INTRODUCTION

The parotid gland is composed of many different tissue types, including secretory units, intraparenchymal lymphoid tissue, and myoepithelial cells. Abnormalities of any one of these tissue types may present as a parotid mass. As such the differential diagnosis of a parotid mass is lengthy including inflammatory, neoplastic, autoimmune, traumatic, infectious, or congenital lesions (Kuan 2016). A rare immune-mediated cause of a parotid mass is immunoglobulin G4-related disease (IgG4-RD). In 1995 Yoshida and colleagues described and coined the term autoimmune pancreatitis (AIP) (Deltefsen 2013). In 2003 Kamisawa described the presence of other autoimmune diseases in a large percentage of AIP patients; sclerosing cholangitis, retroperitoneal fibrosis, rheumatoid arthritis, and Sjögren’s syndrome. From this, Kamisawa concluded that AIP was a systemic autoimmune disease and coined it IgG4-related systemic disease (Kamisawa 2003). Since then, the number of conditions comprising IgG4-RD has increased greatly. The extensive extrapancreatic manifestations of IgG4-RD are shown in TABLE 1.

The salivary glands are the second most common site of extrapancreatic organ involvement in IgG4-related AIP. IgG4-related sialadenitis sometimes involves the whole submandibular or parotid gland but more often is found as circumscribed lesions occupying the majority of the glandular parenchyma. Obliterative phlebitis is seen in 50% of cases. There is typically a robust infiltrate of IgG4-positive cells as well as a T helper (Th) ratio of at least 0.4. Historically IgG4-related sialadenitis dates back to the first description of Mikulicz’s disease in 1892 and later Kuttner tumor in 1972. Today, we look to Stone’s 2012 consensus statement to properly categorize this disease phenomenon (Stone 2012; Takano 2016).

Okazaki’s unifying hypothesis states that in early stages of IgG4-RD, autoantigens may decrease the suppressive effect of regulatory T cells. This is followed by a Th1-type immune response and increase in proinflammatory cytokines interferon-gamma, interleukin-2, and TNF-alpha. Th2-type immune responses then upregulate IgG, IgG4, and autoantibodies. Ultimately, upregulation of TGF beta contributes to the deposition of extracellular matrix and fibrogenesis seen in later stage IgG4-RD (Okazaki 2011).

CASE PRESENTATION

44-year-old male with a history of chronic bronchitis, eosinophilic esophagitis and a 17-year history of intermittent right parotid swelling, variable in size, non-painful. Notably the mass wound regress when the patient was treated with systemic steroids for bouts of bronchitis. Exam revealed an intact facial nerve with 3 x 3 cm right parotid mass. MRI showed a well-circumscribed homogeneously enhancing mass with low T1 and intermediate T2 signal involving the superficial right parotid gland. FNA showed polymorphous population of lymphocytic cells. Given indeterminate cytology and concerning features, patient underwent a right superficial parotidectomy. Given indeterminate cytology and concerning features, patient underwent a right superficial parotidectomy.

The patient’s symptoms resolved. Given the lack of symptoms or diffuse adenopathy, treatment with immunosuppression was forgone.

TABLE 1. Extrapancreatic Manifestations of IgG4-RD

<table>
<thead>
<tr>
<th>Metal inflammatory pseudotumor</th>
<th>Chronic sialadenitis</th>
<th>Immunofluorescent sialadenitis</th>
<th>Immunofluorescent cholangitis</th>
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</thead>
<tbody>
<tr>
<td>Idiopathic sialadenitis</td>
<td>Solid-nodular</td>
<td>Pelagocytolytic</td>
<td>Scierosing cholangitis</td>
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<td>Sclerosis cholangitis</td>
<td>Inflammatory adenopathy</td>
<td>Periarterialfibrosis</td>
<td>Retropertione fibrosis</td>
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<td>Inflammatory pseudotumor</td>
<td>Liver, kidneys</td>
<td>IgG4-related lymphadenopathy</td>
<td>IgG4-related lymphadenopathy</td>
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<td>Hypophysitis</td>
<td>Idiopathic hypotropic</td>
<td>Pachymeningitis</td>
<td>Scierosing dacytaenoditis</td>
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<td>Bronchial and interstitial</td>
<td>Lymphoplastic sialadenitis</td>
<td>Masses</td>
<td>Constrictive paracoiditis</td>
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<td>Pulmonaryis</td>
<td>Gastrointestinal reactive</td>
<td>Nodular fibrous tumor</td>
<td>Scierosing angioiodal nodular transformation (SANT) of spleen</td>
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<td>Autoimmune hepatitis</td>
<td>Adenopathy</td>
<td>Injury</td>
<td>Sclerosing mesenteritis</td>
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<td>Scierosing mesenteritis</td>
<td>Tubulointestinal nephritiss (TIN)</td>
<td>Sclerosing mesenteritis</td>
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TABLE 2. Labs / Serologies. Notably the patient has a normal total IgG, elevated IgG1 level, and a predominance of IgG4, typically the least common IgG subclass. Despite this the ratio of serum IgG4:Total IgG is 0.14.

LAB VALUE RANGE
IgE 114 IU/mL (<1000)
IgG1 331 mg/dL (382 – 929)
IgG2 355 mg/dL (241-700)
IgG3 78 mg/dL (22-178)
IgA 103.1 mg/dL (4-86)
Total IgG 715 mg/dL (694-1618)

FIGURE 1: MRI Neck with Contrast. Left to Right: Ax TSE T1; Ax TSE T1 FS Post; Cor T1 TSE FS Post. Right parotid mass with right cervical chain lymphadenopathy. Ovoid 2.5 x 3.1 x 3.7 cm well-circumscribed homogeneously enhancing mass with low T1 and intermediate T2 signal within the superficial parotid lobe. Small internal flow voids are identified on the coronal T2- weighted images suggesting internal vascularity. The presence of adjacent abnormal appearing lymph nodes and possible extraparotid origin is suggestive of a generalized process involving the lymph nodes such as metastatic carcinoma or lymphoma.

FIGURE 2: H&E Stain of excised intraparotid lymph node. (A) H&E, 40x, lymph nodes shows immunohistochemistry stains for IgG and IgG4 demonstrating a IgG4/IgG ratio > 40%. (B) A different region between lymphoid follicles again demonstrating a IgG4/IgG ratio > 40%.

FIGURE 3: Immunostaining of intraparotid lymph node for IgG and IgG4. (A) Lymphoid follicle with immunohistochemical stains for IgG and IgG4 demonstrating a IgG4/IgG ratio > 40%. (B) A different region between lymphoid follicles again demonstrating a IgG4/IgG ratio > 40%.

DISCUSSION

In contrast to other autoimmune diseases, such as Sjogren’s and primary biliary cirrhosis, IgG4-RD exhibits a male predominance of around 2.8:1 and is seen in patients typically in their 5th-6th decades of life. Presentation is typically subacute to chronic in patients who are not constitutionally ill.

Histopathology is the cornerstone for the diagnosis of IgG-RD. Critical histopathologic features include: dense lymphoplasmacytic infiltrate, storiform fibrosis pattern, and obliterator phlebitis. Other suggestive features include plitibets without luminal obliteration and increased numbers of eosinophils (Deshpande 2012). Up to 40% of patients with IgG-RD may have concomitant allergic disease such as asthma or chronic bronchitis with serologies demonstrating peripheral eosinophilia.

Diagnosis can often be made on base serum IgG4 cut-off of 135mg/dL, however there does exist serologically negative patients with IgG4-RD supported by strong histologic evidence of the disease (30% of patients) (Deltefsen 2013). As such elevated concentrations of IgG4 in tissue and serum help in the diagnosis of IgG-RD, but neither are specific or sufficient. Reliance upon elevated serum levels of IgG4 has led to the frequent misdiagnosis of IgG-RD. Furthermore, IgG-RD may be more difficult to diagnose in the later phases of this chronic disease. Namely, late phase disease is characterized by fewer plasma cells and greater degrees of fibrosis.

IgG4-RD may lead to devastating organ dysfunction and failure. As such, when vital organs are involved, aggressive treatment is warranted. Mainstay is systemic glucocorticoids; prednisolone 0.6 mg/kg/day for 2 – 4 weeks; taper over 3 – 6 months to 5 mg/day. Then continue maintenance doses of 2.5 – 5.0 mg/day for up to 3 years. Steroid-sparing azathioprine, mycophenolate mofetil, and methotrexate may also be used. Quick systemic response and serum IgG4 level resolution has also been seen with rituximab B-cell depletion.

CONCLUSIONS

Critical to always rule out malignancy. Can see elevated numbers of IgG4-positive cells and serum IgG4 levels in malignant neoplasms. However, IgG4/IgG ratios above 0.4 are typically not seen. The greatest histopathological mimickers of IgG-RD are lymphomas. Quality and clonality of immune cell infiltrate can help to distinguish them.

IgG-RD may present with isolated organ involvement or as a multi-organ disease. Multi-organ involvement can evolve metachronously and as such a thorough work-up and long-term follow-up are critical.

REFERENCES