclerosing pancreatitis, Reidel thyroiditis, retroperitoneal fibrosis, and inflammatory pseudotumors in the breast, lung, liver, and orbit.

Our patient presented to our institution with parotid and submandibular gland enlargement and the rapid onset of severe salivary gland dysfunction. The severe salivary hypofunction contributed to his 25-pound weight loss. The initial diagnostic impression was one of SS and prompted referral to the SICCA research registry in order to complete the diagnostic evaluation in a coordinated fashion. However, there were a number of findings evident on medical evaluation that indicated an alternative diagnosis, such as lymphoma. These included the rapid onset of severe salivary gland dysfunction, the induration of the salivary glands, marked peripheral eosinophilia, and the mediastinal lymphadenopathy. The diagnosis of IgG4-related systemic disease was established with the demonstration of IgG4 plasmacytic infiltration of the minor labial salivary glands and documentation of an elevated level of serum IgG4. The finding of lymphoplasmacytic aortitis with increased IgG4 cells at surgery one year later was also consistent with this diagnosis. Our patient's rapid development of parotid and submandibular gland swelling and weight loss is in keeping with other case reports of this disease (22,23).

A markedly elevated level of peripheral blood eosinophils ( $6880/\text{mm}^3$ ) was present in our patient at presentation. Peripheral blood eosinophilia is a known feature of autoimmune pancreatitis and IgG4-related systemic disease, but not to this degree (24,25). It has been noted in approximately 12% of patients with IgG4-related autoimmune pancreatitis (type I) (26). Moderate-to-severe eosinophilic infiltration is noted in up to two-thirds of pancreas resection specimens from patients with autoimmune pancreatitis (26). Additionally, such eosinophilic tissue infiltration has been observed in other forms of IgG4-related organ involvement, including tubulointerstitial nephritis (27), eosinophilic angiocentric fibrosis of the orbit and upper respiratory tract (28), and prostatitis (29).

Our patient developed chronic obstructive pulmonary disease coincident with the development of the sialadenitis. This remains a source of considerable morbidity for him. Adult-onset asthma has been described as a complication of IgG4-related autoimmune pancreatitis (30,31) suggesting a pathogenetic link. The basis for this is not understood and needs further study.

As of September 21, 2011, there were 2594 labial salivary gland biopsy diagnosis results in the SICCA registry database. The patient reported herein is the only one who had morphologic findings consistent with those described for IgG4 plasmacytic disease. Other histopathologic diagnoses were focal lymphocytic sialadenitis (1479 registrants), non-specific or sclerosing chronic sialadenitis (n=1008), granulomatous inflammation/within

normal limits (n=52), MALT lymphoma (n=1) and inadequate specimen (n=54). This implies that this disease is rare among a cohort of individuals recruited with clinical and laboratory features shared by patients with SS. Identification was based on the striking morphologic features which were distinct from other histopathologic patterns of sialadenitis. These findings include the complete fibrosis of the salivary glands with total loss of acini in concert with a lymphoplasmacytic infiltrate. IgG4-related sialadenitis must be distinguished from sclerosing chronic sialadenitis. In the latter, involvement is often not uniform from gland to gland in the specimen (suggesting ductal obstruction as a potential etiology) and ductal dilatation is a prominent feature. The fibrosis of IgG4-related sialadenitis is characterized by highly cellular proliferation with plump fibroblast admixed with inflammatory cells as opposed to the more extensive collagenous deposition seen in sclerosing chronic sialadenitis. It is not known whether this difference reflects the relative chronicity of the disease processes before the diagnostic biopsies are performed. Immunohistochemical staining for IgG4-positive plasma cells was not performed as a part of the routine histopathologic assessment of labial salivary glands in the SICCA study. Thus, we cannot exclude the possibility that earlier or less severe forms of IgG4-related sialadenitis might have been overlooked with the routine histologic techniques utilized in the SICCA study.

In summary, IgG4-related sialadenitis is a rare entity despite a number of recent case series of IgG4-related sialadenitis from Japan. However, its recognition is important since it may be associated with clinically important lesions of other organs, such as lymphoplasmacytic aortitis. Our case highlights the utility of the lip biopsy in establishing the diagnosis of diverse systemic diseases with oral manifestations, including IgG4-related systemic disease.

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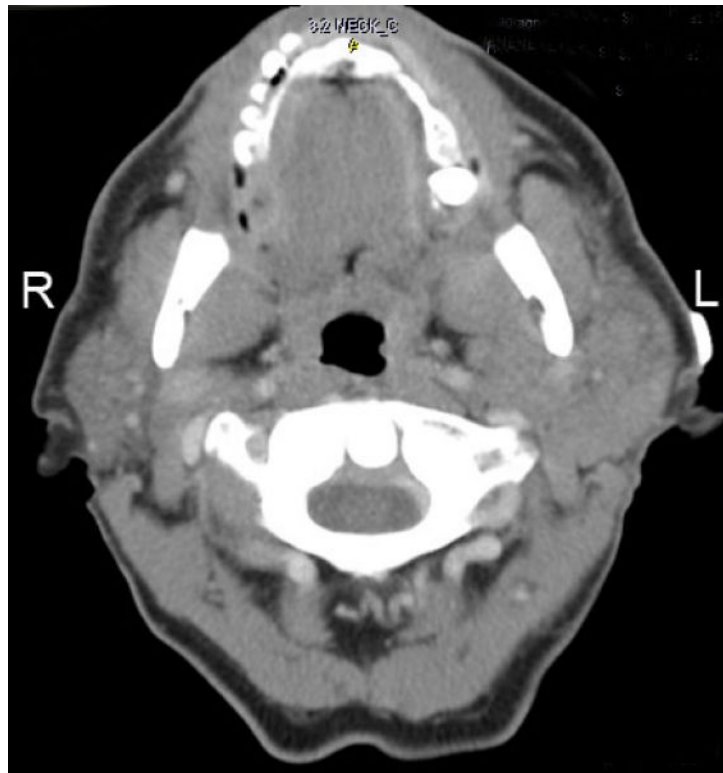
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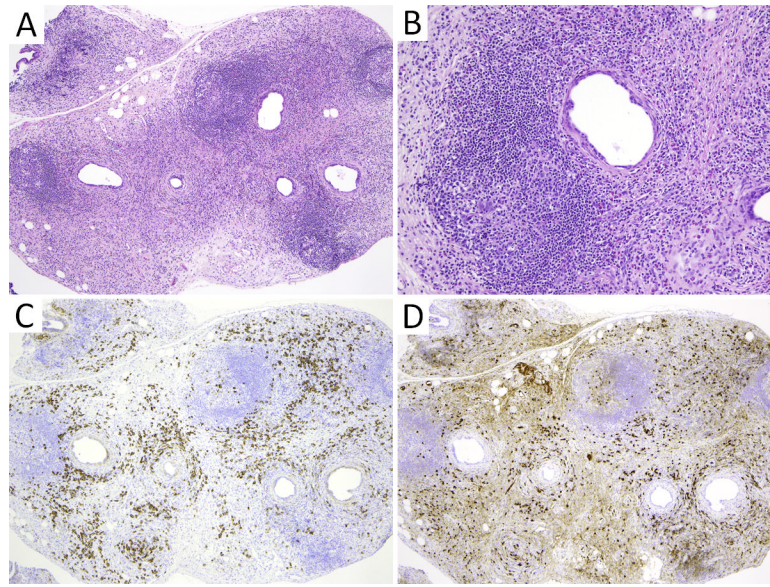
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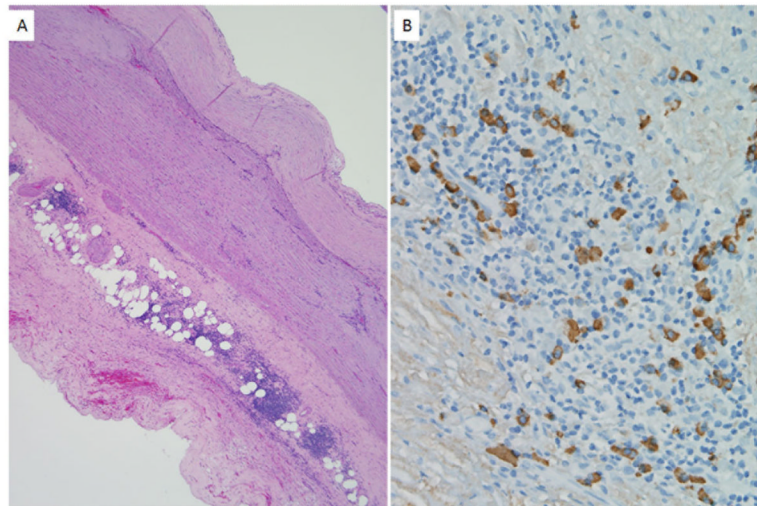




**Figure 1.** CT scan of the neck. There is enlargement of the left parotid gland relative to the right, without a discrete mass or surrounding soft tissue stranding.



**Figure 2.** Minor salivary gland. The salivary gland lobule exhibits diffuse fibrosis and almost complete parenchymal atrophy, with only dilated central ducts remaining (Panel A, 40X). There are multiple germinal centers surrounded by an inflammatory infiltrate with many eosinophils (Panel B, 100X). The inflammatory infiltrate contains numerous plasma cells (Panel C, CD 138 immunostain, 40X), the majority of which also stain for IgG4 (Panel D, IgG4 immunostain, 40X). More than 50% of the CD138+ plasma cells were also IgG4+.



**Figure 3.** Thoracic aorta. There is a prominent lymphoplasmacytic infiltrate with associated sclerosis involving the adventitia with extension into the media (Panel A, 40X). An IgG4 immunostain shows a relative increase in the number of IgG-4 plasma cells (Panel B, 400X).