Diagnostic approach to lymphoid lesions of major salivary glands

Gary L Ellis

Abstract

Among lesions of the major salivary glands (parotid, submandibular, and sublingual glands), those with a prominent lymphoid component are encountered frequently in the surgical pathology laboratory and range from reactive lesions to benign and malignant neoplasms. A majority of these lymphoid lesions have a co-mingled epithelial component, which also ranges from benign to malignant. As a result, many of these lesions have similar and overlapping histopathologic features, and attention to details, sometimes subtle, is required to accurately distinguish one from another. This review will discuss these lymphoid-epithelial lesions of major salivary glands, with emphasis on features that help in the differential diagnosis. Entities discussed include lymphoepithelial sialadenitis, HIV-associated salivary gland disease, extranodal marginal zone B-cell lymphoma, lymphoepithelial carcinoma, lymphadenoma, sebaceous lymphadenocarcinoma, chronic sclerosing sialadenitis, and Warthin tumour.

Keywords epithelial; lymphoid; neoplasm; reactive; salivary

Introduction

Although epithelial neoplasms of the parotid gland and chronic sialadenitis of the submandibular gland are the most common specimens from the major salivary glands in the surgical pathology laboratory, a surprisingly high portion of specimens have a remarkably prominent lymphoid component. These specimens comprise a range of diseases from reactive to benign and malignant neoplasms, and the histopathologic distinction among them can often be quite subtle. Lymphoepithelial sialadenitis (as occurs in Sjögren syndrome), HIV-associated sialadenitis, extranodal marginal zone B-cell lymphoma, lymphadenoma, and lymphoepithelial carcinoma all have an epithelial component within a dense lymphoid component, yet the prognosis and treatment of these diseases can have marked differences. Warthin tumour, the most common epithelial-lymphoid tumour, has unique histomorphologic and cytomorphologic features that distinguish it from the other lesions. In this paper, the histopathologic features and diagnostic criteria that differentiate these lymphoid-prominent lesions are discussed.

Lymphoepithelial sialadenitis

Lymphoepithelial sialadenitis (LESA), also previously known as benign lymphoepithelial lesion and myoepithelial sialadenitis, is an autoimmune disease affecting the parotid gland and, sometimes, the submandibular gland.[1,2] The lymphocytic infiltrate is the salivary manifestation of acquired *mucosa-associated lymphoid tissue* (MALT).[3] It is a component of Sjögren syndrome, although not all cases of LESA manifest the spectrum of features identifiable as Sjögren syndrome. Sjögren syndrome is a disease complex that includes lacrimal and salivary gland disease with keratoconjunctivitis sicca, xerostomia, and serum autoantibodies like anti-SSA, anti-SSB, rheumatoid factor, and salivary duct antibodies.[4] Sometimes, it is associated with other autoimmune diseases, such as rheumatoid arthritis, and referred to as *secondary Sjögren syndrome*. Women are affected more than men, and it is the most frequent in the fourth to seventh decades of life.[1] Both parotid glands are usually affected, but one side is often more severely affected. Recurring, and often progressive, swelling and, sometimes, discomfort or pain are signs and symptoms.

The hallmark histopathologic features are intense lymphocytic infiltration of the parotid gland with parenchymal atrophy and, paradoxically, foci of epithelial proliferation. There is preservation of the glandular lobular architecture. The degree of lymphocytic infiltration is often variable among lobules of gland, but with disease progression, all of the parenchyma becomes affected. Lymphoid germinal centres are often conspicuous, but their number varies from few to many. Scattered foci of residual ducts remain visible among the lymphoid cells, but acinar cells are mostly absent (Figure 1). Among the residual ductal elements are foci of ductal epithelial hyperplasia that are permeated by lymphocytes and referred to as *lymphoepithelial lesions* or *lymphoepithelial complexes*.[3] Within the lymphoepithelial lesions, lumens sometimes persist within the epithelial proliferations, which are irregularly shaped islands of polygonal and spindled cells, often with deposits of intercellular eosinophilic hyaline material (Figure 2).[5] The proliferative epithelium is predominantly ductal basal cells, which lack immunohistochemical markers of myoepithelial differentiation.

While CD3 positive T-cell lymphocytes are predominant in the lymphoid infiltrate, within the lymphoepithelial complexes, CD20 positive B-cells predominate.[5] Many of these intraepithelial B-cell lymphocytes have features of monocytoid B-cells or centrocyte-like cells known as marginal zone B-cells and are larger with more cytoplasm than the surrounding small lymphocytes.[3,5] Within lymph nodes, these cells are post-germinal centre B-cell lymphocytes that are destined to differentiate to plasma cells. As a component of MALT, they are epitheliotropic. Within some of the lymphoepithelial complexes of LESA, the marginal zone B-cells are clonal.

In the context of Sjögren syndrome, minor salivary glands also exhibit lymphocytic infiltrates but typically lack lymphoepithelial lesions. Labial minor salivary gland biopsy is commonly used as a surrogate for parotid gland biopsy for assessment of Sjögren syndrome, where one or more foci of 50 or more lymphocytes per 4 mm^2 of salivary gland tissue is an important supportive factor, among several criteria, for Sjögren syndrome.

Although LESA and Sjögren syndrome are not curable, they are often controllable with anti-inflammatory therapies, such as corticosteroids.[6] Compared to the general population, patients with LESA and Sjögren syndrome have a high risk of

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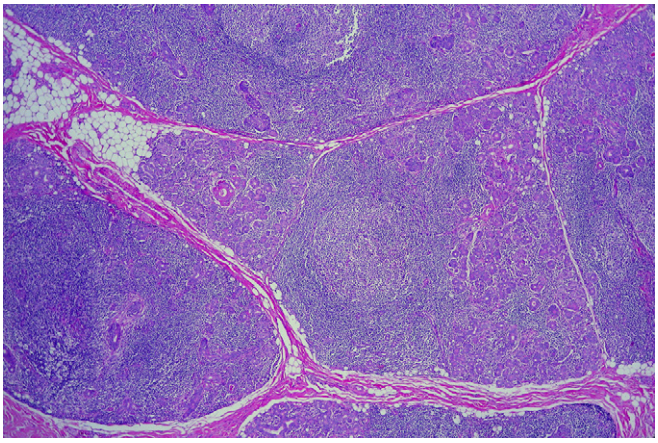

Figure 1 Lymphoepithelial sialadenitis. The lobular architecture of the parotid gland is intact. There is a dense lymphoid infiltrate with foci of germinal centres. Glandular acini are mostly absent, but there are a variable number of residual ducts. Foci of epithelial hyperplasia are evident in the upper lobule. (H&E-stain, original magnification ×20).

development of lymphoma. The lymphomas are usually extranodal marginal zone B-cell lymphomas (MZBCLs).[3]

HIV-associated salivary gland disease

HIV-associated salivary gland disease (HSGD) is an uncommon manifestation of infection with the human immunodeficiency virus (HIV).[7] HIV infection is an aetiology for acquired immunodeficiency syndrome (AIDS). Since the introduction of antiviral therapies for HIV infection, in parts of the world where HIV-infected patients have good access to anti-viral therapies, the incidence of HSGD and AIDS has significantly decreased.[7] Transmission of HIV from person to person has been associated with homosexual and heterosexual contact, intravenous drug use, transfusion, and congenital transmission from infected mother to child. Thus, men and women and adults and children can be affected. HSGD can occur without the development of AIDS and is sometimes the first manifestation of HIV infection. Bilateral parotid gland involvement, and sometimes submandibular gland involvement, is typical and commonly accompanied by cervical lymphadenopathy.

Similar to LESA, dense lymphoid infiltration of the parotid gland with acinar destruction and formation of lymphoepithelial complexes are characteristic of HSGD. An additional characteristic feature is the development of cystic lymphoepithelial lesions, i.e. lymphoepithelial cysts (Figure 3). Computed tomographic scans often can identify these multiple cystic lesions. However, the presence or absence of lymphoepithelial cysts does not reliably distinguish HSGD from LESA. Parotid gland disease resembles both persistent generalized lymphadenopathy and lymphoepithelial sialadenitis. This has also been called salivary diffuse infiltrative lymphocytosis syndrome.[1,7] Within the lymphoid infiltrate, typically, there are numerous lymphoid follicles. Unlike LESA, many of these lymphoid follicles are large and irregularly shaped with attenuated mantles and follicle lysis, and tingible body-macrophages and mitotic figures are numerous in the follicles (Figure 4). Also unlike LESA, the inter-follicular lymphoid tissue contains many histiocytes, clusters of large monomorphic, pale round cells, neutrophils, and plasma cells (Figure 5). In the lymphoepithelial lesions and cysts, the majority of intraepithelial lymphocytes are CD20+ centrocyte-like B-cells, as in LESA, while most inter-follicular lymphocytes are CD8+ T-cells.[8]

Immunostaining for the p24 core antigen of HIV is positive in follicular dendritic cells and inter-follicular macrophages and is useful for the diagnosis of HSGD. Clinical testing for HIV infection should be performed to confirm a diagnosis of HIV-associated salivary gland disease.

Regression of parotid gland swelling after initiation of antiviral therapy has been reported.[9]

Marginal zone B-cell lymphoma

Nodal lymphoid tissue occurs both within and peripheral to the parotid gland. As such, these parotid lymph nodes are sometimes involved by lymphoma, similar to the cervical lymph nodes. Follicular lymphoma is the most common type of lymphoma of the parotid lymph nodes, which can expand to involve the

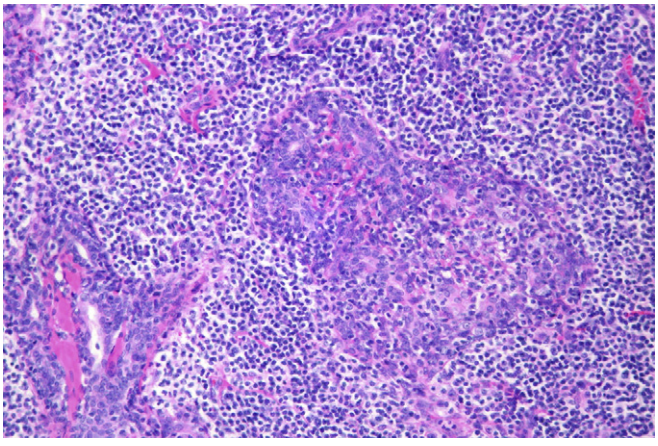

Figure 2 Lymphoepithelial sialadenitis. Two foci of epithelial proliferation are surrounded and permeated by the lymphocytic infiltrate. In the lower left focus, a glandular lumen is evident as well as eosinophilic hyaline material. (H&E-stain, original magnification ×400).

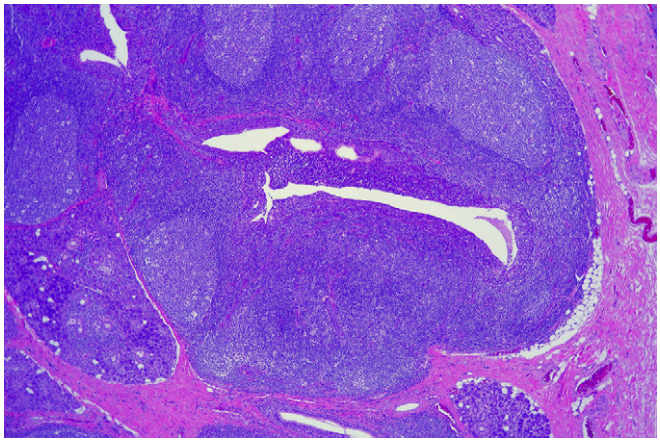

Figure 3 HIV-associated salivary gland disease. There is a variable, dense lymphoid infiltrate of the parotid gland with prominent, large germinal centres. A lymphoepithelial cyst is in the centre. (H&E-stain, original magnification ×20).