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Case Report

IgG4-related disease in an adolescent with radiologic-pathologic correlation

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ABSTRACT

Immunoglobulin G4-related disease (IgG4RD) is an immune-mediated condition characterized by lymphoplasmacytic infiltrates and fibrosis of affected organs. IgG4RD may affect many different organs either individually or together in a multiorgan condition and, thus, incorporates a wide range of fibroinflammatory phenotypes with shared pathologic features. Although IgG4RD most commonly occurs in late adulthood, it may affect children and adolescents. Only one case of IgG4RD presenting as isolated submandibular gland involvement has been reported in the pediatric population. Radiographic features of IgG4RD are often nonspecific making diagnosis challenging, but it is important for radiologists to be familiar with this disease as its inclusion in the differential for diffuse salivary enlargement may be the first step in making an accurate diagnosis. Here, we report a case of a child presenting with bilateral submandibular gland swelling to increase awareness of this condition in the pediatric population.

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Introduction

Chronic-sclerosing sialadenitis is an immune-mediated condition of the salivary glands that was first described in 1896 as isolated enlargement of the submandibular glands of adults and elderly patients and is often referred to as Küttner tumor. Although chronic-sclerosing sialadenitis has a clear

predilection for the submandibular glands, it may involve the parotid glands, thus mimicking other causes of salivary gland enlargement such as Sjögren syndrome and Mikulicz disease. Sjögren syndrome is an autoimmune disease primarily affecting salivary and lacrimal glands. Mikulicz disease—a term that has fallen from contemporary use—was initially described in the 19th century to characterize idiopathic

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chronic enlargement of the submandibular, parotid, and lacrimal glands.

Immunohistochemical technology to identify immunoglobulin (Ig) G4 molecules on plasma cells has permitted reclassification of a subgroup of salivary gland swelling cases previously considered idiopathic. IgG4 is a subclass of IgG usually found at low serum concentrations and, unlike other subclasses, is elevated in association with allergic reactions and autoimmune diseases rather than microbial infection [1]. High IgG4 titers can be found in various fibroinflammatory conditions such as bronchiectasis, primary sclerosing cholangitis, vasculitis, and the newly classified spectrum of diseases entitled IgG4-related disease (IgG4RD). Despite this association with various pathological processes, increased IgG4 levels are not thought to initiate inflammation or fibrosis but rather are believed to modulate chronic inflammation.

Although knowledge regarding IgG4RD has increased over the last decade, diagnostic challenges remain. The variability of clinical presentation due to the wide range of potentially affected organs in IgG4RD makes the diagnosis difficult—sometimes taking years to establish [2]. This report is intended to increase awareness of IgG4RD as a process that may present as isolated submandibular gland swelling in a child.

Case report

A 16-year-old Hispanic male was referred to a regional hospital after bilateral neck masses were noted during a routine examination. The masses were first noted by the patient 2 months before his initial visit with slowly progressive enlargement thereafter. He denied fever, sweating, weight loss, and local phlogistic signs. Initial physical examination was unremarkable other than firm bilateral submandibular masses. Due to concern for possible bacterial infection, a course of antibiotics was prescribed but without improvement in submandibular gland swelling.

Evaluations by otolaryngology and rheumatology confirmed the isolated submandibular gland enlargement. The neck was symmetric with enlargement of firm submandibular glands approximately 4 cm in diameter (Fig. 1). Initial diagnostic considerations included tuberculosis, Sjögren

syndrome, and lymphoma. Computed tomography (CT) demonstrated homogenous enlargement of the bilateral submandibular glands without ductal dilation or ductal stones. Parotid and lacrimal glands were normal in appearance. No lymphadenopathy or thyroid abnormalities were appreciated (Fig. 2).

The initial pathologic analysis of open surgical biopsy of the left submandibular gland revealed a dense lymphocytic infiltrate composed of a mixture of B and T lymphocytes as shown by immunohistochemical staining with evidence of reactive secondary lymphoid follicle formation, consistent with a reactive inflammatory process without evidence of lymphoid neoplasia (Fig. 3A and B).

Abnormal laboratory results revealed low C3 (87 mg/dL; normal lower limit, 90 mg/dL) and elevated total IgG of 1885 mg/dL (normal upper limit, 1584 mg/dL). These findings may occur in inflammatory states such as with several autoimmune rheumatologic diseases. Low complements (such as C3) in children may reflect genetic deficiency, which can predispose to rheumatic disease, though in such cases, the levels of C3 are much lower than just below normal as noted here. Other blood tests were normal including Quantiferon gold TB test, urinalysis, renal and liver function, blood cell counts, hepatitis B and C tests, and inflammatory markers (erythrocyte sedimentation rate max of 10 mm/h, C reactive protein <5 mg/dL). Autoantibodies (including SS-A, SS-B, antinuclear antibody, and rheumatoid factor) which may be positive in Sjögren syndrome or other rheumatologic diseases were all negative. Together, these findings suggested against lymphoma or tuberculosis as the underlying etiology. Although the histopathology was consistent with possible Sjögren syndrome and a minority of children with Sjögren syndrome may be negative for autoantibodies, the CT findings of normal parotid glands was highly atypical for childhood Sjögren syndrome. Because IgG4RD may present with isolated salivary gland swelling, further diagnostic evaluation specifically for IgG4RD was recommended. Immunostaining of the biopsy specimen revealed 365 IgG+ cells per high power field (hpf) and 266 IgG4+ cells/hpf, resulting in an IgG4+/IgG ratio of 72.8% (Fig. 3C). Quantitative serum IgG subclass analysis revealed markedly elevated IgG4 at 1050 mg/dL (normal upper limit 89 mg/dL) and elevated IgG2 at 874 mg/dL (normal upper limit 549 mg/dL), with IgG1 and IgG3 within reference range.



Fig. 1 – Lateral (A and C) and frontal (B) views of the neck. No erythema or signs of acute infection of overlying skin, except for healing scar from surgical biopsy seen on picture (C).

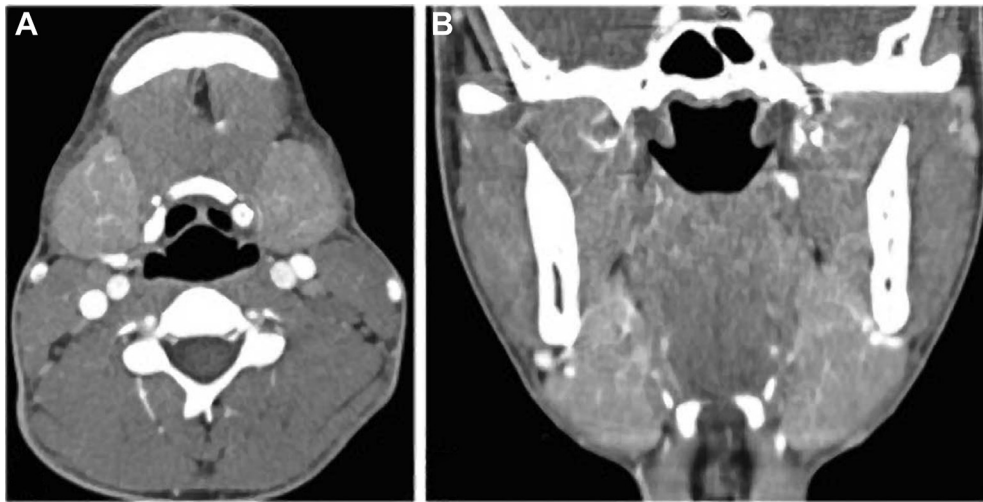


Fig. 2 – Contrast-enhanced neck CT. Axial (A) and coronal (B) images at the mandible plane shows homogeneously enlarged bilateral submandibular gland without duct dilatation. There is no abnormal lymphadenopathy.

These findings of markedly elevated IgG4+/IgG+ cell ratio within the gland as well as markedly elevated serum IgG4 confirmed the diagnosis of IgG4RD manifested by chronic sialadenitis.

After diagnosis, oral prednisone therapy was started at 40 mg per day for 2 weeks with a subsequent tapering dose over the next 4 weeks. Submandibular gland swelling improved markedly with only subtle persistent swelling present at follow-up 1 year after discontinuation of prednisone. Throughout the course and at follow-up, no submandibular gland tenderness was noted, and no other organ manifestations developed.

Discussion

IgG4RD has gained attention due to identification of fibrosis in multiple organ sites associated with intense tissue infiltration by IgG4+ cells. Common involvement with IgG4+ infiltration has linked CCS along with other inflammatory conditions such as type 1 autoimmune pancreatitis and Reidel thyroiditis, which are all now considered part of the IgG4RD spectrum. [3] The differential diagnosis for IgG4-related sialadenitis includes infection (such as tuberculosis), lymphoma, Sjögren syndrome, sarcoidosis, and

sialodocholithiasis. [4] The pathogenesis of IgG4RD remains uncertain but is thought to be linked to upregulation of genes involved in cell proliferation and extracellular matrix formation. [4]

IgG4RD has become better recognized in adults (mean age, 53 years) in whom it mostly presents with symptoms involving the salivary and lacrimal glands, pancreas, and lymph nodes. [5,6]

Children and adolescents have not been included in larger IgG4RD studies and have been discussed mainly by case reports. In the pediatric population, pancreatic involvement was less common, whereas head and neck involvement continues to be predominant, albeit with different organ distribution than adults. Most pediatric patients had orbital involvement, followed by sinonasal disease, lacrimal gland disease, and sialadenitis. [7] Other manifestations included disease of the mediastinum, retroperitoneum [8], pancreas, lung, and mesenterium.

Histologic IgG4RD is suggested when at least one of the following is seen: dense lymphoplasmacytic infiltrate, storiform-type fibrosis, or obliterative phlebitis. Tissue immunostaining should reveal at least 10 IgG4+/hpf, but for lacrimal and salivary glands, a more expressive count of

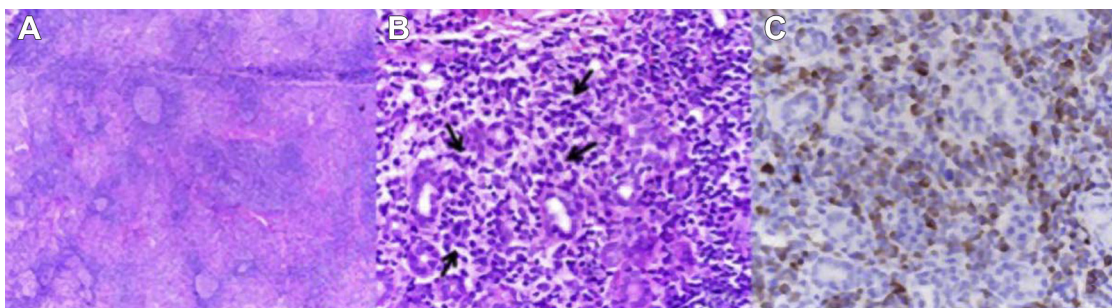


Fig. 3 – H&E 4X. Salivary gland with dense lymphoplasmacytic infiltration and reactive lymphoid follicle formation (A). H&E 40X. Lymphoplasmacytic infiltrate with increased plasma cells, arrows (B). Immunostaining of submandibular gland biopsy showing IgG4+ plasma cells (C).

IgG4+ plasma cell per hpf is recommended (>100 IgG4+/hpf). In addition, tissue IgG4+/IgG+ ratio must be >40% in any circumstance. [9] Serum IgG4 is frequently elevated but can be normal in up to 50% of patients with active IgG4RD. [10] In our case, dense lymphoplasmacytic infiltrate was observed, with 266 IgG4+/hpf count, but other characteristic histologic features were absent. The combination of the patient's clinical findings, serum IgG4 titer, tissue IgG4+/IgG ratio, and imaging studies demonstrates a pattern consistent with IgG4RD. [11]

Radiological studies often reveal nonspecific findings such as diffuse organ enlargement, homogeneous contrast enhancement, and lymphadenopathy of 1–3 cm in diameter. [3,12] Although the radiologic findings associated with IgG4-related disease may be nonspecific, it is important for radiologists to be familiar with this disease process to help raise suspicion for this difficult to diagnose disease. In the head and neck, the most common sites of involvement include the salivary glands, lacrimal glands, perineural involvement, lymph nodes, and the pituitary gland. Radiologists assume an important role by initially suggesting the disease, followed by further diagnostic investigation. [6] Fluorodeoxyglucose positron-emission tomography/computed tomography (PET/CT) is currently used to investigate subclinical and multiorgan disease for specific cases of IgG4RD, [13] in a similar process that allows IgG4-related pancreatitis to be diagnosed without tissue biopsy [14].

Treatment is still controversial, but corticosteroids are accepted as first-line therapy for IgG4RD, including pediatric population [7], with response rates generally beginning after 2 weeks of treatment. Recurrent salivary swelling has been reported at a rate of 24% after complete clinical remission [6] and tends to be higher among younger patients [15]. Longstanding periods without treatment may lead to irreversible fibrotic damage [3,11]. In addition, IgG4RD has been associated with various types of malignancy, particularly in individuals with high-serum IgG4 titer, regardless of treatment with corticosteroids. [16]

Conclusion

IgG4RD is a systemic disease that can affect many different organs. Although the imaging features of IgG4RD can be nonspecific, radiologists play an important role in suggesting this disease, as patients respond well to corticosteroid therapy. Inclusion of IgG4RD in the differential of pediatric patients with bilateral homogenous salivary gland involvement can help avoid delayed diagnosis as well as avoid unnecessary procedures.

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