Lymphoid lesions of salivary glands: Malignant and Benign

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ABSTRACT

Lesions of salivary glands with a prominent lymphoid component are a heterogeneous group of diseases that include benign reactive lesions and malignant neoplasms. Occasionally, these pathologic entities present difficulties in the clinical and pathological diagnosis and prognosis. Lymphoepithelial sialadenitis, HIV-associated salivary gland disease, chronic sclerosing sialadenitis, Warthin tumor, and extranodal marginal zone B-cell lymphoma are examples of this pathology that are sometimes problematic to differentiate from one another. In this paper the author reviewed the main clinical, pathological and prognostic features of these lesions.

Key words: *Lymphoepithelial sialadenitis, HIV-associated salivary gland disease, chronic sclerosing sialadenitis, Warthin tumor, extranodal marginal zone B-cell lymphoma.*

INTRODUCTION

Lymphocytic infiltrates of the major salivary glands are involved in a spectrum of diseases that range from reactive to benign and malignant neoplasms. In many cases, the lymphocytic infiltrate is a minor inflammatory component that is easily distinguished from the primary disease processes. In some cases, however, the lymphocytic infiltrate is a major component of the disease, and histopathologic features that distinguish reactive and benign lesions from malignant lesions are often subtle. Lymphoepithelial sialadenitis (as occurs in Sjögren syndrome), HIV-associated sialadenitis, and extranodal marginal zone B-cell lymphoma are good examples of diagnoses that are often problematic to differentiate from one another. In this paper, benign and malignant diseases of salivary gland with a prominent lymphocytic component will be discussed with an emphasis on their distinguishing histopathologic featurers and differential diagnoses.

MARGINAL ZONE B-CELL LYMPHOMA

Clinical features. Lymphomas are malignant neoplastic proliferations of lymphocytes. When major salivary glands are involved, they are commonly the first clinical manifestation of disease, and disease is often confined to the salivary glands. Because normal parotid glands contain intra-parenchymal nodal tissue, some parotid lymphomas have a nodal origin, but most do not. Salivary gland involvement by Hodgkin lymphoma is rare and probably always secondary to nodal disease outside of the salivary glands.(1)

Lymphomas are a significant proportion of malignancies of the major salivary glands, accounting for 1.7 to 7.7 percent of tumors.(1) Use of flow cytometry, immunohistochemistry, and other molecular studies has most likely increased the frequency of diagnosis of lymphoma.

Patients with autoimmune disease, particularly Sjögren syndrome, have a markedly increased risk of developing lymphoma, which may be 44 times greater than in the general population.(1) However, most patients with salivary lymphomas do not have Sjögren syndrome.(2) Viral DNA in lymphomatous tissue or increased antibody titers against virus have been detected in some patients.(3)

Females are affected more than males, especially when there is preceding autoimmune disease, as is the case with marginal zone B-cell lymphomas. Disease in children is rare, and patients average 63 years of age. Patients often have diffuse glandular enlargement, which is sometimes bilateral.(1)

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Pathologic features. Most salivary lymphomas are non-Hodgkin, B-cell lymphomas, and T-cell lymphomas are rare.(4) Many different types of lymphoma occur, but the majority is extranodal marginal zone B-cell lymphoma. Follicular and diffuse large B-cell lymphomas comprise most of the others.(1)

Proliferating lymphocytes alter the normal lobular salivary gland architecture, replace acini and ducts, surround nerves, and infiltrate into fat and interlobular and periglandular connective tissues. Marginal zone B-cell lymphomas are composed of small lymphocytes that proliferate as multiple foci or large confluent sheets. The neoplastic cells are post-germinal center B-cell lymphocytes, which in their normal, non-neoplastic state are destined to differentiate to plasma cells. These neoplastic lymphocytes are slightly larger than normal small lymphocytes and have a centrocyte-like or monocytoid appearance. The latter have pale-stained cytoplasm, which makes them conspicuous in histologic sections. Most, if not all, marginal zone B-cell lymphomas arise within pre-existing lymphoepithelial sialadenitis, which is the histopathologic presentation of autoimmune sialadenitis and acquired mucosal associated lymphoid tissue (MALT). Most of the salivary parenchyma is destroyed, but some hyperplastic ductal epithelium persists and is permeated by neoplastic lymphocytes, so called lymphoepithelial lesions. An emerging MZBCL is recognized by foci of expansion of marginal zone B-cells around lymphoepithelial lesions. Typically associated with the neoplastic lymphocytic proliferation is a non-neoplastic lymphoid infiltrate of T-cells, B-cells, plasma cells, reactive germinal centers, and scattered centroblasts or immunoblasts.

The neoplastic marginal zone lymphocytes are immunoreactive for CD20 and CD79a and non-reactive for CD3, UCHL-1, and cyclin D1. They are usually negative for CD5, CD10, and CD23, but frequently express CD43. Most cases express monotypic surface immunoglobulin.(5) The epithelial component of the lymphoepithelial lesions is reactive for cytokeratin.

Gene translocations t(11;18)(q21;q21) and t(1;14)(p22;q32) are frequent in gastric and pulmonary marginal zone lymphomas but rare in those of salivary glands. Translocation t(14;18)(q21;q32) of the MLT/MALT1 gene and immunoglobulin heavy chain locus is relatively frequent in tumors of the parotid.(2,6)

Prognosis. Salivary MZBCL lymphoma is rather indolent and usually remains localized. Some patients are cured with local therapy, and spontaneous regression has been reported.(1,7) Transformation of low-grade marginal zone lymphomas to higher grade, diffuse large B-cell lymphomas sometimes occurs.

Other types of lymphomas that occur in the salivary glands have a prognosis similar to nodal lymphomas.

Differential Diagnosis. The two principal considerations in the differential diagnosis are lymphoepithelial sialadenitis and HIV-associated sialadenitis (see below). The lymphocytic infiltrate in chronic sclerosing sialadenitis tends not to alter the glandular lobular architecture or surrounding tissue. Immunostaining for MT-2, bcl-2, and CD10 helps distinguish follicular lymphoma.

LYMPHOEPITHELIAL SIALADENITIS

Clinical features. Lymphoepithelial sialadenitis is a benign lymphocytic infiltrate of salivary gland with parenchymal atrophy and foci of ductal hyperplasia with lymphocytic epitheliotropism. The lymphocytic infiltrate is the salivary manifestation of mucosa-associated lymphoid tissue (MALT), which in the salivary glands is acquired MALT. It is an autoimmune lesion and a component of Sjögren syndrome. Sjögren syndrome is an autoimmune disease complex that includes lacrimal and salivary gland disease, keratoconjunctivitis sicca, xerostomia, and serum autoantibodies like anti-SSA, anti-SSB, rheumatoid factor, and salivary duct antibodies. Sjögren syndrome is sometimes associated with other autoimmune diseases and called secondary Sjögren syndrome. It affects women 3:1 over men. It occurs most frequently in the fourth to seventh decades of life and affects parotid glands in about 90% of cases.(1)

Bilateral disease is typical, although one gland may be more severely affected. Patients experience recurring and often progressive swelling and sometimes experience discomfort or pain.

*Pathologic feature*s. Lymphocytic infiltration, parenchymal atrophy, and foci of epithelial proliferation characterize lymphoepithelial sialadenitis. The lobular architecture of the gland is usually preserved. In the early stages, the extent of lymphocytic infiltrate varies among lobules of gland, but in late stage disease, nearly all of the parenchyma is infiltrated. The number of lymphoid germinal centers varies from few to numerous. Multiple foci of ductal epithelial hyperplasia are permeated by lymphocytes, lymphoepithelial lesions. Within the lymphoepithelial lesions, lumens are sometimes evident, but most are irregularly shaped islands of polygonal and spindled cells, often with deposits of intercellular eosinophilic hyalin material. The hyperplastic epithelium is predominantly ductal basal cells that lack immunohistochemical markers specific to myoepithelium.

The lymphoid infiltrate has a predominance of T-cells, but within the foci of epithelial proliferation, lymphocytes have features of monocytoid B-cells or centrocyte-like cells, i.e. marginal zone B-cells. In some cases, some foci of intra-epithelial B-cell infiltration are clonal;(8) however, in the absence of expansion of these B-cell clones, it is controversial whether they represent the very earliest manifestation of lymphoma.

In Sjögren syndrome, minor salivary glands manifest chronic sialadenitis but typically lack lymphoepithelial lesions. Labial minor salivary gland biopsy is commonly used, in conjunction with other clinical and laboratory parameters, for assessment of Sjögren syndrome (Table 1).(9) One or more foci of 50 or more lymphocytes per 4mm2 of salivary gland tissue are supportive of Sjögren syndrome.

The majority of lymphocytes are reactive with T-cell markers while the lymphocytes in and around the lymphoepithelial lesions are mostly reactive with B-cell markers. Foci of epithelial hyperplasia are reactive for cytokeratin but are unreactive for myoepithelial specific markers.

Table 1. American-European classification criteria for Sjögren syndrome

Evaluation Factors:
I. Ocular symptoms: at least one of: 1. Daily dry eyes for more than 3 months 2. Sensation of sand or gravel in eyes 3. Use of tear substitutes more than 3 times a day
II. Oral symptoms: at least one of: 1. Dry mouth for more than 3 months 2. Recurrent or persistent swelling of salivary glands 3. Liquids needed to aid swallowing dry food
III. Ocular signs: at least one of: 1. Schirmer's I test, without anesthesia, ≤ 5 mm in 5 minutes 2. Positive vital dye staining
IV. Labial salivary gland biopsy: focus score§ ≥ 1
V. Salivary gland involvement: at least one of: 1. Unstimulated whole salivary flow ≤ 1.5 ml in 15 minutes 2. Parotid sialography with diffuse sialectasias without obstruction of major ducts 3. Salivary scintigraph with delayed uptake, reduced concentration and/or delayed excretion of tracer
VI. Autoantibodies to Ro(SSA) or La(SSB) in serum Classification: Primary SS a. Any 4 of 6 positive evaluation factors, as long as IV or VI is positive b. Any 3 of positive evaluation factors III, IV, V, and VI Secondary SS Positive evaluation factor I or II plus any 2 of positive factors III, IV, and V Exclusions: Radiation to head and neck Hepatitis C infection Acquired immunodeficiency syndrome Lymphoma Sarcoidosis Graft versus host disease Use of anticholinergic drugs

§A focus is an aggregate of 50 or more lymphocytes in the salivary gland; the focus score is the number of foci per 4 mm2 of salivary gland tissue.

Prognosis. Lymphoepithelial sialadenitis and Sjögren syndrome are not curable but are often controllable with anti-inflammatory therapies, such as corticosteroids.(10) These patients have a much higher risk of development of lymphoma, and most, if not all, salivary extranodal MZB-CLs are preceded by lymphoepithelial sialadenitis.

Differential Diagnosis. Extranodal MZBCL is the principal differential diagnosis. In the earliest stage of transition to lymphoma, distinction is difficult and diagnostic features are not well defined, but expansion of clonal monocytoid or centrocyte-like B-cells around lymphoepithelial complexes is considered diagnostic. In more advanced disease, the areas of marginal zone B-cell expansion become confluent. The foci of epithelial hyperplasia persist. Distinction from lymphoepithelial sialadenitis (LESA) is based on the number and distribution of marginal zone and monocytoid B cells. In lymphoma, they are located outside, as well as within, the lymphoepithelial lesions, as surrounding halos and anastomosing strands that often interconnect several different lymphoepithelial lesions. Sometimes follicles are extensively infiltrated by marginal zone B cells. Furthermore, unlike LESA, there are often sheets of plasma cells with or without Dutcher bodies.(2)

The histopathologic features of HIV-associated salivary gland disease are also remarkably similar to LESA (see below).

HIV-ASSOCIATED SALIVARY GLAND DISEASE

HIV-associated salivary gland disease (HSGD) is a lymphoid hyperplasia in the parotid, and sometimes submandibular, glands with lymphoepithelial cysts and lymphoepithelial lesions in HIV+ patients. This has also been called salivary diffuse infiltrative lymphocytosis syndrome.(1,11)

Clinical features. The incidence of HIV-associated salivary gland disease is 3 to 10% among HIV infected patients, but the incidence may be influenced by the availability of anti-viral therapy.(11) Children and adults and males and females are affected. Patients have been intravenous drug users, homosexual men, heterosexual women and men, transfusion recipients, and congenitally infected. Salivary gland involvement in HIV+ patients may be related to viral load.

Salivary gland disease usually develops before AIDS, and is sometimes the first manifestation of HIV infection.(12) It is usually bilateral and accompanied by cervical lymphadenopathy. Computed tomographic scans often identify multiple parotid cysts.

Pathologic features. Parotid gland disease resembles both persistent generalized lymphadenopathy and lymphoepithelial sialadenitis. Florid lymphoid follicular hyperplasia replaces normal parotid parenchyma. Many lymphoid follicles are large and irregularly shaped with attenuated mantles and follicle lysis and contain numerous tingible body-macrophages and mitotic figures. The extra-follicular tissue contains many histiocytes, clusters of large monomorphic, pale round cells, neutrophils, and plasma cells. Lymphoepithelial cysts and lymphoepithelial lesions (see Lymphoepithelial Sialadenitis) are usually numerous.

The majority of intraepithelial lymphocytes are CD20+ centrocyte-like B-cells while most other extra-follicular lymphocytes are CD8+ T-cells.(13) Follicular dendritic cells and interfollicular macrophages are positive for p24 core antigen of HIV.

Prognosis. Regression of parotid gland swelling after initiation of anti-viral therapy has been reported.(12)

Differential Diagnosis. While the described histopathologic features are characteristic of HIV-associated salivary gland disease, similar features occur in some cases of HIV-negative lymphoepithelial sialadenitis. Clinical testing for HIV infection is needed to confirm a diagnosis of HIV-associated salivary gland disease.

CHRONIC SCLEROSING SIALADENITIS

Chronic sclerosing sialadenitis is a chronic inflammation of salivary gland that progresses with increasing fibrosis and parenchymal atrophy. This entity is also known as Küttner tumor (14)

Clinical features. It is the most common disease of the submandibular gland, which it more frequently affects than any other salivary gland.(14) It is usually unilateral but sometimes bilateral. There is a slight female predilection. Most lesions occur in the fifth through seventh decades of life.(1)

Sialoliths are associated with 50 to 83% of cases, usually in the extraglandular excretory ducts,(15) but patients with bilateral disease are less likely to have sialoliths. It is not determined whether the sialoliths are the cause or the result of sialadenitis. Some cases, however, are probably immune disorders.(16)

Firm swelling of the submandibular gland is frequently accompanied by recurrent pain. Radiography detects most sialoliths, although up to 20% of sialoliths are radiolucent.(15) Durations are usually months but sometimes many years.

Pathologic features. Microscopic features change with progression of disease. Early stage disease is characterized by foci of chronic inflammation, usually periductal, with periductal fibrosis and ductal ectasia. As the disease progresses, there is increased fibrosis, acinar atrophy, and ductal dilatation. The amount of inflammation and fibrosis varies from lobule to lobule, but in end stage disease the entire gland is fibrotic and inflammation is decreased. The inflammatory infiltrate is predominantly lymphocytic, usually with some plasma cells and histiocytes, which sometimes form small granulomas. Lymphoid follicles vary from none to numerous.

Prognosis. Removal of sialoliths, with surgery or lithotripsy,(17) in extraglandular salivary ducts often resolves early stage disease. In later stage disease, gland excision is necessary.

Differential Diagnosis. Sarcoidosis of salivary gland is characterized by several epithelioid granulomas and less fibrosis and ductal ectasia. Lymphoepithelial complexes distinguish lymphoepithelial sialadenitis. Immunohistochemical staining for markers such as CD10 and Bcl2 help differentiate follicular lymphoma from chronic sclerosing sialadenitis with numerous lymphoid follicles.

LYMPHOEPITHELIAL CARCINOMA

Lymphoepithelial carcinoma is a large cell undifferentiated carcinoma embedded within a dense lymphoid stroma. The histopathologic features and propensity for tumor cells to be infected with Epstein-Barr virus (EBV) are quite similar to nonkeratinizing nasopharyngeal carcinoma with lymphoid stroma.(1)

Clinical features. Although it constitutes only 0.4 percent of salivary gland neoplasms, there are unique and distinct geographic and ethnic differences in incidence. Over 75% of patients have been arctic native people from Greenland, Canada, and Alaska and Asians, mostly Southern Chinese, and familial clustering has been reported.(18,19). There is a slight predilection for women except among Chinese. Patients have ranged from young to old.(1) The parotid gland is primarily affected although a few tumors occur in the submandibular gland.

EBV infection of the malignant epithelial cells is demonstrable in most lymphoepithelial carcinomas, although less frequently in Caucasian patients.(18,20) The methodology of testing for EBV can affect the results, and in situ hybridization for EBV-encoded RNA 1 (EBER1) is one of the more sensitive tests.(18) While most lymphoepithelial carcinomas arise de novo, a few occur in lymphoepithelial sialadenitis.(1)

Discomfort, pain, or facial nerve palsy sometimes accompany swelling in the parotid or submandibular gland. Cervical lymphadenopathy is common.(18) Tumors' durations have ranged from months up to 10 years.(1)

Pathologic features. At low-magnification, a lymphoid-dense stroma, often with germinal centers, is most conspicuous. At higher magnification, irregular shaped aggregates of large epithelial cells within the lymphocyte-rich stroma become more readily evident. These epithelial cells are polygonal to slightly spindled cells with amphophilic to eosinophilic cytoplasm, large, round to oval, lightly basophilic to vesicular nuclei, and, often, one or more prominent nucleoli. They are variably arranged as small nests, cords, trabeculae, syncytial masses with indistinct cell borders, or isolated cells. Mitotic figures vary from few to numerous. The lymphoid-rich stroma is a mixture of lymphocytes and plasma cells that surround and permeate the carcinoma cells. The amount of collagenous stroma varies.

A few tumors are associated with lymphoepithelial sialadenitis, and such tumors have lymphocyte-permeated nests of benign epithelium in addition to carcinoma. This benign epithelium has smaller cells that lack pleomorphism, vesicular nuclei, prominent nucleoli, and mitotic figures and often has intercellular deposits of eosinophilic hyalin material.

The carcinomatous cells are immunoreactive for cytokeratin and epithelial membrane antigen. In situ hybridization for EBV encoded RNA 1 (EBER1) and for EBV DNA is positive in almost all tumors from Asian patients.(18) Some tumors from non-Asians and non-Arctic native people are

also positive.(1) They are reactive for EBV latent membrane 1 in 50 to 60 percent of tumors that are positive for EBV-encoded RNA 1 by in-situ hybridization.(20) Lymphoid markers confirm the benign nature of the lymphocytic infiltrate.

Prognosis. About 40% and 20% of tumors metastasize to cervical lymph nodes and distant sites, respectively, and both events indicate an adverse outcome. Histologic indicators of poor prognosis are high mitotic rate, anaplasia, and necrosis. However, over 60% of patients survive when treated with surgery, including neck dissection, and radiation therapy.(18)

Differential Diagnosis. The histopathologic, histochemical, immunohistochemical, ultrastructural, and molecular features of nonkeratinizing, undifferentiated nasopharyngeal carcinoma of the so-called lymphoepithelioma type and lymphoepithelial carcinoma of the salivary gland are practically indistinguishable from one another. Fortunately, the parotid gland is an infrequent site of metastasis for nasopharyngeal carcinoma. Still, thorough evaluation of the nasopharynx and Waldeyer's ring region may be needed.

Lymphoepithelial sialadenitis lacks cytologic features of malignancy and invasion of adjacent tissues. Metastatic amelanotic melanoma to intraparotid lymph nodes often requires immunostaining for cytokeratin, S100 protein, HMB45, Melan A, and tyrosinase to determine the correct diagnosis. Likewise, lymphoid and histiocytic immunohistochemical markers help differentiate large cell lymphocytic and histiocytic neoplasms.(1)

Small cell carcinoma of salivary gland is a rare, primary malignant tumor that is composed of small, undifferentiated cells, usually exhibits focal neuroendocrine differentiation, and occasionally has small areas of better differentiated carcinoma or adenocarcinoma. The tumor cells have a characteristic paranuclear, globular staining pattern with anti-cytokeratin (AE1/3 and CK20). They are variably immunoreactive for Leu-7 (CD57), CD56, synaptophysin, chromogranin A, epithelial membrane antigen, neurofilament, and neuron-specific enolase, but most express one marker indicating neuroendocrine differentiation.(1) Immunoreactivity for cytokeratin and lack of reactivity for lymphoid markers facilitate distinction from lymphoma. Distinction from metastatic pulmonary oat cell carcinoma and Merkel cell carcinoma is difficult and largely relies on clinical evaluation. About 20 percent of salivary small cell carcinoma may also express thyroid transcription factor-1 (TTF-1).(1) These tumors lack the prominent lymphoid component that characterizes lymphoepithelial carcinoma.

Large cell undifferentiated carcinoma of salivary gland is a malignant epithelial neoplasm that lacks histomorphologic features of either glandular or epidermoid differentiation and cannot be characterized as any other type of salivary gland carcinoma. The tumor cells are much larger than those of small cell carcinoma but similar to those in lymphoepithelial carcinoma. Rarely, there are bizarre, osteoclast-like, multinucleated giant cells. Mitotic figures are typically common. Invasion of adjacent tissues is characteristic. They lack the prominent lymphoid component of lymphoepithelial carcinoma, and in situ hybridization for Epstein-Barr virus RNA has been negative.(18) They are typically reactive for cytokeratins and have a high prevalence of c-erbB-2 immunoreactivity. Rapid growth, short duration, and cervical lymphadenopathy are typical. The prognosis is worse than for lymphoepithelial carcinoma.

WARTHIN TUMOR

Warthin tumor is an adenoma composed of bilayered columnar and basaloid oncocytic epithelium that forms multiple cysts with numerous papillae accompanied by a proliferation of follicle-containing lymphoid tissue. It occurs almost exclusively in the parotid gland.(1) The older term papillary cystadenoma lymphomatosum is descriptively accurate and synonymous with the eponymic term Warthin tumor. Adenolymphoma and cystadenolymphoma are other terms that have been used, but their use is discouraged to avoid confusion with lymphoid malignancy.

Clinical features. It is the second most common benign parotid salivary gland tumor.(1,21) Nearly all Warthin tumors occur in the parotid gland or periparotid region. Most involve the tail of the gland, but about 10 percent occur in the deep lobe. Rare examples occur in sites other than the parotid gland.

Historically, it has been conceptualized that Warthin tumor is a neoplasm that develops from heterotopic salivary ducts trapped within intraparotid or paraparotid lymphoid tissue. A more likely explanation is that it is a metaplastic process with a secondary lymphoid reaction. In support of this proposal is the finding that several other benign and malignant salivary gland tumors appear to incite a prominent tumor-associated lymphoid proliferation.(22). The observation that multicentric growth occurs more often with Warthin tumor than any other salivary gland tumor argues against coincidental intra-nodal development.(23) Perhaps both pathogeneses occur.

Smokers have eight times the risk of developing Warthin tumor than nonsmokers, and patients with Warthin tumor are heavier smokers than patients who develop pleomorphic adenomas.(24)

Recent studies note a reduced male predilection ratio of between 1.1:1 and 1.6:1 from the previously reported marked male predominance.(23) The decreasing male predilection from previous eras may be related to the increasing proportion of female smokers. The average age of patients is 62 years.(1) Less than 6 percent of Warthin tumors occur before the age of 40 years.

Warthin tumors are usually painless, fluctuant swellings in the lower portion of the parotid gland. Mild to severe pain is experienced by about 9 percent of patients. Earache, tinnitus, and deafness also occur. Most are 2-4 cm in diameter, but they sometimes are considerably larger. Secondary inflammation following rupture of a cyst obscures the usually well-defined borders of the tumor.

Warthin tumor concentrates sodium pertechnetate (99mTc),

making it amenable to scintigraphic examination.(25) Oncocytomas, however, also concentrate 99mTc.

Pathologic features. Warthin tumor is spherical to ovoid and nearly always well circumscribed except when secondarily inflamed. The cut surface of the tumor has a variable number of cysts that exude clear, mucoid, or brown fluid or caseous, semisolid debris. The cysts vary from small to large slit-like spaces and lumens of the cysts have small, knob-like excrescences. The intercystic areas are composed of small tan to white nodular foci and, occasionally, contain focal hemorrhage.

Microscopically, cystic spaces are lined by a papillary proliferation of bilayered, oncocytic epithelium whose supporting stroma is composed largely of lymphoid tissue. The luminal epithelium is tall, columnar cells whose centralized or apical ovoid nuclei often align in a palisade. The cytoplasm is finely granular and brightly eosinophilic. The granularity is due to abundant mitochondria, which is verifiable with phosphotungstic acid-hematoxylin stain or electron microscopy. Beneath and between the columnar cells are less obvious, smaller basaloid cells that have granular eosinophilic cytoplasm similar to that of the columnar cells. In some tumors, there are also scattered mucous, squamous, or sebaceous cells. Fibrovascular stroma that contains a dense component of small lymphocytes supports the epithelium. In a majority of tumors, there are well formed germinal centers and mantle zones. Rarely, tumors have undergone carcinomatous or lymphomatous transformation of the epithelial or lymphoid elements, respectively.(26,27)

A study with polymerase chain reaction found no dominant B- or T-cell clonal populations, but a minor clonal expansion of both B and T cells was detected in some tumors. (28) Identification of follicular dendritic cells suggests that they have an immunological role in Warthin tumor.

Reported increased levels of base pair deletions in mitochondrial DNA in Warthin tumor may be related to oxidative damage that occurs with smoking.(29) In one study, 11of 12 cases had no evidence of clonal allelic loss, supporting the hypothesis that these lesions are non-neoplastic.(30)

Prognosis. Most studies indicate a recurrence rate of two percent or less.(1) Some recurrences may actually be multifocal occurrence.

Differential Diagnosis. The cystic, papillary oncocytic epithelium and associated lymphoid element are so characteristic that the diagnosis is usually straightforward. Focal oncocytic hyperplasia, mucocyte hyperplasia, and squamous metaplasia occur in a few tumors. There is a wide variation in the proportion of epithelial and lymphoid components. Some cystadenomas have papillary, oncocytic epithelium, but they lack a well organized lymphoid element.

Sometimes Warthin tumors undergo infarction with resultant necrosis, fibrosis, and squamous and mucinous metaplasia. In these cases, careful examination is needed to rule out squamous cell and mucoepidermoid carcinomas. Recognition of the outlines of necrotic intracystic papillae formed by tall columnar and basal cells is diagnostic. In addition, there is absence of infiltrative growth.

Tumors with prominent tumor-associated lymphoid proliferation, such as mucoepidermoid carcinoma, acinic cell adenocarcinoma, and cystadenocarcinoma, have some similarity to Warthin tumor.(22) However, the epithelium of these tumors lack characteristic bilayered epithelium of Warthin tumor.

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