Lymphoepithelial Carcinoma of Salivary Glands

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KEYWORDS

• Lymphoepithelial carcinoma • Salivary gland • Immunohistochemistry • EBER

Key points

- Lymphoepithelial carcinoma is a rare undifferentiated primary salivary carcinoma that is associated with a florid lymphoid background.
- Epstein-Barr virus association is near 100% in endemic populations (e.g., Eskimo/Inuit) while the association in nonendemic populations is not as reproducible.
- Morphology, immunohistochemical stains, and Epstein-Barr virus encoded small RNA (EBER) in situ hybridization (ISH) are insufficient to distinguish lymphoepithelial carcinoma from nasopharyngeal carcinoma, which requires clinical evaluation.
- These tumors, irrespective of race or ethnicity, may express EBER, but a negative EBER-ISH does not exclude the diagnosis.

ABSTRACT

Lymphoepithelial carcinoma of salivary glands (LECSG) is an uncommon neoplasm. This article summarizes the findings of 438 cases in a review of the literature. Concurrent lymphoepithelial lesions may suggest a primary tumor. The tumor shows a nonkeratinizing carcinoma intimately associated with a rich lymphohistiocytic infiltrate, destroying adjacent salivary gland tissue. Irrespective of race or ethnicity, the tumors usually express Epstein-Barr virus, with Epstein-Barr virus encoded small RNA (EBER) and/or latent membrane protein-1 (LMP-1), although a subset does not. There is an overall good prognosis of about 80% at 5 years.

OVERVIEW

Undifferentiated carcinoma with an associated prominent, nonneoplastic, lymphoplasmacytic cell infiltrate is now called lymphoepithelial carcinoma (LEC).[1] It was originally described by Hilderman and colleagues[2] in 1962, as the possible malignant transformation of benign lymphoepithelial lesions (BLEL). LEC has gone by a diverse nomenclature, including but not limited to undifferentiated carcinoma, anaplastic parotid carcinoma, lymphoepitheliomalike carcinoma, lymphoepithelial-like carcinoma, undifferentiated carcinoma with lymphoid stroma, malignant lymphoepithelial lesion, nonnasopharyngeal undifferentiated carcinoma, and carcinoma ex lymphoepithelial lesion.[1,3–13] The historical names are not inherently inaccurate, but LEC most accurately reflects the intimate relationship between the epithelial and the lymphoid components of this neoplasm. Undifferentiated nasopharyngeal carcinoma (NPC) is the prototypical LEC.[8,14–16] It is most commonly reported in patients from Southeast Asian and Arctic Inuit populations, as well as descendants of these ethnic groups who migrate to nonendemic

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countries.[17–19] Nearly all of the LECs in endemic patients express Epstein-Barr virus (EBV) in the neoplastic cells, which can be confirmed by a variety of different techniques. Within the salivary gland, LEC is rare, although it shows a strikingly high frequency in Arctic Inuit populations (Greenland, northern Canada, Alaska), southeastern Chinese, and Japanese, among others. Further, in Inuits especially, LEC of salivary gland (LECSG) is the most common salivary gland malignancy, mostly identified in the parotid gland. It accounts for up to 90% of all salivary gland malignancies.[4,5,8,9,12,20–24] It is always prudent to exclude a nasopharyngeal primary before making a definitive diagnosis of a salivary gland primary given similarly affected ethnic groups.[6,8,12]

CAUSE AND PATHOGENESIS

In almost all cases, the causal role of EBV is well documented, with EBV identified in the neoplastic epithelial cells by in situ hybridization or latent membrane protein 1 (LMP1) reactivity.[4–6,8,9,12,22,23,25–37] The neoplasm may progress as a malignant transformation of glandular or ductal inclusions in intraparotid gland lymph nodes or transformation of BLELs (epimyoepithelial islands),[3,12,38–46] although these structures may be reactive to the advancing tumor. There is clearly a complex interaction between genetic (ethnic), environmental, geographic, behavioral, and viral (EBV) factors in the oncogenic process of LEC.[6,47,48] Although there is a near-constant association of EBV with LEC in all ethnic groups, even in the salivary glands, it still must be recognized that EBV-negative LECs are documented in patients in nonendemic regions (**Table 1**).[49]

Most of the EBV-associated carcinomas are of the lymphoepithelial type. It may be that the active or vesicular nuclear appearance of the neoplastic cells is morphologically similar to the blastic transformation that occurs in EBV-infected B lymphocytes, suggesting that the lymphoid infiltrate may represent a host reaction to the virus-associated antigens that are expressed on the neoplastic cells.[50] Thus, an EBV infection seems to precede the oncogenic process, showing clonal episomal expansion.[51] Through a complex process, including EBV nuclear antigens and LMP1, EBV immortalizes B lymphocytes and prevents apoptosis.[52,53] Further, LMP1 in human epithelial cells has been shown to deregulate epithelial growth and inhibit differentiation, with the cells showing loss of contact inhibition, spindling, and a tendency to proliferate.[54] As such, the undifferentiated appearance may be caused by the role of LMP1.[6] Still sinonasal undifferentiated carcinoma shows a similar histologic appearance but is not EBV-associated. As such, the histologic appearance of LEC does not always indicate EBV association, nor is EBV association always associated with a lymphoepithelial pattern.[26] There is an increased risk of lymphoepithelial carcinomas (salivary or nasopharynx) in patients with human immunodeficiency virus (HIV) infection who progress to acquired immunodeficiency syndrome (AIDS).[55] However, HIV-associated salivary gland disease usually encompasses lymphoid hyperplasia, follicular involution, lymphoepithelial cysts (usually bilateral), and lymphoepithelial lesions.[56–59]

DEMOGRAPHICS

The incidence of a rare tumor is alwys difficult to estimate, and even more so when there is geographic diversity. As presented in **Table 2**, there is wide diversity in the incidence of LECSG in endemic regions, ranging from 0.3% to 54.8% of all tumors versus 3.6% to 92% of all malignant tumors.[9,11,20,34,37,60–64] By contrast, in nonendemic regions (see **Table 2**), the tumors represented 0.3% to 0.7% of all malignant tumors.[47,65] Higher incidences of LEC are reported in Arctic region natives (Eskimos/Inuits from Alaska, Canada, Greenland), southern Chinese, Japanese, northern Africans, and Mongolians.[4,6,21,22,37,66] Of these endemic populations, the Eskimo/Inuit population seems to be the most affected.[11,32] When white people are included in the published cases, they represent about 7% of all reported cases, although higher numbers (62%) are found in nonendemic reports.[49]

Individual case series have shown a sex bias, even when endemic considerations are taken into account. However, when all reported cases are aggregated, there is no sex predilection (see **Table 1**).

Patients of a wide age range are affected, from 10 to 86 years, with a mean of 47.1 years and a median of 46.0 years. However, nonendemic patients tend to be older (mean, 55.4 years; median, 55 years).[25,28,33,35,36,47,49,55,67–69]

CLINICAL FINDINGS

Given the rarity of LECSG, clinical findings are difficult to extrapolate, but patients present with nonspecific symptoms, including swelling or a mass in the salivary gland (**Fig. 1**), with pain (approximately 5%) and nerve findings (approximately 2.5%) uncommonly recognized.[5,60,66] In

Table 1
Literature summary of 438 patients with lymphoepithelial carcinomas of salivary gland

Characteristics[a]	Number (n = 438)
Sex	
Female	210
Male	211
Age (y)	
Range	10–86
Mean	47.1
Median	46.0
Ethnicity	
Asian	321
Inuit/Eskimo/Native Canadian Indian	49
White	40
Black	6
Middle East	1
Symptom Duration (mo)	
Range	0.5–240
Mean	20.8
Median	11.5
Clinical Presentation	
Swelling/mass	413
Pain	21
Nerve paralysis/paresis	14
Site	
Parotid	333
Submandibular gland	75
Sublingual gland	2
Minor salivary gland	26
Palate	17
Laterality	
Left	35
Right	44
Tumor Size (cm)	
Range	0.7–15
Mean	3.9
Median	3.8
Women (mean, cm)	4.4
Men (mean, cm)	3.6
White (mean, cm)	4.2
Inuits/Eskimos and Asians (mean, cm)	3.8
Black (mean, cm)	4.2
Epstein-Barr virus encoded small RNA Status	
Positive	265
Negative	16
Lymph node metastasis identified	73
Therapy	
Surgery (including neck dissection)	389
Surgery and radiation	156
Surgery, radiation, and chemotherapy	20
Patients with follow-up (n = 141) (mean months of follow-up)	
Alive, no evidence of disease	106 (63.3)
Alive with disease	8 (53.5)
Dead, no evidence of disease	5 (32.3)
Dead of disease	22 (40.4)
Follow-up (mo)	
Range	2–303
Mean	57.7

[a] Not stated in all cases.
Data from Refs.[2,4–10,12,13,20,21,23–28,30–40,43,49,60,66,67,69,74–78,80,82,84–88,121,129,137–139,141–160]

advanced cases, skin and soft tissue fixation may be seen. Symptoms are present over an exceptionally broad time frame, ranging from 0.5 to 180 months, although most patients report slightly less than 2 years of symptoms, with a median of 11.5 months. Clinically or radiographically obvious cervical lymphadenopathy is detected in about 17% of patients (see **Table 1**). Almost all tumors affect the major glands, with the parotid (76%) and submandibular glands (17%) accounting for 93% of all tumors. Minor salivary gland sites are uncommon, but, when identified, the palate accounts for approximately 65% of all tumors. On imaging, patients show a partially circumscribed or ill-defined mass with a lobular or plaquelike lesion (**Fig. 2**), with homogeneous to heterogeneous enhancement. Occasionally, intratumoral necrosis or cystic change is noted. Soft tissue invasion into adjacent structures is common, along with radiographically involved cervical lymph nodes.[60,70–73]

LABORATORY STUDIES

Most patients show some serologic evidence of previous infection with EBV. Although EBV viral capsid antigen (VCA) to immunoglobulin (Ig) A, IgM, and/or IgG, EBV nuclear antigen (EBNA)

Table 2
Lymphoepithelial carcinomas of salivary gland incidence variation

Cohort Reported	Number of LECSG Cases	All Salivary Gland Tumors[a]	Total Number of Malignant Salivary Gland Tumors	Cases
Endemic Population				
Arthaud,[9] 1972	7	19	NR	36.8% of all tumors
Nielsen et al,[11] 1978	23	42	25	54.8% of all tumors 92% of malignant tumors
Nagao et al,[37] 1996	5	1676	NR	0.3% of all tumors
Saku et al,[20] 2003	162 total 124 southern China only	NR	4330 (at least) 1965 southern China only	3.7% of all malignant tumors 6.3% of southern China only
Wang et al,[60] 2004	16	NR	295	5.4% of malignant tumors
Zhang et al,[61] 2005	16	NR	444	3.6% of all malignant tumors
Li et al,[62] 2008	52	3461	1392	1.5% of all tumors 3.7% of all malignant tumors
Tian et al,[63] 2010	121	6982	2239	1.7% of all tumors 5.4% of all malignant tumors
Wang et al,[64] 2012	28	1176	289	2.4% of all tumors 9.7% of malignant tumors
Li et al,[34] 2014	50	NR	235	21.3% of malignant tumors
Nonendemic Population				
Jones et al,[65] 2008 (United Kingdom)	1	741	260	0.1% of all tumors 0.3% of all malignant tumors
Zhan et al,[47] 2016 (United States)	238	NR	36,224	0.66% of all malignant tumors

Abbreviation: NR, not reported.
[a] Major and/or minor salivary gland sites.

IgG, and early antigen (EA)-IgG antibodies are seen in patients with a past infection, they are not always seen in patients with LEC.[32] It is interesting that sometimes these findings precede the documentation of LEC. However, levels of IgA antibodies to EBV VCA are usually increased in patients with carcinoma.[74]

CYTOLOGY

Smears show single to clustered large polygonal and spindled cells in syncytial sheets. The cells have limited to moderate amounts of cytoplasm and have a high-grade, undifferentiated appearance (**Fig. 3**). The nuclei are vesicular with prominent nucleoli. Mitotic activity is brisk. Most have a prominent mixed lymphoid population that may mask the isolated epithelial elements, resulting in a misdiagnosis.[69,75–78] Metastatic nasopharyngeal carcinoma to an intra–salivary gland lymph node may also be a consideration. Further, a dense lymphoplasmacytic infiltrate may mimic an intra–salivary gland lymph node, and, depending on the type of population present, may suggest a lymphoma. If the epithelial cells are not atypical, lymphoepithelial sialadenitis or lymphoepithelial cyst

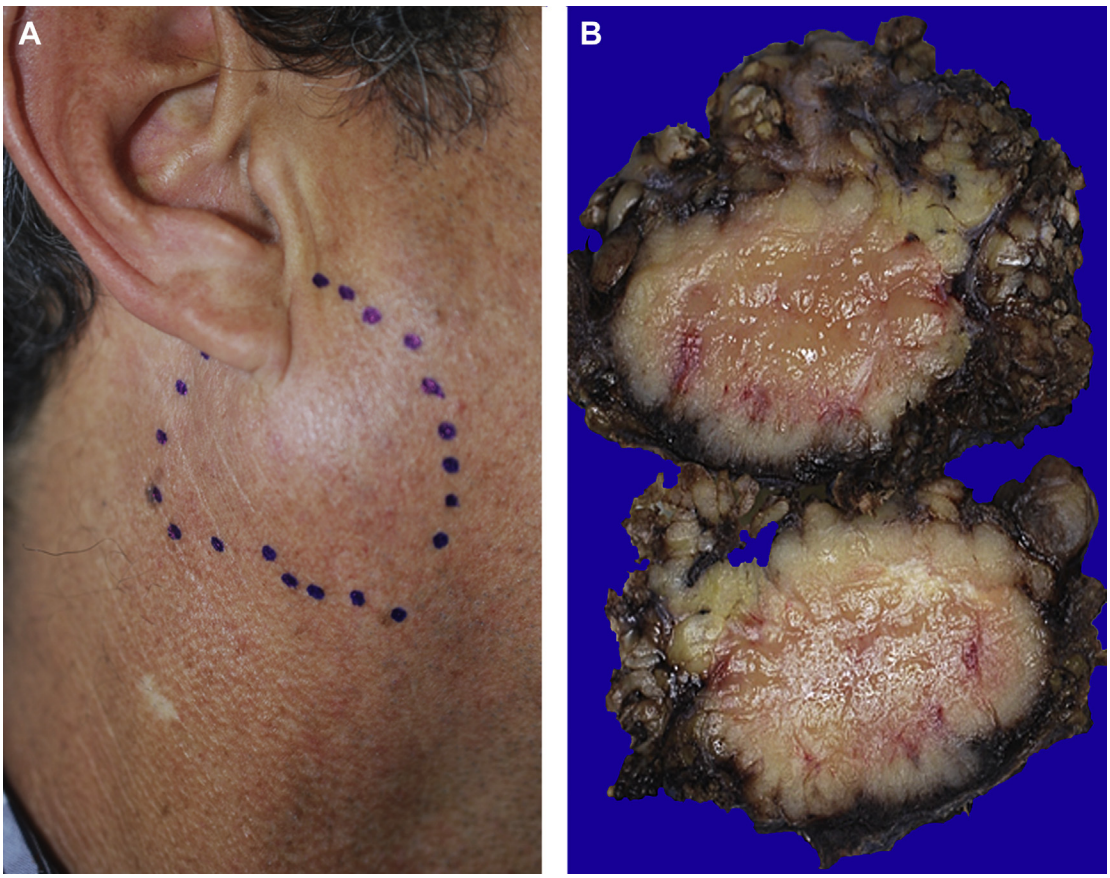

Fig. 1. (*A*) Clinical examination showed a parotid gland swelling without skin erythema in a patient without a nasopharyngeal mass. (*B*) There is a fish-flesh pale cut surface of the parotid gland, showing a mass replacing the entire gland.

may also be considered. Many primary salivary gland neoplasms have a prominent lymphoid stroma associated with them, such as mucoepidermoid carcinoma and acinic cell carcinoma, and these tumors should not be confused with LEC. If cell block material is available, especially in endemic patients, EBER may aid in separation between the epithelial lesions and even lymphomas that are EBV associated.

MACROSCOPIC FEATURES

LECSGs grossly are typically circumscribed but not encapsulated, with a lobulated, firm, tan-white cut appearance (see **Fig. 1**). Other cases show an infiltrative appearance into the adjacent salivary glands, fat, skeletal muscle, and skin. The tumors range up to 15 cm,[16,47,69] with most greater than 2 cm.

MICROSCOPIC FEATURES

Although the histologic features are characteristic and identical to nonkeratinizing nasopharyngeal carcinoma, it is important to recognize that variability in amount and type of epithelial elements may be present, along with the amount and type of lymphoid infiltrate (sparse to heavy). Original descriptions suggested malignant transformation from lymphoepithelial sialadenitis (LESA) or myoepithelial sialadenitis (MESA).[8,16,35,46,56,79–81] Thus, in some cases, it is possible that LESA may be seen adjacent to or even within the tumor (**Fig. 4**), a finding that favors a primary tumor rather than a metastatic lesion. It may be that LESA is a reaction rather than a precursor, but a precursor is favored. However, there are investigators who do not agree that LESA or MESA is seen in or adjacent to these tumors.[6] There does not seem to be an

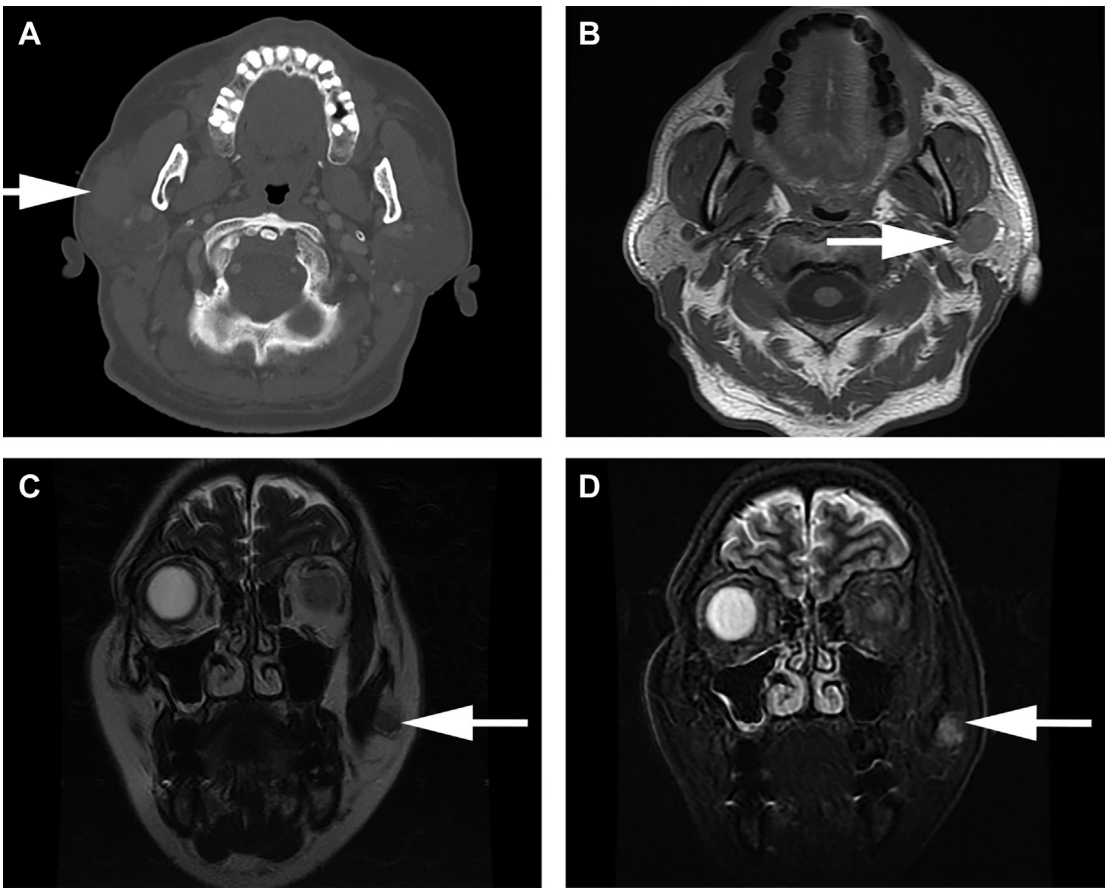

Fig. 2. LEC affecting the: (*A*) Right parotid gland as a soft tissue swelling (*arrow*) by axial computed tomography; (*B*) A left parotid gland well-defined hypointense mass (*arrow*) on T1-weighted axial magnetic resonance (MR); (*C*) A hypointense mass (*arrow*) on coronal T2-weighted MR; and (*D*) Hyperintense mass on coronal T2-STIR (short T1 inversion recovery) sequence MR (*arrow*).

association with autoimmune disorders (e.g., Sjögren disease).[16,46,49,56,74] In classic form, the epithelial component shows a syncytium of crowded, large, undifferentiated cells with a high nuclear to cytoplasmic ratio; irregular to geometric or oval nuclei; vesicular to open nuclear chromatin; and large, prominent, brightly hypereosinophilic nucleoli (**Fig. 5**). The cytoplasm is sparse, delicate, and lightly staining. Smudged nuclei may be seen within some of the neoplastic cells (see **Fig. 5**). Pleomorphism in the nuclei is often easily recognized (**Fig. 6**).[60,66,74] Definitive squamous differentiation, including keratinization, may be present (see **Fig. 6**), although usually limited in extent, whereas tumor cell spindled and even a basaloid morphology can be identified, resulting in some patients showing a hybrid morphology.[82] In general, the adjacent salivary gland tissue is unremarkable, lacking any prominent lymphoid infiltration (see **Fig. 6**).

All tumors are infiltrative by definition, frequently expanding beyond the salivary gland parenchyma into the adjacent soft tissues, and even showing positive surgical margins in about a quarter of patients.[47] Two major patterns of growth are recognized, described by their eponyms, named after the German pathologist Alexander Schmincke (1877–1953) and French radiologist Claude Regaud (1870–1941), who researched this tumor type and independently reported their cases in the same year.[20] The Schmincke-type pattern shows syncytial clusters of undifferentiated tumor cells in an intimate relationship with the lymphoid cells and seemingly overrun by them (**Fig. 7**), making it challenging to detect the epithelial cells. The Regaud-type shows sheets, cords, and cohesive nests that are set within and even separated by the lymphoid stroma, which may contain germinal centers, usually showing epithelial groups well circumscribed and distinct from the adjacent

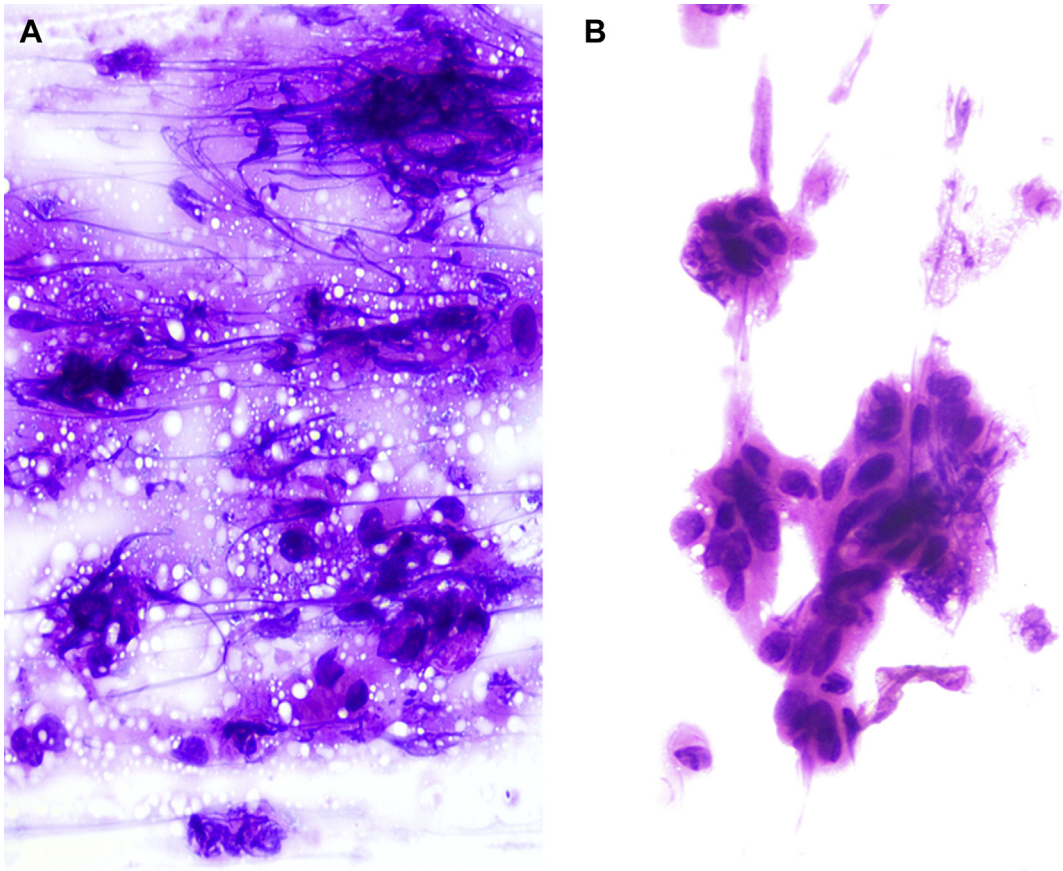

Fig. 3. (*A*) The smears are cellular, showing prominent lymphoid matrix tangles in the background with large, polygonal, syncytial epithelial cells (air dried, May-Grüwald–Giemsa [MGG]). (*B*) There is a cluster of atypical epithelial cells with a high nuclear to cytoplasmic ratio (air dried, MGG).

parenchyma (**Fig. 8**). It is common to have the islands resemble a jigsaw puzzle (see **Fig. 8**). Mitoses are easily identified and include atypical forms. Tumor necrosis is usually not a prominent finding (see **Fig. 8**), except in the basaloid LEC. The lymphoid stroma is rich, containing a nearly equal number of polyclonal B and T lymphocytes and plasma cells. Germinal center formation is frequently identified (i.e., nonneoplastic lymphoid elements). The reactive histiocytes within the lymphoid compartment can be prominent, yielding a starry-sky appearance (**Fig. 9**). Importantly, there is nothing to suggest the formation of a true lymph node: no medullary zone, no subcapsular sinus or sinus histiocytosis, and no cortical zone. This finding can be confirmed by performing CAM5.2 immunohistochemistry, which highlights extrafollicular reticulum cells seen in a true lymph node.[83] Noncaseating granulomatous inflammation along with multinucleated giant cells may be seen, either as a reaction to the neoplastic cells or to debris (see **Fig. 9**). Amyloid in the form of extracellular, acellular, eosinophilic matrix material may be seen, sometimes surrounded by the neoplastic cells.[2,5,24,49,74] There is usually an absence of stromal reaction in the form of desmoplasia, a finding frequently seen in other types of salivary gland neoplasm. Salivary gland ducts, glands, and acini may be seen at the periphery of the tumor, occasionally entombed.

Squamous differentiation is usually not the dominant finding, but areas of squamous differentiation can be seen. When present, a metastatic neoplasm to the salivary gland and/or lymph nodes must be considered.[16,74] Tumor cell spindling may be prominent (**Fig. 10**), resulting in a fascicular pattern, sometimes with desmoplastic stroma. This finding brings to mind other tumor categories such as basal cell adenoma and myoepithelial carcinoma, among others.[16,35,37,40,45] Rare cases of epithelial-myoepithelial carcinoma may be EBV associated, highlighting a

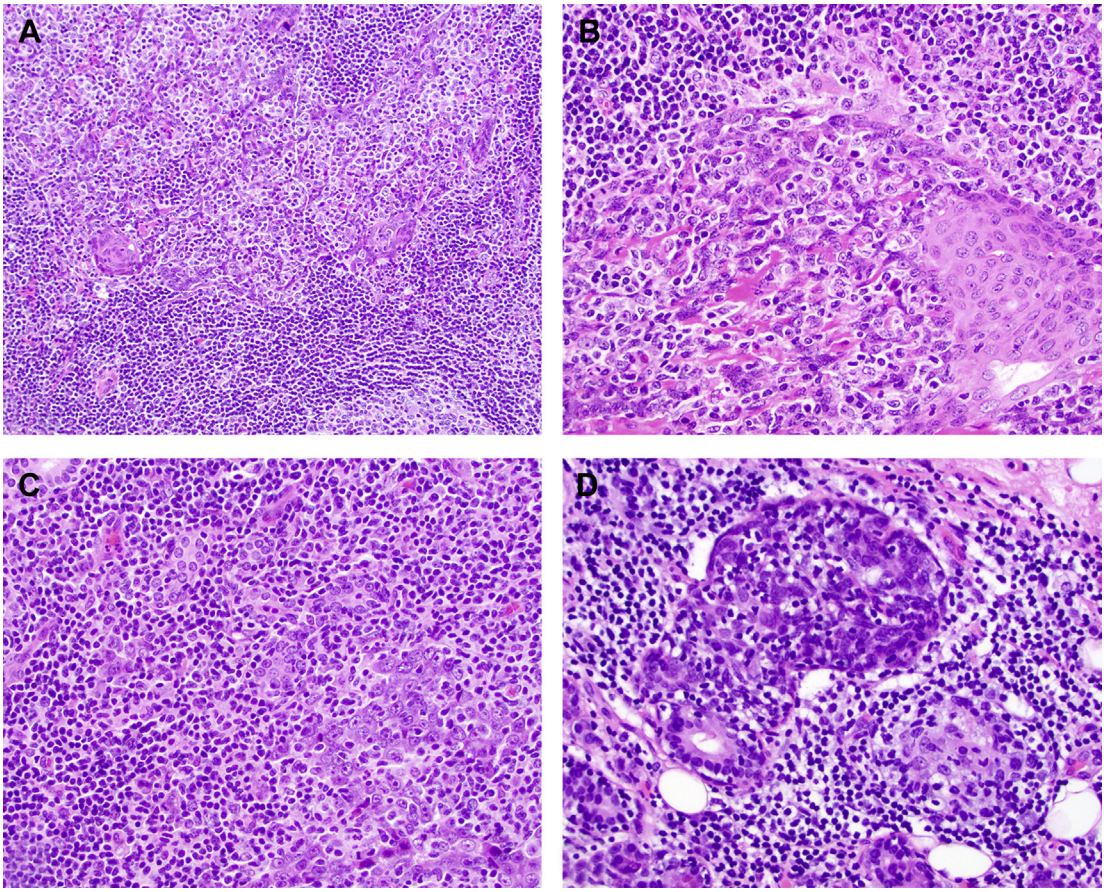

Fig. 4. LESA adjacent to LEC. (*A*) Monocytoid lymphocytes are seen associated with a terminal acinar duct lobule. (*B*) Squamous metaplasia intimately associated with lymphoid elements. (*C*) Epithelial proliferation associated with lymphocytes, but lacking cytologic atypia. (*D*) A terminal duct with inflammatory cells. Histiocytes are noted in the lower right corner.

transformation from the benign spindled cells of an MESA to LEC.[84] The basaloid morphology has been described primarily in Inuit populations, with a consistent EBV association identified,[82] showing a sclerotic stroma, limited lymphoid tissue, and angulated cord or "syringoma-like" nests. Perineural invasion may be prominent (see **Fig. 10**). Importantly, a cutaneous basal cell carcinoma must be eliminated, because they may directly invade into the parotid salivary gland.

ULTRASTRUCTURAL FINDINGS

Although almost never used in the twenty-first century, it is important to recognize the findings on electron microscopy, because they underpin the diagnosis. The tumor cells are usually closely apposed and joined by well-developed desmosomes (although in limited numbers). The nuclei are large, slightly irregular, with peripheral condensation of heterochromatin and large, single, central nucleoli. Spherical fibrillary nuclear bodies may be seen in the neoplastic cells but not in the lymphocytes. The cytoplasm contains a variable number of bundles of tonofilaments. Lymphocytes can be seen intimately associated with the neoplastic cells.[31,40,45,77,85,86] Importantly, no secretory lumina or vacuoles or tight junctions are seen.

IMMUNOHISTOCHEMISTRY AND IN SITU HYBRIDIZATION FINDINGS

LECSGs are epithelial neoplasms, and thus are highlighted with a variety of markers of epithelial differentiation, to include pancytokeratin, AE1/AE3 (**Fig. 11**), CAM5.2, CK903, CK5/6 (see **Fig. 11**), and epithelial membrane antigen (EMA), along with p40 and p63 (**Fig. 12**).[5,16,20,30,49,87,88] The reactivity may be strong and diffuse, or yield

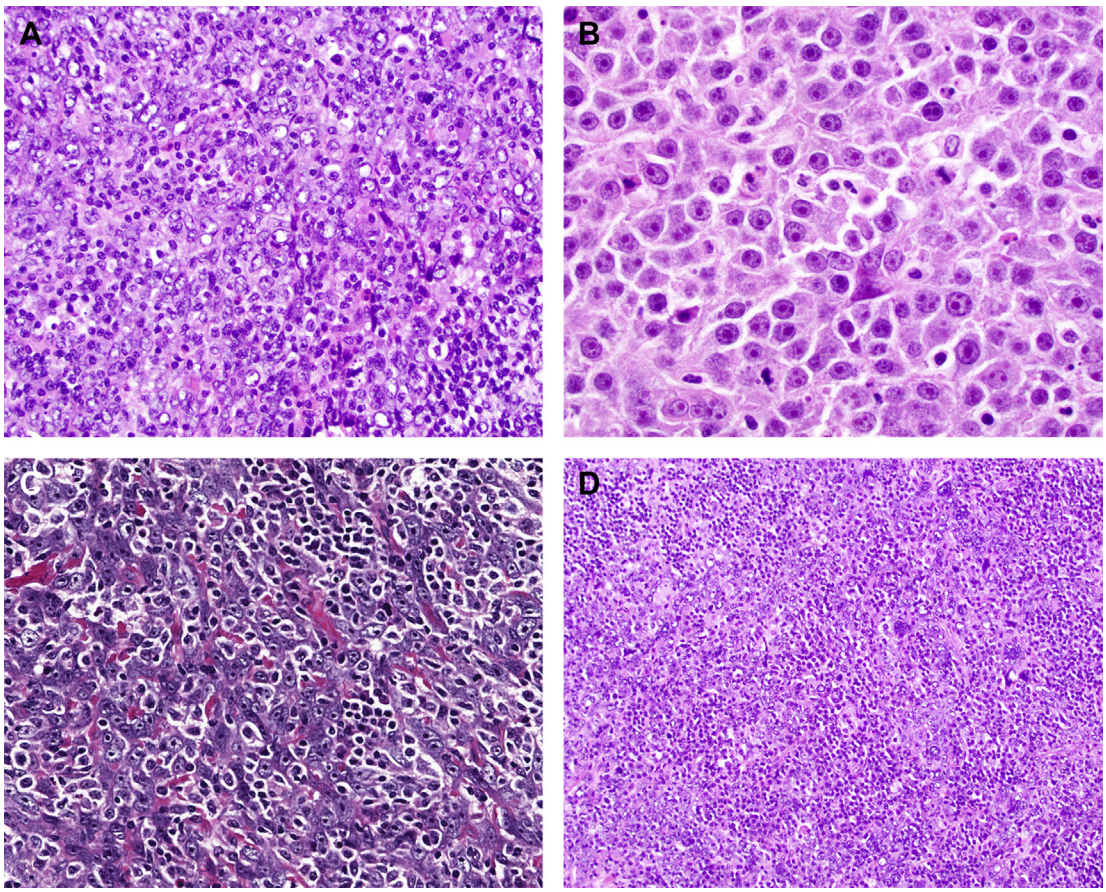

Fig. 5. Cellular features of LEC. (*A*) Syncytium of large, polygonal neoplastic cells with vesicular chromatin. (*B*) Large, prominent, hypereosinophilic nucleoli. (*C*) Cytoplasmic extensions surround vesicular nuclei. (*D*) Smudge and focal tumor giant cells within a sea of neoplastic cells.

a more characteristic lace-like or lattice-like wispy staining of the delicate cytoplasmic extensions that are pushed by the inflammatory infiltrate (see **Fig. 11**). SOX10 may highlight basaloid-type cells,[89] whereas dendritic cells are highlighted with S100 protein. CD117 is noted in some cases, but p16 and high-risk human papillomavirus (HPV) by in situ hybridization (ISH) are negative.

Considered to be most helpful, especially in separating from other neoplasms in the salivary gland, is the strong and diffuse reactivity with either a membranous and granular cytoplasmic EBV LMP1 pattern or a nuclear EBER by ISH (see **Fig. 12**), the latter confirming the presence of the EBV-encoded small RNAs (EBERs).[4,6,20,25,29,37,40,48,49,69] The EBER signals are often localized to the perinucleolar area and along the nuclear membrane. Of course, no signals are identified in the adjacent lymphocytes. Although these EBV studies confirm the diagnosis in endemic populations, they are not always seen in nonendemic populations (see **Table 1**). Thus, the absence of EBV in LEC suggests that other factors (e.g., environmental and genetic predisposition) may also contribute to the pathogenesis of the tumor.[4,35,48,49,67,78]

POLYMERASE CHAIN REACTION AMPLIFICATION AND DNA SEQUENCING

Not routinely performed, polymerase chain reaction (PCR) amplification of LMP1 shows that the 30-bp deleted variant (from the C-terminal region of the EBV LMP1 gene) is the most consistently identified within tumors found in patients from the endemic areas. Point mutations in codons 322 (Gln to Asn) and 334 (Gln to Arg) are found in nearly all tested patients, along with mutations in codons 335 and 338, suggesting highly shared mutations in EBVs seen in salivary gland LEC, findings similar to those reported in nasopharyngeal

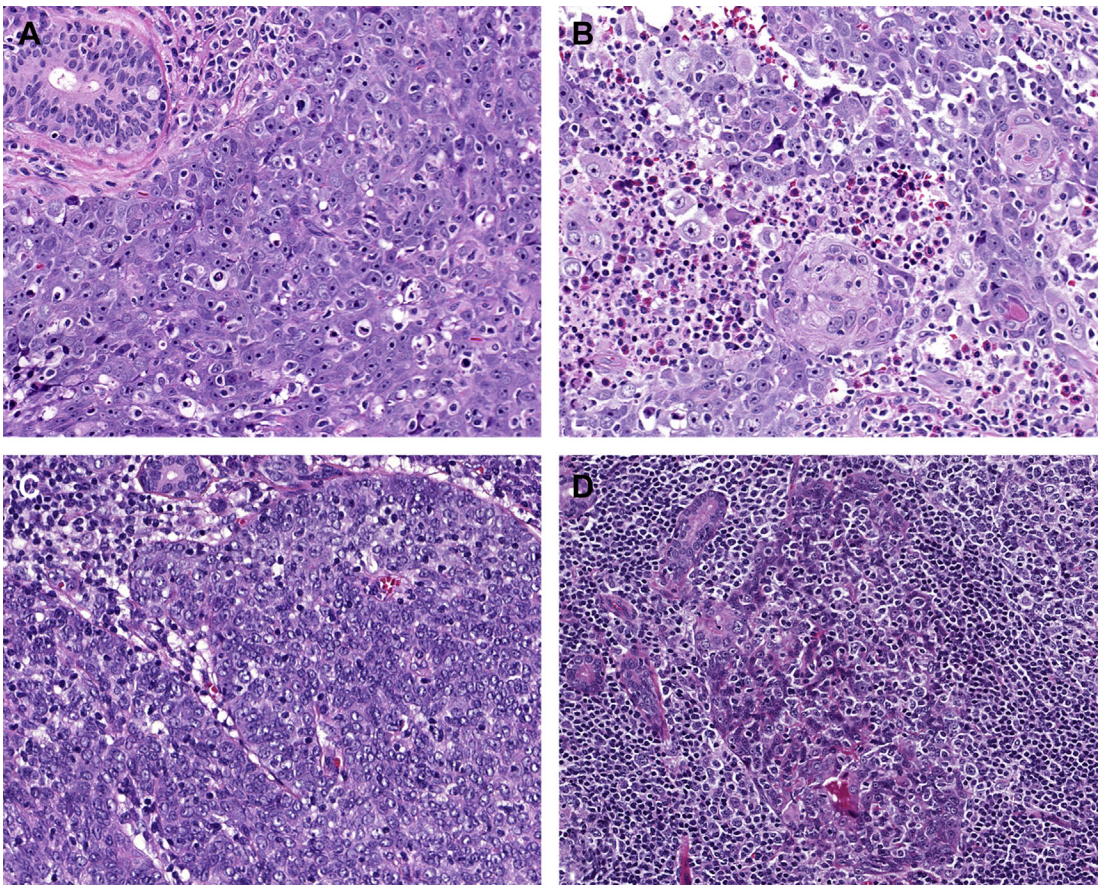

Fig. 6. (*A*) Cellular pleomorphism is easily noted, with a benign duct for comparison. (*B*) Keratin pearl formation is seen, along with an acute inflammatory infiltrate. (*C*) Adjacent ducts are unremarkable, with tumor arranged in a sheet. (*D*) There is subtle atypia in this central island of tumor, adjacent to a duct and a germinal center.

carcinomas.[90] In most patients, the EBV is specific to the tumor, documented by a strong EBER in the nuclei of the neoplastic cells, but completely lacking in the adjacent normal or uninvolved tissues.[6,32]

DIFFERENTIAL DIAGNOSIS

The histologic appearance of LECSG should bring to mind a variety of undifferentiated lesions that develop in the salivary gland, along with tumors that have a rich inflammatory infiltrate. Depending on the proportions of each element, the differential diagnosis may be different.

When the lymphoid component is dominant, a lymphoepithelial lesion, reactive tumor-associated lymphoid proliferation (TALP), lymphadenoma, Warthin tumor, and lymphoma are all brought to the fore. LESA lacks a destructive infiltration, maintaining a lobular appearance,[56,91] and may have associated clinical and laboratory features of Sjögren syndrome. The lymphoid component can be prominent in these lesions, partly obscuring the epithelial islands, with remnants of the glandular and ductal epithelium seen scattered in the background. However, the ducts and acini affected with LESA do not become cytologically atypical, and lack overt cytomorphologic features of malignancy, showing epithelial and myoepithelial cells within more characteristic patterns, frequently showing squamous metaplasia. LESA or BLEL do not show EBER or LMP1 reactivity, a finding that helps with separation from the EBV-associated LECSG. Clinically, a rapidly enlarging mass over a few weeks favors carcinoma. Clearly in EBV-unassociated LECSG, this test would not be useful. Chronic sclerosing sialadenitis shows marked sclerosing fibrosis, a rich plasma cell infiltration with parenchymal atrophy, known to be part of IgG_4-sclerosing disease.[92] TALP is commonly encountered in acinic cell carcinoma and in mucoepidermoid carcinoma, and

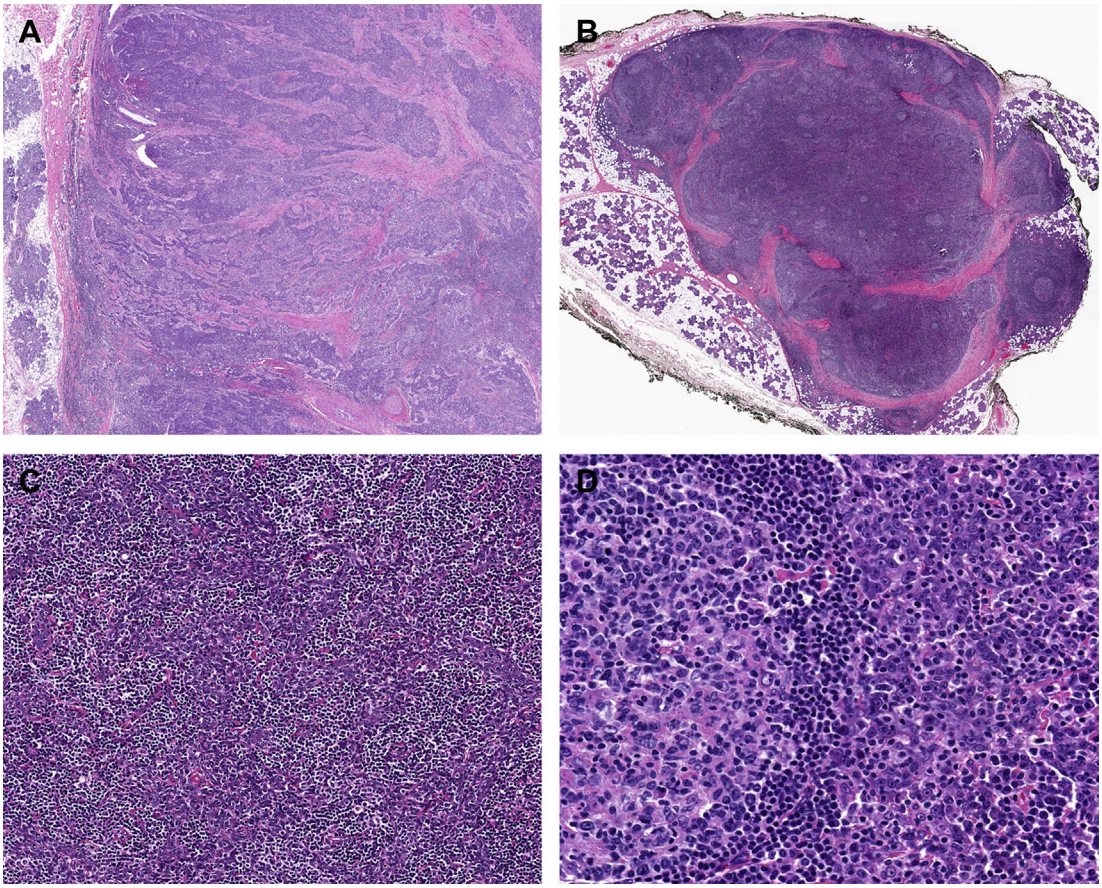

Fig. 7. Classic Schmincke pattern. (*A*) Circumscribed tumor, arranged in sheets with separating fibrosis. (*B*) Multinodular tumor with prominent lymphoid component, showing numerous germinal centers. (*C*) Subtle epithelial component intermixed with the lymphoid cells. (*D*) A germinal center (*left*) as a point of comparison for the neoplastic cells (*right*).

less commonly in lymphoepithelial cystadenocarcinoma. The epithelial elements of an acinic cell carcinoma tend to be more cohesive, lack a syncytial architecture, lack vesicular nuclear chromatin, and usually have cytoplasmic, dark blue zymogen granules.[93–96] The epithelial cells are DOG1, SOX10, and NR4A3 immunoreactive, findings that are not seen in LECSG.[97] Mucoepidermoid carcinoma, especially if higher grade, may have some similarities in growth. However, the transitional epithelium and mucinous differentiation are findings not identified in LEC. The immunohistochemistry findings might be similar (CK-pan, CK5/6, p40, p63), and so, in some instances, a *MAML2* fluorescence in situ hybridization (FISH) evaluation may be the only definitive way to make a separation.[98–102] Lymphadenoma, sebaceous lymphadenoma, and lymphadenocarcinoma (often cystic) are tumors associated with a rich lymphoid infiltrate where the epithelial cells are basaloid, squamous, and glandular, forming solid nests, cords, tubules, and cysts. Sebaceous differentiation is seen in some of these tumors, whereas malignant transformation is rare. In lymphadenoma, the tumors are well defined, lack infiltration, and lack cytologic atypia. There is an even distribution of the epithelial elements within the lymphoid stroma. The tumor cells are negative with EBV markers.[103–105] A Warthin tumor must show oncocytically altered epithelium, usually in a characteristic bilayered, tram-track appearance, with cysts and papillary structures, associated with a rich inflammatory infiltrate. There is no pleomorphism, no vesicular nuclear chromatin, and a lack of EBER.[56,106–108] Although rarely an EBV-associated diffuse large B-cell lymphoma may be seen in a Warthin tumor,[109–111] generally the lymphomas of the salivary gland are either extranodal marginal zone B-cell lymphomas (which are not EBV associated) or diffuse large B-cell

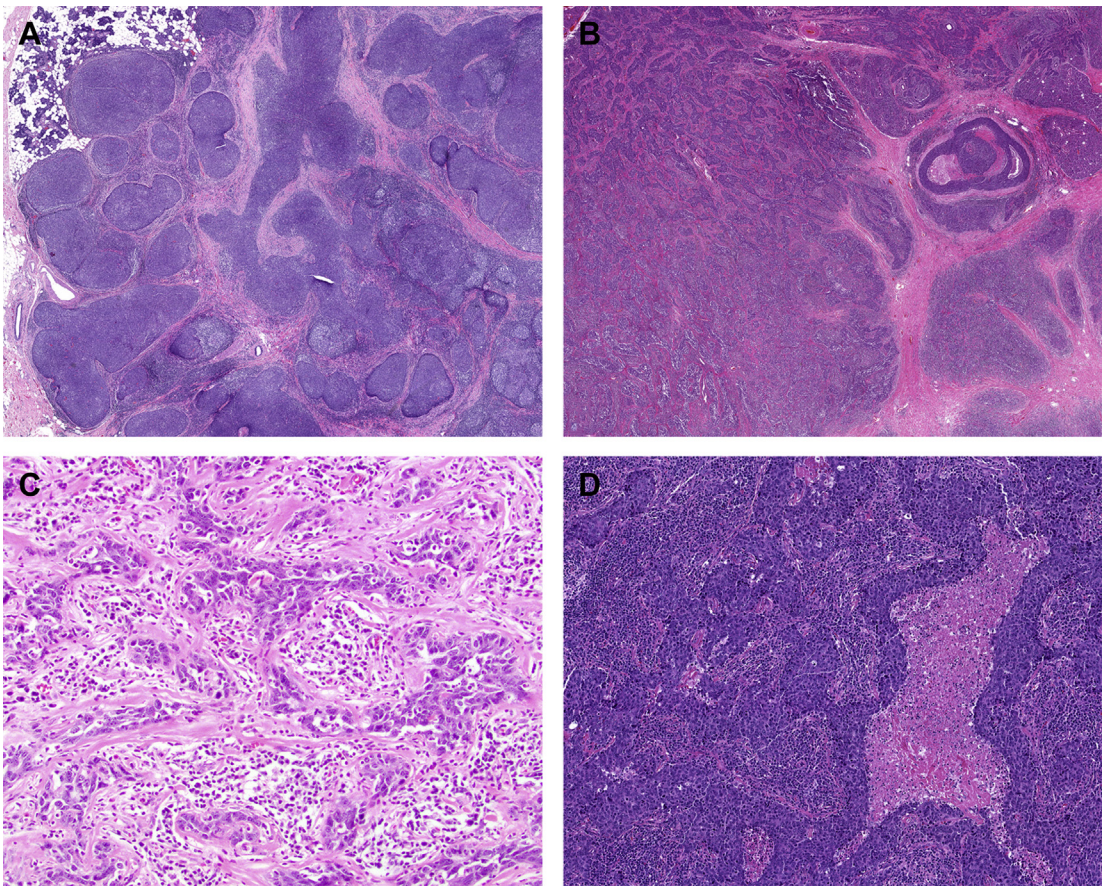

Fig. 8. Classic Regaud pattern (*A*) There are large nests and lobules of tumor. (*B*) Large cell nests separated by heavy fibrosis, creating a jigsaw appearance. (*C*) High-power view of a jigsaw pattern with a more prominent stroma. (*D*) Central area of comedonecrosis surrounded by ribbons of neoplastic cells.

lymphomas, some of which may be EBV associated.[56,112–118] In such cases, the lack of any epithelial markers in a sheetlike tumor population that destroys the native salivary gland parenchyma, and in which it is the lymphoid cells that are reactive with EBV, among other lymphoid markers, can help to confirm a lymphoma diagnosis (including Hodgkin lymphoma).[113,116,119,120]

When the epithelial cells predominate, an undifferentiated or high-grade transformation that may be seen in some primary salivary gland neoplasms and metastatic tumors must be excluded. The most important distinction when LEC is considered is to exclude a metastasis from a nasopharyngeal primary. The highest incidence of NPC is in the same endemic group of patients with the highest incidence of LECSG, and both are EBV associated to a very high degree. As such, clinical, endoscopic, imaging, and even biopsy findings of the nasopharynx must be incorporated to exclude this possibility, with many of the case reports and clinical series in the literature documenting these findings.[4,6,9,10,12,16,21,26,31–33,35,37,38,47,60,74,77,78,88,121] Rarely, a lymphoepithelial pattern may be seen in oropharyngeal squamous cell carcinoma (SCC), usually HPV associated, and salivary gland metastasis may be seen. A strong, diffuse, nuclear, and cytoplasmic p16 reaction in more than 70% of the neoplastic cells and/or ISH for high-risk HPV may be helpful in this setting to confirm an oropharyngeal primary.[122–124] Especially when poorly differentiated, SCC may present as metastatic disease to the parotid gland and lymph nodes. The tumors may not be keratinizing and may have a morphologic appearance that is identical to LEC when presenting in a lymph node. However, most metastatic SCCs to salivary glands are from skin primaries, whereas mucosal primaries are much less common. Skin primaries are not EBER reactive, but are difficult to separate

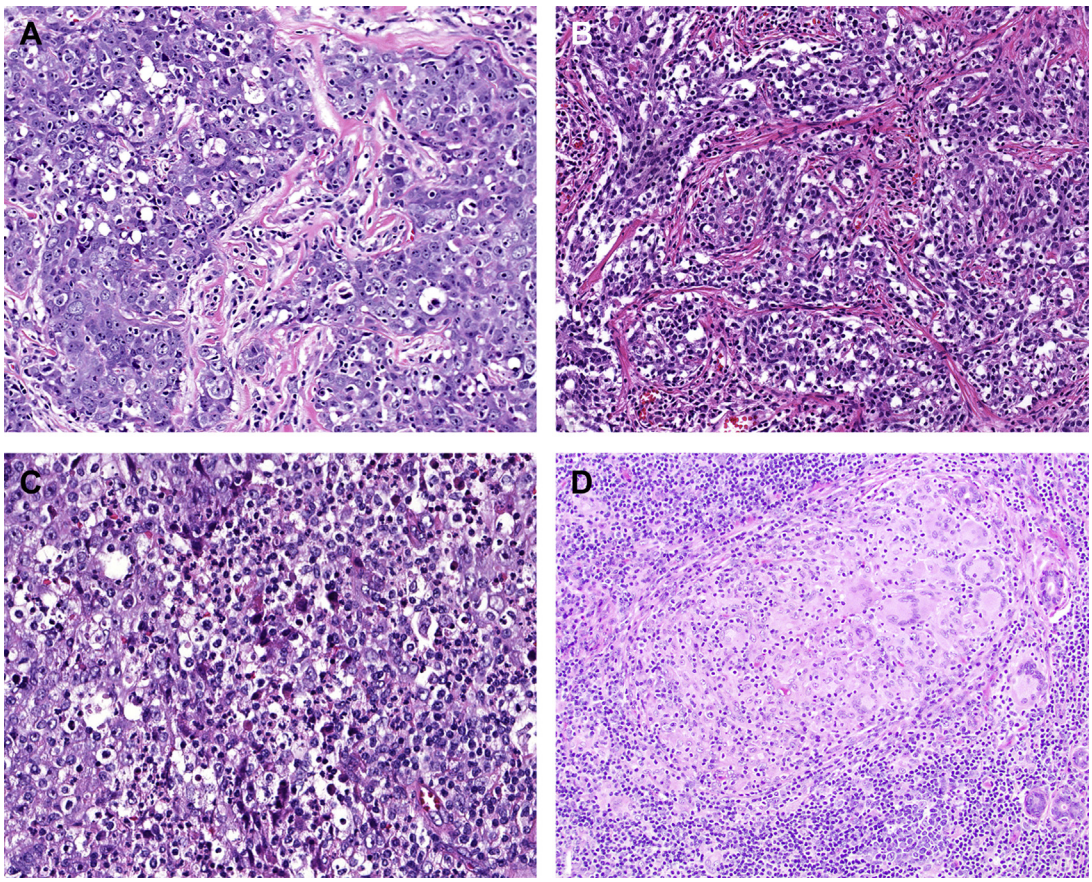

Fig. 9. (*A*) Starry-sky appearance is composed of both lymphocytes and epithelial cells. (*B*) Numerous histiocytic cells create a starry-sky appearance. (*C*) Neoplastic cells adjacent to areas of acute inflammation and histiocytes. (*D*) Multinucleated giant cells with histiocytes are present adjacent to the tumor.

in EBV-negative LECSG. Careful clinical correlation with known skin or mucosal primary SCC must be achieved. NUT carcinoma is exceptionally rare in salivary gland (primary or metastatic), showing poorly cohesive small to medium-sized cells with abrupt and focal squamous differentiation, and must show NUT immunohistochemical reactivity.[125] Adamantinoma-like Ewing sarcoma may be primary in the salivary gland but tend to show a basaloid morphology, infiltrative growth, and nuclear monotony, and tend not to have overt keratinization, while showing CD99 and NKX2.2 reactivity but lacking EBER.[126,127] Poorly differentiated carcinomas of the salivary gland are primary carcinomas that include a large cell undifferentiated category, in addition to neuroendocrine carcinomas. Large cell undifferentiated carcinoma (lacks evidence of glandular, squamous, or neuroendocrine differentiation) has an organoid growth, minimal differentiation, high mitotic rate, and coagulative necrosis, but lacks the lymphoid infiltrate and, by definition, lacks EBV.[60,128–130] Thus, in EBV-negative LECSG, the lack of lymphoid infiltrate helps to make this distinction, which is a challenge if reviewing only core needle samples. Neuroendocrine carcinomas must have neuroendocrine morphologic features as well as neuroendocrine immunohistochemistry, findings usually absent in LECSG. Melanoma metastatic to the salivary gland is usually not cohesive, may contain pigment, and is reactive with various melanocytic markers.[131–136]

TREATMENT AND PROGNOSIS

The optimal management of LEC of the major salivary glands is complete excision with clear surgical margins followed by adjuvant radiotherapy to the tumor bed and neck. Importantly, before therapy is started, exclusion of a nasopharynx primary must be done, otherwise the field for radiotherapy may be underestimated or

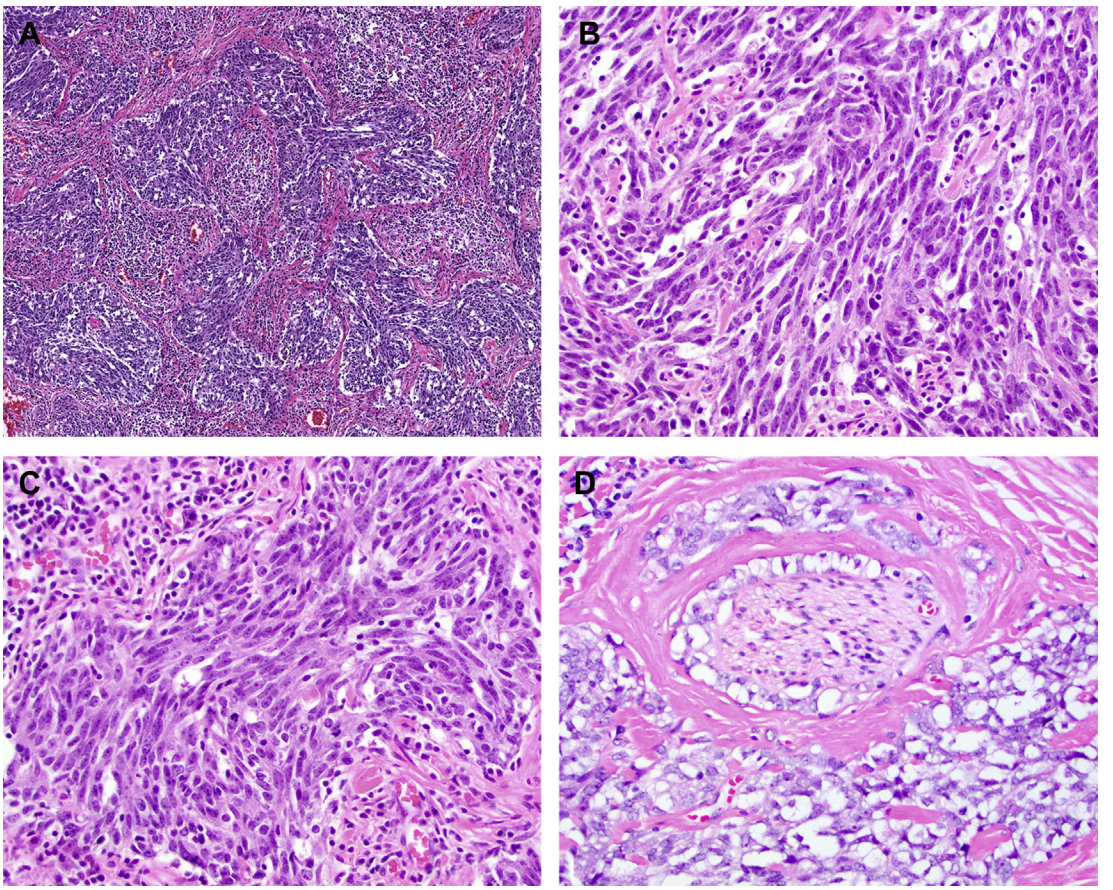

Fig. 10. (*A*) Spindled morphology with a background stroma. (*B*) Spindled morphology with histiocytes. (*C*) Spindled appearance with stippled nuclear chromatin. (*D*) Perineural invasion is easily identified.

incorrect. Several series showed that wider surgical excisions decreased the progression-free survival, and neck fibrosis was seen in patients treated with radical neck dissection, suggesting that aggressive and extended resections do not aid in tumor control or improved patient outcome.[16,34,47,121]

At the time of presentation, about 17% of patients have cervical lymph node metastases (see **Table 1**).[6,12,13,21,24,33,34,38,60,69,74,88,129,137–144] The intra–salivary gland lymph nodes are affected primarily (peripheral lymph node metastasis or by direct invasion from adjacent salivary gland), followed by the upper cervical lymph node chains, and then other lymphatic drainage basins of the neck, including the supraclavicular nodes. Imaging findings during work-up, especially to exclude a nasopharyngeal primary, usually highlight abnormal lymph nodes. Although personalized to the individual patient and local practices, elective neck dissections are not usually indicated, reserved for biopsy-proven metastases or suspicious findings on imaging.[6,21,34,60,88] Lymph node status at presentation, extra–salivary gland extension, and marginal status do not seem to affect prognosis.[47,49] Although radiation is generally used after surgery, combination surgery and radiation therapy is only documented in 156 of 438 patients reported in the literature (see **Table 1**). It may be that therapy was excluded from the article, data was aggregated, or the treatment and outcome were not the end points of the evaluation. Suffice it to say that large clinicopathologic series included radiation in the management,[4,6,12,20,21,24,26,32,37,38,49,60,74,82,88] and it is well known that LEC is highly radiosensitive with high rates of locoregional tumor control. However, additional study is needed to establish the appropriate radiation field and dose for LECSG.[35] It has been suggested that submandibular gland tumors tend to present at higher stages and are associated with worse outcome,[47] but, when the aggregated literature is reviewed, only 3 of 36 reported patients had developed local or

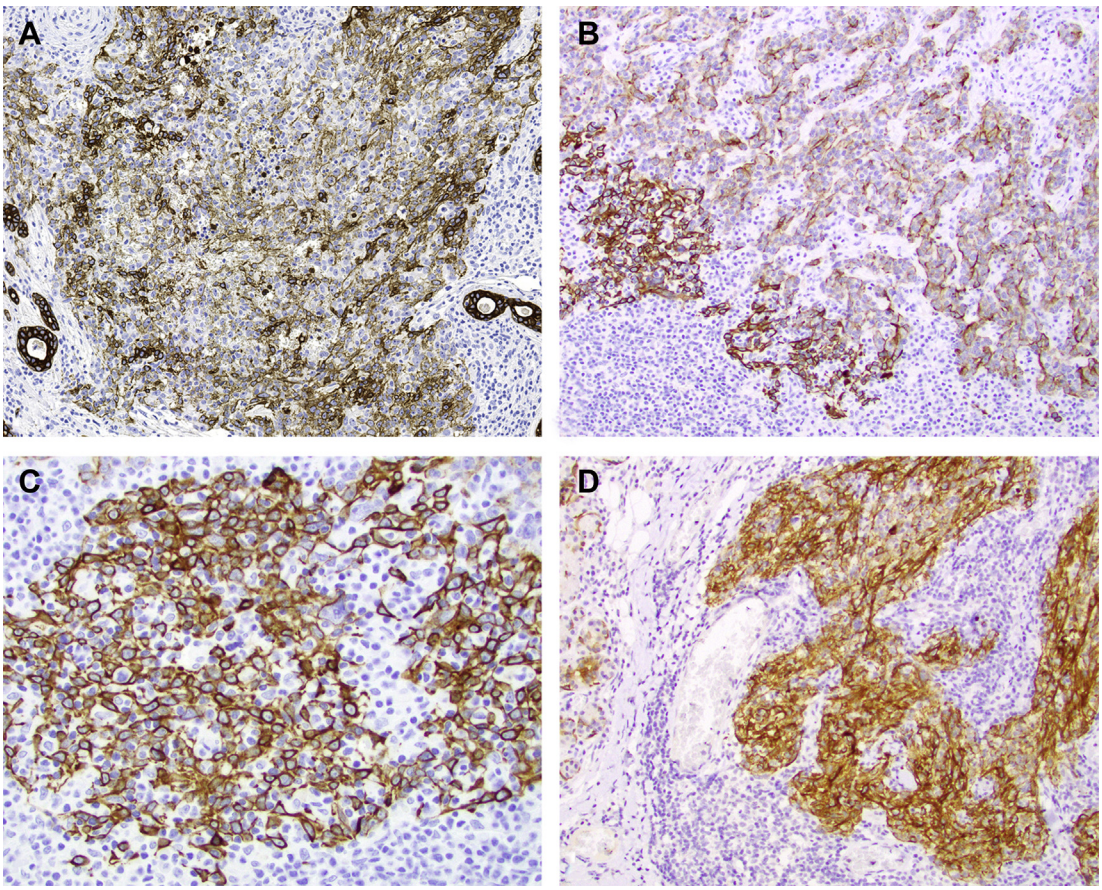

Fig. 11. Variable reactivity in the neoplastic cells with: (*A*) pancytokeratin in a solid to latticelike reaction; (*B*) reactivity with AE1/AE3 shows a strong to more patchy reactivity; (*C*) diffuse cytoplasmic reaction with keratin; (*D*) CK5/6 shows a strong membranous reactivity.

metastatic disease, and 2 had died with disease (6%), which is lower than the 26 of 141 who had died of disease overall (18.4%). Overall, 26 of 438 patients developed distant metastasis (5.9%), which was strongly correlated with death caused by the disease (69%).[2,6,24,32,34,38,47,49,60,69,88,129,145] This trend was observed more in patients from endemic areas than in those from nonendemic areas.[47] When distant metastases are identified, they are most common to lung, bones, liver, kidney, brain, spleen, and mediastinum.

When aggregating the literature (follow-up available in 141 patients), 114 of 141 patients were alive (mean follow-up of 60.7 months), whereas 22 of 141 were dead with disease (mean follow-up, 46.2 months), suggesting an overall 81% 5-year raw survival (see **Table 1**).[16,34,44,47,60,66,73,137,146] Therefore, it seems that lymph node metastases do not alter outcome, with a generally excellent response of this tumor type to radiotherapy. The tumor category has a better prognosis than other undifferentiated carcinomas of the salivary gland (such as neuroendocrine carcinoma, NUT carcinoma, metastatic SCC), and thus correct classification is warranted in order to appropriately treat these uncommon neoplasms.

SUMMARY

Irrespective of race or ethnicity, LECSG may express EBER and is sensitive to radiation. Concurrent lymphoepithelial lesions may help suggest a primary tumor; even so, it cannot be emphasized enough that a clinical evaluation for an alternative primary should be performed. There is overall good survival, especially because of tumor radiosensitivity.

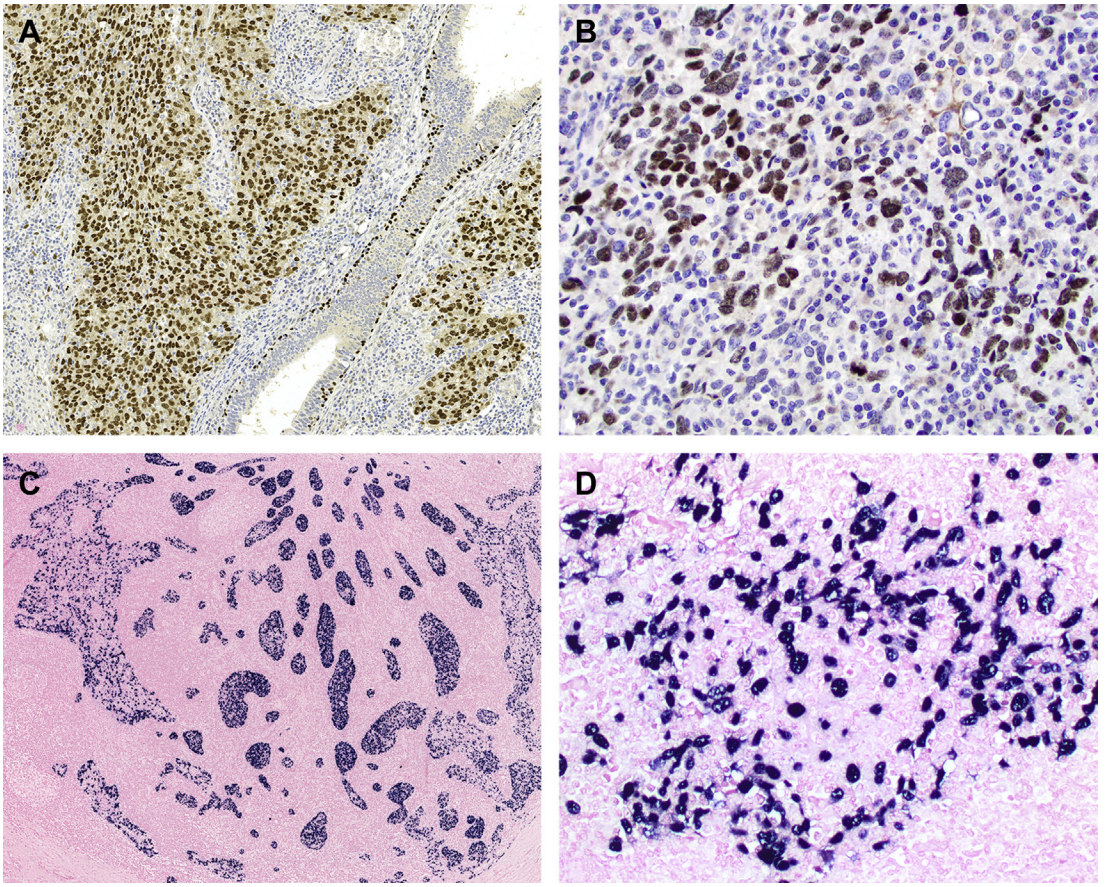

Fig. 12. (*A*) There is a strong reactivity with p63 in the neoplastic cells (basal internal control in the duct). (*B*) p40 highlights the individual neoplastic cells within the background lymphoid stroma. (*C*) Two patterns of reactivity with EBER in situ hybridization (ISH), highlighting the 2 major patterns of growth. (*D*) Single, atypical neoplastic cells show strong EBER-ISH reactivity.

CLINICS CARE POINTS

- Exclusion of a primary tumor outside of the salivary gland is paramount. These tumors are sensitive to radiation but the primary must be included in the field of treatment.
- Concurrent lymphoepithelial lesions may help suggest a primary tumor; even so, it cannot be emphasized enough that a clinical evaluation for an alternative primary should be performed.

Pitfall

! Morphology, immunohistochemical stains, and EBER-ISH are insufficient to distinguish lymphoepithelial carcinoma from nasopharyngeal carcinoma, which requires clinical evaluation.

DISCLOSURE

Both authors declare that they have no conflict of interest related to this research project. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of Southern California Permanente Medical Group.

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