Lymphoepithelial Carcinoma of the Parotid Glands and Its Relationship With Benign Lymphoepithelial Lesions

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The salivary glands, despite their relatively simple morphology, give rise to more than 30 histologically distinct benign and malignant tumors. Salivary gland neoplasms comprise less than 2% of all tumors in humans and 3% of all head and neck tumors. They arise in the parotid gland in 80% of cases, and approximately 80% are benign and 20% are malignant. Among them are lymphoepithelial lesions, rare lesions of the salivary glands and especially of the parotid gland that are characterized by lymphocytic infiltration associated with an epithelial proliferation. They are divided into benign, which is considered as a tumorlike condition, and malignant, which is a rare carcinoma of the salivary glands. This article provides a review of the current knowledge on lymphoepithelial carcinoma with a look at its association with benign lesions and on the importance of making the correct diagnosis for the appropriate treatment.

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Lymphoepithelial lesions of salivary glands were first described by Godwin in 1952.¹ He designated with the term benign lymphoepithelial lesions several cases reported in the literature and called different names (Mikulicz disease, myoepithelial sialoadenitis²–⁴) but with similar histologic features, namely the presence of epithelial and lymphoid elements in variable proportions.

Benign lymphoepithelial lesions (BLELs) are to be considered a pathologic rather than a clinical diagnosis² because the histologic pattern is common to a variety of clinical conditions such as Mikulicz disease, Sjögren syndrome, sarcoidosis, calculous sialadenitis, chronic sialadenopathy, immune sialoadenitis, chronic lymphoepithelial sialoadenopathy with sialodochiectasis, and others.⁵

Benign lymphoepithelial lesion usually manifests in the parotid glands (85%), less frequently in the submandibular glands (15%), and most often in patients with Sjögren syndrome.⁴ Sjögren syndrome is an autoimmune disease complex that involves lacrimal and salivary glands with the manifestations of keratoconjunctivitis sicca and xerostomia, often associated with other autoimmune or connective tissue diseases (secondary Sjögren syndrome). Nevertheless, BLEL can also occur in patients without the clinical and laboratory signs of Sjögren syndrome.

Benign lymphoepithelial lesion predominantly affects women (the female-male ratio is about 3:1) in the fourth to seventh decades of life. Clinically, they present with recurrent, firm swelling of the affected glands, which may or may not be associated with discomfort or pain. Histologic features are lymphocytic infiltration, parenchymal atrophy, and foci of ductal epithelial hyperplasia and metaplasia leading to the formation of lymphoepithelial nests, composed of ductal and basal cells⁶ (Figure 1). The lymphoreticular infiltration proceeds, with the evolution of the disease from early stages to late, to total replacement of acinar tissue, but the lobular architecture of the gland is usually retained and the interlobular fibrous septa are preserved. In the lymphoreticular infiltrate, germinal centers are often seen; these can vary from rare to extensive, and the infiltrate is formed by mature polyclonal lymphocytes, predominantly T cells. In the last stages of the disease, plasma cells and immunocytes are conspicuous. The lymphoepithelial nests are formed by hyperplastic residual ductal structures, which maintain their lumen in the early stages but subsequently become irregularly shaped nests of polygonal and spindle cells sometimes with deposits of eosinophilic hyaline material. In the lymphoepithelial nests, there are some lymphocytes, often larger than surrounding lymphocytes, with clear cytoplasm, features of the so-called monocytoid B cells of mucosa-associated lymphoid tissue (MALT) (Figure 2).

In most cases, BLELs involve only a major salivary gland. However, in a few patients there is an evolution to a disseminated form in which all salivary and lacrimal glands are affected, producing clinical signs of Sjögren syndrome or sicca syndrome. In any case, the histopathologic pattern is the same⁹,¹⁰

Patients with BLELs and Sjögren syndrome have a markedly increased risk for developing non-Hodgkin lymphoma. Recently, with the recognition of MALT lymphoma, it has become evident that some lesions previously identified as BLELs were early-stage MALT lymphomas and that this entity may remain localized to the salivary glands for long periods before showing evidence of extraglandular dissemination.

The signs of progression in MALT lymphoma are aggregations of the so-called monocytoid B cells that are monomorphic, medium-sized lymphoid cells with abun-
Figure 1. Lymphoepithelial lesion of the parotid gland (hematoxylin-eosin, original magnification ×10).

Figure 2. Lymphoepithelial lesion of the parotid gland (hematoxylin-eosin, original magnification ×20).

Figure 3. Lymphoepithelial carcinoma. In the aggregate of lymphoid cells there is a germinal center (hematoxylin-eosin, original magnification ×20).

Figure 4. Lymphoepithelial carcinoma. The epithelial component of the lesion shows a slight pleomorphism (hematoxylin-eosin, original magnification ×40).

Figure 5. Lymphoepithelial carcinoma. There is 1 mitosis in the epithelial component (hematoxylin-eosin, original magnification ×40).

Figure 6. Lymphoepithelial carcinoma. The lymphoid component consists of small lymphocytes, plasma cells, and rare histiocytes (hematoxylin-eosin, original magnification ×20).
Lymphoepithelial carcinomas have been described arising from a gland in which a biopsy diagnosis had already been made of BLEL.4 This implies malignant transformation of the epithelial elements of a BLEL; on the other hand, most LECs are not diagnosed in a background of BLEL and probably develop de novo.

In affected patients of Mongolian race, a strong association has been demonstrated between the lesion and Epstein-Barr virus (EBV) infection, as in undifferentiated nasopharyngeal carcinoma (which also has histologic features in common). The association with EBV and nasopharyngeal carcinoma was first described by Zur Hausen et al24 in 1970, and this association in the salivary glands was reported by Salmundsen et al in 1982.25 In their review of 160 cases from Russia-Asia, Saku et al20 conclude that EBV plays an important role in the pathogenesis of these lesions.

In 1991, the presence of EBV was detected by Hamilton-Dutoit et al28 with in situ hybridization in paraffin sections of 11 salivary LECs in the Eskimo population of Greenland. They demonstrated that the viral DNA was specifically located in the malignant cells and not in the lymphocytes or in the benign epithelium and that there was no EBV DNA in a non–lymphoepithelioma-type poorly differentiated salivary gland carcinoma of 2 Danish patients. Sehested et al27 have also described intranuclear bodies referred to as viral particles in the anaplastic cells of LEC.

The clinical presentation of the LEC is usually a parotid or submandibular painless mass of variable duration, although pain or discomfort may be present; 20% of cases present with facial nerve palsy and 40% with cervical lymphadenopathy.4 Lymphoepithelial carcinoma develops most frequently in the parotid gland (82%) and in the submandibular gland. The mean age at presentation is between 20 and 60 years, with a median age of 40 years, although there have been reports of cases in a 10-year-old and an 86-year-old patient. A female prevalence has been noted with a female-male ratio of 1.5:1. A 7:1 ratio of occurrence in the parotid versus the submandibular gland and familial clustering of affected patients has also been reported.28

Macroscopically, these tumors are firm 1- to 10-cm masses, multilobulated, circumscribed, or clearly infiltrative into adjacent salivary gland, fat, muscle, or skin, with a cut surface that varies from a grey-tan to yellow-gray. Zonal necrosis and hemorrhage are not typical features.29

The microscopic examination reveals diffuse or circumscribed dense aggregates of lymphoid cells sometimes with germinal centers and an epithelial component composed of irregular shaped islands of pleomorphic, large, polygonal or slightly spindle-shaped cells with abundant amphophilic to eosinophilic cytoplasm and round to oval, lightly basophilic to vesicular large nuclei that usually contain 1 or more prominent nucleoli. The membranes of these cells are often indistinct (Figure 3). Sometimes the cells have cytoplasmic vacuoles or clear cytoplasm. These epithelioid cells grow in small islands, syncytial masses, cords, trabeculae, or isolated cells dispersed in the lymphocyte-rich stroma (Figures 4 and 5). Mitotic rates vary from 1 to 10 or more per high-power field. The cells are usually uniform, but sometimes the anaplasia is marked, and although epidermoid features are manifest, the over-
all appearance is that of undifferentiated carcinoma. Peripheral invasion may also be present.25

In the dense lymphocytic infiltrate that surrounds the epithelial islands there are small lymphocytes and plasma cells predominantly, at times with interspersed histiocytes (Figure 6).

The presence of lymphoid follicles with germinal centers varies from none to many, with sometimes a "starry sky" pattern and variable amounts of collagenous tissue present within the lymphoid component. In some tumors, there are irregularly shaped nests of epithelial cells surrounded and infiltrated by lymphocytes with poorly defined borders, called lymphoepithelial nests. These are characteristic of BLELs and are present in addition to the aggregates of undifferentiated carcinoma cells. These cells differ from the neoplastic cells in their cytologic features because they lack mitotic figures, cellular and nuclear pleomorphism, vesicular nuclei, and prominent nucleoli.

Electron microscope studies generally confirm the epithelial origin of these cells, with the presence of desmosomal cell attachments and conspicuous cytoplasmic microfilaments and tonofilaments. Immunohistochemistry is used to demonstrate the intimate relationship between the epithelial and lymphoid components with anti-cytokeratin and anti-leukocyte common antigen stains.

This tumor has a strong tendency to metastasize, first of all to the parotid nodes, then to the upper cervical and retroauricular nodes, and later to the supravacuicular and parapharyngeal nodes. On presentation 40% of patients have metastases to the cervical lymph nodes, 20% develop local recurrence or lymph node metastases, and 20% have distant metastases within 3 years following therapy. Distant recurrence or lymph node metastases, and 20% have distant metastases to the cervical lymph nodes, so it becomes a very rare event.

In establishing the histologic diagnosis of LEC, the most important finding is the presence of associated BLEL. If it is not present, there must be lymphoepithelial nests similar to those of BLEL. If lymphoepithelial nests are absent, one must suspect metastasis from an undifferentiated nasopharyngeal carcinoma of the so-called lymphoepithelialoma type, which has very similar cytologic and architectural features, the same ethnic predilection, and a strong association with EBV infections, which also suggests a common pathogenesis. It is very important to make the correct diagnosis for the appropriate treatment. In fact a nasopharyngeal carcinoma with metastasis to the salivary gland, if treated as a primitive tumor of the salivary gland, will not receive the correct radiotherapy in the primary site.20 This differential diagnosis can be difficult because histologic, histochemical, and ultrastructural studies cannot reliably distinguish between these 2 neoplasms, so only careful clinical assessment and a meticulous fiber-optic nasopharyngoscopy or panendoscopy with random biopsies of the nasopharynx and Waldeyer ring should be performed to exclude the possibility of metastatic disease.22 In reality, the parotid gland is the predominant site of occurrence of LEC and an exceptional site of metastasis from nasopharyngeal carcinoma, which more typically metastasizes to the cervical or submandibular lymph nodes, so it becomes a very rare event.

Another differential diagnosis is with amelanotic melanoma, but immunohistochemistry with the anti-cytokeratins, anti-S100 protein, and anti-HMB-45 can help make a distinction. Differential diagnosis from large cell lymphocytic and histiocytic neoplasms is helped by lymphocytic and histiocytic immunohistochemical markers, such as antibodies to CD20, CD45RO, CD68, Leu-M1, and Ki-1 and epithelial markers.26

Lymphoepithelial carcinoma seems to have a better prognosis than the other undifferentiated carcinomas of the salivary glands, perhaps because of the lymphoid stroma that has a role in limiting the aggressiveness of this carcinoma. Advanced disease, the presence of metastases on diagnosis, and histologic features such as high mitotic rate, anaplasia, and necrosis are predictors of a worse prognosis.

Therapy is based on complete excision with clear surgical margins and treatment of the periparotid lymph nodes and the lymphatics of the upper part of the neck with neck dissection or adjuvant radiation therapy. Data suggest that the latter treatment is preferable, which is not surprising given the radiosensitivity of nasopharyngeal carcinoma.28

Because of the rarity of this tumor it is difficult to tabulate survival data; 1 report estimates 2-, 5-, and 10-year survival rates of 91%, 66%, and 29%, respectively, for LEC of the salivary glands.29 Further studies are necessary to establish the appropriate radiation field and dose for the parotid gland.25

References


