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IgG4-related disease in the head and neck

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Lymphoid infiltrates are relatively common in the ocular adnexa and the salivary glands. They are of a variety of types and include both reactive processes and lymphomas. Within the ocular adnexa in years past, lymphoid proliferations were classified as inflammatory pseudotumor, reactive lymphoid hyperplasia, atypical lymphoid hyperplasia, and lymphoma. With improvements in diagnostic techniques and with advances in lymphoma subclassification, it became clear that many of the dense lymphoid infiltrates, including cases classified as lymphoma and likely some classified as atypical lymphoid hyperplasia, represented low-grade B-cell lymphomas, the most common of which by far were extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) lymphomas. Ocular adnexal inflammatory pseudotumor, reactive lymphoid hyperplasia, and chronic sclerosing sialadenitis were recognized, but the focus in diagnosis had been on avoiding misdiagnosis as a neoplastic process and in planning appropriate therapy. Recently, it has become clear that many cases of these reactive processes fall into the spectrum of immunoglobulin G4 (IgG4)-related disease, offering new insight into the pathogenesis of inflammatory lesions occurring in the ocular adnexa and the salivary glands. The majority of entities previously classified as chronic sclerosing sialadenitis, Mikulicz disease, orbital pseudolymphoma, and eosinophilic angiocentric fibrosis are now considered a part of the IgG4-related disease spectrum. In this review, we discuss the histologic and immunohistochemical features of IgG4-related disease of the head and neck and provide guidance for distinguishing this disease from its many mimics.

Idiopathic orbital inflammatory processes were first described in 1930 by Birch-Hirschfeld in the German literature (reviewed by Plaza et al[1]). These disorders have been called idiopathic orbital inflammation, inflammatory pseudotumor, idiopathic sclerosing inflammation, sclerosing dacryoadenitis,[2] and others. In 1980, Knowles and Jakobiec[3] evaluated a large series of patients with orbital lymphoid infiltrates, both reactive and neoplastic, and subclassified them as pseudolymphoma, atypical lymphoid hyperplasia, plasmacytoma, and malignant lymphoma; the latter were subclassified according to the Rappaport Classification. The pseudolymphoma category included the following: (1) inflammatory pseudotumor, a hypocellular lesion that could involve lacrimal gland or soft tissue, with a mixed infiltrate of small lymphocytes, plasma cells, histiocytes, and scattered lymphoid follicles in a background of fibrosis, and (2) reactive lymphoid hyperplasia, characterized by a cellular proliferation of lymphocytes, plasma cells, histiocytes, and hyperplastic lymphoid follicles, without prominent fibrosis.[3] Although monumental advances have been made in the study of lymphoma, and multiple lymphoma classifications have come and gone since this study was published, the nomenclature of inflammatory processes in the orbit has remained nearly static, and these processes have for the most part remained idiopathic and a diagnosis of exclusion.

The situation regarding lymphoid proliferations in the salivary glands is similar. A wide variety of lymphoid

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proliferations involves the salivary glands, with a spectrum of reactive inflammatory processes to proliferations that may be preneoplastic, to overtly neoplastic lymphomas. They include the simple lymphoepithelial cyst, cystic lymphoid hyperplasia, chronic sclerosing sialadenitis, lymphoepithelial sialadenitis (LESA), mucosa-associated lymphoid tissue (MALT) lymphoma, and other types of lymphoma. The development of cystic lymphoid hyperplasia, which mainly involves the parotid gland, is thought to be related to obstruction of ducts by floridly hyperplastic lymphoid tissue, with cystic dilatation of ducts beyond the obstruction; many, but not all patients with this disorder are HIV+.[4-6] LESA shows a female preponderance. About half of patients with LESA have Sjögren syndrome. LESA mainly, but not exclusively, affects the parotid gland. Neither LESA nor cystic lymphoid hyperplasia belongs to the immunoglobulin G4 (IgG4)-related disease spectrum.

Chronic sclerosing sialadenitis, also known as Küttner tumor, is now widely considered an IgG4-related disease. The lesion that has come to be called "Küttner tumor" was originally described by Küttner in 1896, who reported a "hard swelling" of 1 or both submandibular glands.[7] Over time this scenario has proven to be the usual pattern; Küttner tumor is most common by far in the submandibular gland but can rarely involve the parotid.[7,8] Chronic sclerosing sialadenitis is not a rare disorder, but, until recently, its etiology has been poorly understood. Before its inclusion within the spectrum of IgG4-related disease, a number of other etiologic hypotheses were considered, including abnormal glandular secretions resulting in inspissation, sialolithiasis, and/or infection, resulting in inflammation and fibrosis in the salivary gland parenchyma, possibly with an immunologic or autoimmune component to the inflammation playing a role.[9]

In recent years, chronic sclerosing sialadenitis and sclerosing inflammatory lesions in the orbit were noted to share clinical and pathologic features with autoimmune pancreatitis,[1,7,10] an entity which is the prototype of IgG4-related disease. Further evaluation of orbital and salivary gland lesions in both the Far East and the Western hemisphere confirms that in many cases, they do indeed represent examples of IgG4-related disease with distinctive clinical and pathologic features.

In the end of the 19th century Johann von Mikulicz-Radecki described the case of a 42-year-old man with bilateral painless symmetric enlargement of lacrimal, parotid, and submandibular glands.[11-13] The term Mikulicz disease has been used for patients with this clinical picture, with no known etiology, persisting for at least 3 months. Mikulicz syndrome has been used as a designation for patients with the manifestations of Mikulicz disease, but of known cause, such as Sjögren syndrome or lymphoma. Some have suggested that the patient originally described by Mikulicz-Radecki most likely had IgG4-related disease, but this remains controversial[11] and difficult to resolve given the many years that have elapsed. However, it is now clear that although a variety of disease processes can result in the clinical picture of Mikulicz disease, it does appear that many cases of Mikulicz disease are likely a manifestation of IgG4-related disease.[12,14]

Clinical and pathologic features of IgG4-related disease in the orbit and salivary glands

Despite some differences in inclusion criteria for IgG4-related disease among published studies (see later in the text), an entity with distinctive clinical and pathologic features emerges. The salivary glands and lacrimal glands are among the more common sites for involvement by IgG4-related disease. In a study of 114 cases of IgG4-related disease, 23 patients had involvement of salivary gland (17 cases) and/or lacrimal gland (10 cases) but did not have involvement outside the area of the head and neck. In a group of 35 patients with "systemic" disease, not confined to 1 anatomic area, an additional 22 cases of salivary gland involvement and 4 cases of lacrimal gland involvement were found.[15]

Submandibular and parotid glands

Patients with IgG4-related disease of the salivary gland present with a unilateral or bilateral hard mass that is often clinically suspicious for a salivary gland neoplasm.[10,14] Patients are adults, almost all between the ages of 40 and 80, with a mean or median age of approximately 60 years[7,10,16]; younger patients are rarely affected.[7] Men appear to be affected roughly as often, or perhaps slightly more often, than women.[7,10,16] In almost all cases, the salivary gland affected is the submandibular gland.[7,10,16] Only rare cases affecting the parotid gland are described.[7,17] Rarely, minor salivary glands are affected in conjunction with submandibular involvement.[10] In those cases with bilateral disease, involvement is usually synchronous but may be metachronous.[10] Allergic disorders, including asthma, allergic rhinitis, and atopic dermatitis, are common.[1,2] Peripheral blood eosinophilia, elevated serum immunoglobulin G (IgG), and positive antinuclear antibodies are commonly, although not uniformly, found.[10,15] Most patients have elevated serum IgG4, currently the most robust biomarker for this disease.[1,18,19] However, in up to 40% of cases, the serum IgG4 may not be elevated.

Examination of submandibular glands with chronic sclerosing sialadenitis reveals mass lesions that range from 1.5 to 5 cm, with a median size of approximately 3 cm.[10,16,20] Microscopic examination shows some distortion but overall preservation of the lobular architecture, a dense lymphoplasmacytic infiltrate with numerous hyperplastic lymphoid follicles and fibrosis.[7,10,14,16,20] Low-power evaluation shows a jigsaw puzzle-like appearance, created by expanded cellular fibrous septae that separate the inflamed lobules