Case Report

Immunoglobulin G4-related chronic sclerosing sialadenitis: An emerging entity

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Abstract

Chronic sclerosing sialadenitis is associated with the immunoglobulin G4 (IgG4)-related disease (RD) spectrum. IgG4-RD is a newly recognized immunomediated fibroinflammatory condition characterized by several features: a tendency to form tumefactive lesions at multiple sites, lymphoplasmacytic infiltrate, fibrosis and obliterative phlebitis. Often but not always, the serum IgG4 concentrations are also elevated. Immunohistochemistry for IgG4 is helpful to clinch the diagnosis. Here, we describe a case of 65-year-old male with IgG4-related chronic sclerosing sialadenitis of the s ubmandibular gland. We have discussed the histopathological criteria to diagnose this entity.

Keywords: Chronic sclerosing sialadenitis, immunoglobulin G4-related disease, Küttner's tumor, Mikulicz's disease

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INTRODUCTION

Immunoglobulin G4-related diseases (IgG4-RD) are a recently emerged entity. They are defined as a systemic fibroinflammatory disorder of unknown origin which can affect virtually every organ of the body. They have a predilection for Japanese and Chinese population.[1] Chronic sclerosing sialadenitis is a part of the IgG4-RD spectrum.[2] It presents as a painless mass lesion in any of the major or minor salivary glands and often mimics malignancy. Küttner's tumor is a fibroinflammatory disorder which classically affects the submandibular salivary gland.[3]

We report one such case in a 65-year-old male patient.

CASE REPORT

A 65-year-old male presented with a complaint of swelling in the right submandibular region for 2 months. It was painless and had gradually increased in size. There was no associated history of fever, dryness of mouth or eyes and weight loss. Fine-needle aspiration cytology (FNAC) was done outside and was nonconclusive.

We received an excised specimen of the right submandibular gland. On gross, it measured 5.5 cm × 5 cm × 3 cm. Cut section showed a grayish white, firm, noncapsulated nodule measuring 3.5 cm × 2.5 cm × 2 cm [Figure 1]. Similar small gray white patches were also seen in the rest of the normal appearing gland.

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Sections from the nodular area on microscopy showed marked atrophy of the glandular tissue, extensive lymphoplasmacytic infiltrate with the presence of lymphoid follicles and large areas of fibrosis [Figure 2a]. Few areas with storiform pattern of fibrosis were seen [Figure 2b]. Obliterative phlebitis was noted with few eosinophils in the vessel wall along with lymphocytes, plasma cells and fibrosis [Figure 2c]. Section from the relatively normal-appearing salivary gland showed some preserved glandular parenchyma along with few lymphoid follicles. Immunohistochemistry for IgG4 was done which came out to be positive in >150 plasma cells per high-power field [Figure 2d].

DISCUSSION

In 1892, Dr. Johann von Mikulicz described a patient with lacrimal, parotid and submandibular gland enlargement with fibrosis and named it "Mikulicz's disease."[4] In 1896, Dr. Hermann Küttner described a patient with a tumor-like lesion exclusively of the submandibular gland with very severe fibrous sclerotic tissue and named it "Küttner's tumor."[3] Both these lesions have similar features on histopathology. Many workers in recent studies have found these lesions to contain increased IgG4-positive plasma cells.[2,5,6] Therefore, IgG4-related chronic sclerosing sialadenitis is said to encompass many previously diagnosed cases of Mikulicz's disease and Küttner's tumor.

IgG4-RD forms a distinct, novel, clinically independent disease category which is not very rare and is attracting clinical attention as a new entity. Many questions and problems still remain to be elucidated, including its pathogenesis and the role of IgG4. The various organs with the corresponding diseases in which IgG4-positive plasma cell infiltration has been observed are listed in Table 1.[7]

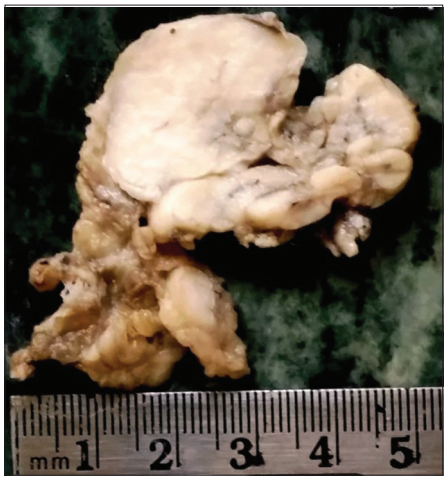

Figure 1: Cut section of the excised right submandibular gland showing a grayish white, firm, noncapsulated nodule along with similar small nodular areas in the rest of the normal-appearing gland

The histopathologic diagnostic criteria for IgG4-positive Mikulicz's disease/IgG4-positive chronic sclerosing sialadenitis approved by Japanese Society for SjÖgren's Syndrome (2008) were lymphocyte and IgG4 + plasma cell infiltration (IgG4 + plasma cells/IgG + plasma cells ratio >50%) with typical tissue fibrosis.[8]

Recently, according to the Consensus Statement on the Pathology (2012) of IgG4-RD, three histopathological features necessary for their diagnosis (other than in lymph nodes) are dense lymphoplasmacytic infiltrate (often with mild eosinophilia), storiform pattern of fibrosis and obliterative phlebitis. If only 1 or 2 histopathological features are present, then for diagnosis, the tissue IgG4 counts are considered which vary for different organs, for example, in pancreas, liver and kidney biopsy; it is >10/hpf, while for salivary gland, lacrimal gland and lymph node, the IgG4 count should be >100/hpf.[9]

In our study, >150 IgG4-positive plasma cells per high-power field were seen along with storiform pattern of fibrosis and obliterative phlebitis [Figure 2].

Close differential diagnoses of IgG4-related chronic sclerosing sialadenitis include chronic sialadenitis and SjÖgren's syndrome. Chronic sialadenitis does not have storiform pattern of fibrosis or obliterative phlebitis. SjÖgren's syndrome is associated with xerostomia, xerophthalmia and glandular destruction. Furthermore, it is characterised

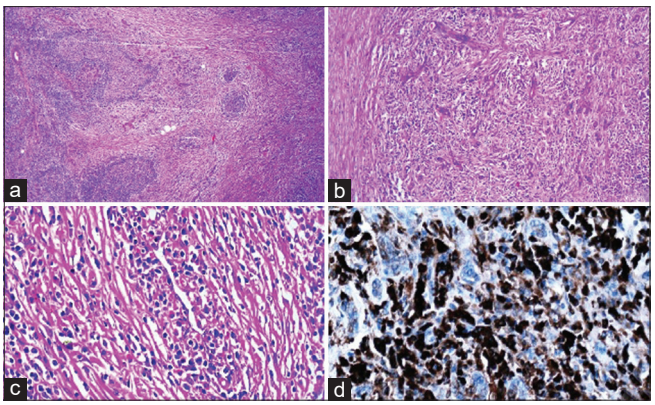

Figure 2: Photomicrograph from nodular area. (a) Marked glandular atrophy, extensive lymphoplasmacytic infiltrate with the presence of lymphoid follicles and large areas of fibrosis (H & E, ×40). (b) An area showing storiform pattern of fibrosis (H & E, ×100). (c) Obliterative phlebitis with lymphocytes, plasma cells, few eosinophils and fibrosis in the vessel wall (H & E, ×400). (d) Immunoglobulin G4 immunohistochemistry showing cytoplasmic positivity in more than 150 plasma cells/hpf

Table 1: List of organs affected with immunoglobulin G4-related diseases along with their clinicopathological features[7]

Body site	Clinicopathologic features
Pancreas	Lymphoplasmacytic sclerosing pancreatitis (type 1 AIP) and idiopathic duct centric chronic pancreatitis (type 2 AIP)
Bile duct	Sclerosing cholangitis
Gallbladder	Acalculous sclerosing cholecystitis
Liver	Sclerosing cholangitis involving intrahepatic ducts, inflammatory pseudotumor, portal inflammation with or without interface hepatitis, portal sclerosis, large bile duct obstruction, lobular hepatitis and canalicular cholestasis
Salivary glands	Chronic sclerosing sialadenitis (Küttner's tumor) and Mikulicz's disease
Lacrimal glands and orbit	Chronic sclerosing dacryoadenitis and inflammatory pseudotumor
Retroperitoneum and mesentery	Retroperitoneal fibrosis and sclerosing mesenteritis
Cardiovascular/aorta	Inflammatory abdominal aortic aneurysm
Mediastinum	Sclerosing mediastinitis
Kidney and ureter	Tubulointerstitial nephritis, membranous glomerulopathy and inflammatory pseudotumor
Thyroid	Hypothyroidism and Riedel's thyroiditis
Breast	Sclerosing mastitis
Lung	Inflammatory pseudotumor and interstitial pneumonia
Central nervous system	Hypophysitis and sclerosing pachymeningitis
Prostate	Prostatitis
Lymph node	Lymphadenopathy with Castleman disease-like features, follicular hyperplasia, interfollicular expansion by plasma cells and immunoblasts

AIP: Autoimmune pancreatitis

by increased antinuclear antibodies such as anti-Sjögren's-syndrome-related antigen A (anti-SSA) and is also said to be unresponsive to steroids.[10]

FNAC of the IgG4 lesions is usually nonconclusive.[11] In our case also, it was noncontributory. Sometimes, the complete histological picture may not be represented on needle biopsy samples also. Therefore, clinicians must consider IgG4-RD as a differential diagnosis in cases of any mass lesion.

Serum IgG4 levels are elevated in majority of the cases of IgG4-RD. Umehara *et al.* have mentioned about elevated serum IgG4 levels >135 mg/dl to be considered as one of the diagnostic clinical criteria.[8] However, these levels are also elevated in vasculitis, sarcoidosis, primary sclerosing cholangitis, liver cirrhosis and allergies.[12] In our case, serum IgG4 level was not done.

Around 30% of the patients undergo spontaneous remissions. Similar numbers of patients may also have relapse. Rapid induction of therapy using glucocorticoids is the first line of treatment. Significant improvement in the gland size and function has been observed, although few cases may be refractory to treatment.[13] Rarely, these lesions have been associated with the development of marginal zone B-cell lymphoma and salivary duct carcinoma.[14,15] A case of adenoid cystic carcinoma arising in a background of this disease has also been reported; however, more studies are needed to establish a definitive risk for such complications.[16]

We present this case to highlight the histopathological features of this considerably new entity as its treatment protocol, disease progression and prognosis differ from that of chronic sialadenitis and SjÖgren's syndrome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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