Epithelioid Cell Clusters With an Extensive Lymphoid Background

A Common Cytologic Architectural Pattern in the Diagnosis of Salivary Gland Lesions by Fine-Needle Aspiration Biopsy

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- **Context.**—Fine-needle aspiration of salivary gland lesions can be particularly challenging for pathologists. There are numerous neoplasms that occur in this area and several cytologic variations of each specific lesion.

- **Objective.**—To present and discuss a practical pattern recognition approach to fine-needle aspiration diagnosis, which includes categorizing lesions that share a certain overall cytologic architectural pattern, followed by identifying unique cellular characteristics that are specific to a certain lesion. An extensive discussion of one cytologic common pattern of salivary gland lesions, “epithelioid cell clusters with an extensive lymphoid background,” is presented. The pathologic entities that fall under this architectural pattern group are discussed, with an emphasis on neoplasms.

- **Data Sources.**—Published literature and personal experience.

- **Conclusions.**—A practical cytologic architectural pattern method can aid the pathologist in rendering a correct diagnosis when evaluating salivary gland lesions. One common pattern in salivary gland cytopathology is epithelioid cell clusters with an extensive lymphoid background. This pattern is often associated with Warthin tumor; however, other benign and malignant entities fall under this diagnostic group. Unique cytologic features separate these lesions into their respective diagnostic category.

Fine-needle aspiration (FNA) biopsies of salivary gland lesions are some of the most challenging for pathologists, because of the sheer number and complexity of pathologic processes that occur in these organs. The traditional method of approaching these lesions is to familiarize oneself with (or memorize) all the cytologic features of these various lesions and apply the knowledge of those characteristics to render a diagnosis. This approach to diagnosis can be successful if the observer is aware of most or all of the cytologic variations of these complex lesions, a daunting task, especially for processes that do not present with “classic features” of that specific lesion. A consistent approach to diagnosis is to categorize lesions that share a certain overall pattern first and then differentiate those processes in that category by unique characteristics specific to a pathologic process. I term this the practical pattern recognition approach to FNA diagnosis. These patterns do not necessarily rely on the presence of a specific cell type, for instance, oncocytic cells in the case of an oncocyotoma. For example, a cytologic pattern may include a specific type of architectural structure that the tumor cells and associated stromal cells or blood vessels exhibit, such as a papillary structure. Another pattern may encompass the interrelationship that clusters of neoplastic cells have with surrounding blood vessels, stromal tissue, extracellular matrix, or inflammatory cells. This approach first emphasizes grouping pathologic processes with an element or elements that they have in common with one another and then subdividing these processes into their respective diagnostic categories based on their unique cellular characteristics. This diagnostic approach includes recognition of a cytologic pattern by examining a case on low to intermediate magnification (×40, ×100, or ×200), followed by identifying unique characteristics of a specific lesion with high-power magnification (×400, ×600). This is intuitive to many experienced cytopathologists; however, it is all too easy to rush to high-power magnification when examining a case, carrying the risk of “missing the forest for the trees.”

Salivary gland lesions can fall into several cytologic patterns on FNA cytology. One such pattern that is relatively common in the case of salivary gland lesions is as follows: “epithelioid cell clusters with an extensive lymphoid background” (Figure 1). Pathologists often associate this pattern with a diagnosis of Warthin tumor; however, this pattern also applies to several other nonneoplastic and neoplastic entities within salivary glands, both benign and malignant, as outlined in the Table. This article focuses particularly on neoplasms of the salivary glands that are associated with an extensive lymphoid component and the unique cellular characteristics that subdivide these lesions.
BENIGN NONNEOPLASTIC LESIONS WITH EXTENSIVE LYMPHOID COMPONENT

Chronic Sialadenitis

Nonneoplastic enlargement of the salivary glands is often due to an inflammatory process. Chronic sialadenitis is often a manifestation of lithiasis or other obstruction of the salivary gland ducts. The obstruction may result in an abnormal swelling of the gland leading to a biopsy.

On FNA, the chronic inflammatory infiltrate often consists of a mixed population of lymphocytes admixed with varying small clusters of acinar cells and ductal epithelium. The number of acini may be reduced in number, atrophic, or absent altogether, depending on the duration and severity of the inflammatory process. The aggregates of ductal cells often have blunted, sharp edges (Figure 2, A and B). Squamous metaplasia of the ductal epithelium may be present, raising the suspicion of a squamous or mucoepidermoid carcinoma. However, the degree of atypia and cellular discohesion is less in chronic sialadenitis as compared with these malignant alternatives. One should keep in mind that areas of chronic sialadenitis may be present adjacent to a neoplastic process, stressing the importance of sampling any lesion adequately.

Chronic Sclerosing Sialadenitis (Kuttner Tumor)

Chronic sclerosing sialadenitis often exclusively involves the submandibular gland, occasionally with a bilateral presentation. In its advanced stage, it can mimic a firm salivary gland neoplasm. The mean age of presentation is in the 40s age group with a slight male predominance. The lesion is characterized by a chronic inflammatory process of the submandibular gland with peri-

| Differential Diagnosis of Lymphoid-Rich Epithelial Lesions of the Salivary Glands |
|-----------------------------------------|---------------------------------|-------------------------------|--------------------------------|
| **A. Benign: Nonneoplastic**            | **B. Malignant**                | **C. Metastatic**              | **D. Miscellaneous** |
ductal fibrosis, loss of acini, and eventually marked fibrosis of the gland.

Fine-needle aspiration of this lesion is characterized by relatively low numbers of epithelial groups, possibly resulting from extensive fibrosis. The smears show a moderate to marked chronic inflammatory infiltrate with scattered ductal structures, with a paucity of acini. The ductal structures often are surrounded by collagen sheaths or lymphoid cells. The findings resemble those of usual cases of chronic sialadenitis with the exception that fragments of sclerotic material may be more prominent (Figure 3, A and B).

This lesion can be confused with lymphoepithelial sialadenitis. Kuttner tumors can be distinguished from lymphoepithelial sialadenitis by the lack of lymphoepithelial lesions and more prominent sclerosis.

**Lymphoepithelial Sialadenitis**

(Lympheoepithelial Lesion)

Lymphoepithelial sialadenitis is previously known as myoepithelial sialadenitis or benign lymphoepithelial lesion. The lesion presents as a recurrent, diffuse, firm enlargement of the salivary glands, with the parotid being the most affected. A significant number of patients with this condition are female, with Sjögren syndrome. There is a risk for the development of lymphoma, particularly those of extranodal marginal zone B-cell type. Lymphoepithelial sialadenitis is characterized by an infiltration of the salivary gland by lymphoid cells. This lymphoid infiltration is associated with a hyperplasia and metaplasia of the ductal epithelium resulting in lymphoepithelial aggregates.

Fine-needle aspirates of this lesion show the presence of a mixed population of lymphocytes, including the occasional presence of germinial centers and plasma cells. The scattered epithelial groups are characterized by tight, cohesive ductal structures or flat, monolayered sheets of epithelial cells that are surrounded or infiltrated with lymphocytes. Acriar groups are often not present (Figure 4).

This lesion may be confused with Warthin tumor. However, Warthin tumors are characterized by aggregates of oncocyes and usually are associated with a more monomorphic population of lymphocytes as compared with the lymphoid population in lymphoepithelial sialadenitis. The oncocytic clusters of Warthin tumors are usually not associated with lymphocyte infiltration either.

A monomorphic proliferation of lymphocytes in a setting of lymphoepithelial sialadenitis should raise the concern of an extranodal marginal B-cell lymphoma, especially if there has been a recent acceleration of growth of the mass. Additional FNA or tissue biopsy material for flow cytometric studies should be considered in such a case.

**Benign Lymphoepithelial Cyst**

Benign lymphoepithelial cysts are most common within the parotid gland. Most patients are older than 30 years, with no sex predilection. The non–human immunodeficiency virus related lesions are usually unilateral and unicystic. Human immunodeficiency virus–associated lesions may present with simultaneous or subsequent bilateral parotid lesions, sometimes associated with significant cervical adenopathy.

Aspirates often yield cystic debris admixed with a mixed population of lymphocytes, histiocytes, and epithelial cells. The epithelial component may consist of squamous, cuboidal, columnar, or ciliated cells; however, squamous epithelium is encountered most commonly.

Other cystic neoplasms, such as Warthin tumor and mucoepidermoid carcinomas, should be considered when confronted with features of a benign nonneoplastic cystic lesion. Any residual mass after a cystic lesion has been aspirated should be rebiopsied to rule out an associated neoplastic process.

**Benign Salivary Gland Neoplasms with Extensive Lymphoid Component**

Warthin Tumor (Papillary Cystadenoma Lymphomatosum)

Warthin tumor is perhaps the most recognized epithelial neoplasm within the salivary glands that is associated with lymphoid component. This neoplasm accounts for approximately 5% of all salivary gland epithelial tumors and is most commonly found within the parotid gland, often within the lower pole. These lesions account for approximately 12% of all parotid benign tumors. Most patients are within the fifth to sixth decades of life. The male-female sex incidence of this neoplasm appears to have changed during the last 50 years. During the 1950s, the male-female ratio was reported as 10:1; however, the reported male-female during the 1990s has ranged from 1.2 to 1.6. Warthin tumor can occur bilaterally, more commonly sequentially than simultaneously.

Warthin tumors present as soft, fluctuant, slowly growing masses that are usually painless. The lesions are often 2 to 3 cm in size, often situated at the angle of the mandible. Warthin tumor can also arise in periparotid and intraparotid lymph nodes. Rare cases of Warthin tumor within the parapharyngeal space have been reported, the result of deep parotid lobe involvement.

Aspiration of a Warthin tumor often yields cloudy, turbid fluid, especially in larger lesions. Under low magnification, the tumor is characterized by variably sized clusters of epithelial cells with large nuclei that are surrounded by a relatively abundant amount of cytoplasm; hence, a relatively low nuclear-cytoplasmic ratio of the neoplastic cells. The clusters of neoplastic cells are often present within a background of relatively monomorphic or less commonly polymorphic, lymphoid cells, admixed with granular debris (Figure 5, A and B). Confirmation that the background cell population comprises lymphocytes, and not stripped nuclei of epithelial cells, is an important step to make the diagnosis. Crushed lymphoid streaks may also be closely associated with the oncocytic cell groups. One should keep in mind that the ratio of granular debris, lymphocytes, and clusters of epithelial cells is highly variable from case to case. On higher magnification with Papanicolaou stain, the epithelial cells are recognized as true oncocyes by their well-defined cytoplasmic borders, granular cytoplasm, and central round nuclei with prominent nucleoli. The epithelial cells may have a round to columnar shape. The cytoplasm on Papanicolaou stain is cyanophilic, whereas it is often blue or grey on Romanowsky stains. Identifying well-defined cytoplasmic borders within clusters of oncocytic cells is critical in making a diagnosis, because intermediate cells of mucoepidermoid carcinomas can have similar abundant cyanophilic or blue grey cytoplasm on Papanicolaou and air-dried stains, respectively. However, intermediate cells of mucoepidermoid carcinomas are often present in syncytial groups.
with poorly defined cytoplasmic borders. In my experience, examination of the clusters of the epithelial cells with increased contrast (without the microscope condenser in place and/or partially closing the annulus of the condenser) often helps identify the definite cytoplasmic borders of oncocytes (Figure 6, A and B). This simple technique works particularly well on alcohol-fixed material. The presence of mast cells in conjunction with oncotypic cells is also a clue for a diagnosis of Warthin tumor.10

Warthin tumors may also demonstrate focal areas of squamous (including nonkeratinizing and keratinized cells), mucinous, and sebaceous metaplasia, including metaplastic cells that have significant nuclear atypia7,8 (Figure 7). The presence of these metaplastic cells may lead to confusion with other tumors such as squamous and mucoepidermoid carcinomas, and sebaceous adenomas and carcinomas. Of note, squamous and mucinous metaplasia within Warthin tumors is usually a localized finding. Definitive confirmation of the presence of abundant oncocytes in Warthin tumor can also avoid misdiagnosis in such a case.

Warthin tumors may also be confused with lymphoid-rich acinic cell carcinomas, especially under low to intermediate magnification.11 Although acinic cell cytoplasm often appears finely vacuolated under high magnification in contrast to the granular cytoplasm of oncocytes, there are times when these 2 neoplasms may be indistinguishable from each other. A diagnosis of “salivary gland epithelial neoplasm with lymphoid tissue; the differential diagnosis includes a Warthin tumor versus acinic cell carcinoma” may be prudent in such a case. Attention to the clinical history, such as the presence of pain, may favor the diagnosis of acinic cell carcinoma. As mentioned previously, Warthin tumor are often painless, whereas 30% of acinic cell tumors present as a painful lesion.8 Additional methods to distinguish these 2 lesions are discussed in the following section about acinic cell carcinomas.

**Sebaceous Lymphadenoma/Lymphadenoma**

Sebaceous lymphadenomas are rare benign tumors, representing approximately 0.1% of salivary gland neoplasms in the Armed Forces Institute of Pathology files.7 Most patients with this neoplasm are 50 to 80 years of age, although patients in their 20s have been reported. The vast majority of these tumors are found within the parotid gland or within the periparotid area. This lesion usually presents as an encapsulated, painless mass.

On histologic examination, the tumor is solid or cystic

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**Figure 5.** Warthin tumor. Clusters of oncocytes in a lymphoid background at low magnification (Papanicolaou, original magnification ×100 [A]; May-Grünwald Giemsa, original magnification ×100 [B]).

**Figure 6.** A cluster of oncocytes in Warthin tumor. A, With microscopic condenser (Papanicolaou, original magnification ×400). B, Without microscopic condenser. Note the well-defined cytoplasmic borders of the oncocytes with the increased contrast of the image (Papanicolaou, original magnification ×400).
Figure 7. Warthin tumor with mucinous metaplasia, demonstrated by the presence of mucin “target vacuoles” (arrowhead) (Papanicolaou, original magnification ×400).

Figure 8. Sebaceous lymphadenoma. A, Intermediate magnification showing the presence of smaller basaloid epithelial cells surrounded by larger foamy sebaceous cells, admixed with a background of lymphocytes (Papanicolaou, original magnification ×200). B, High magnification of sebaceous cells with bland nuclei surrounded by an abundant amount of foamy cytoplasm (Papanicolaou, original magnification ×600). C, Clusters of sebaceous cells (May–Gru¨nwald Giemsa, original magnification ×400).

and is composed of variably sized aggregates of sebaceous cells with possible squamous differentiation, admixed with ductal structures, in a background of lymphoid cells. A histiocytic-rich foreign body giant cell reaction in response to extravasated sebaceous material may be present.8

Reports of sebaceous lymphadenomas on aspiration cytology are rare. Three-dimensional clusters of epithelial cells are present, composed of sebaceous cells with vacuolated cytoplasm, surrounded by basaloid cells. There is a background of lymphoid cells, including plasma cells and tingible body macrophages (Figure 8, A through C).12 The epithelial cells are bland; mitotic figures are usually absent. These latter features help distinguish this benign neoplasm from its malignant counterpart, sebaceous lymphadenocarcinoma (to be discussed later in this article). Sebaceous lymphadenomas may also be confused with Warthin tumor on aspiration biopsy, especially in cases of Warthin tumor in which a minor component of sebaceous differentiation exists. Sebaceous lymphadenomas are usually devoid of oncocytic cells, as compared with Warthin tumors. In addition, sebaceous cells are much more numerous in cases of sebaceous lymphadenomas.

Lymphadenomas are rare neoplasms that show features of a salivary gland adenoma accompanied with a dense lymphoid infiltrate.13 These tumors resemble sebaceous lymphadenomas without evidence of sebaceous differentiation, hence the name nontsebaceous lymphadenoma.7 It is postulated that lymphadenoma is not a specific type of neoplasm but possibly a basal cell adenoma or cystadenoma with a dense lymphoid infiltrate.13 Histologically, this tumor is composed of epithelial aggregates, trabeculae, solid tubules, and cystically dilated glands filled with proteinaceous material or papillary structures. In some cases, the lymphoid population is so dense that the epithelial component is obscured. Periodic acid–Schiff with diastase can be used to visualize the basement membrane–like material around the epithelial clusters. The tumor cells are cuboidal to columnar without significant cytologic atypia. Reports of aspiration cytology of this lesion are very rare. The tumor has been mistaken for Warthin tumor on FNA.14 Lymphadenomas by definition do not contain classic oncocytic cells. More importantly, these tumors may resemble the malignant neoplasm, lymphoepithelial carcinoma. Lymphoepithelial carcinomas show a greater degree of cytologic atypia, mitotic rate, and necro-
sis, as compared with lymphadenomas. In addition, differentiation occurs along the squamous line in lymphoepithelial carcinomas in contrast to lymphadenomas that display differentiation along the glandular cell line. There is no known association with Epstein-Barr virus with lymphadenomas, in contrast to some cases of lymphoepithelial carcinomas.13

MALIGNANT SALIVARY GLAND NEOPLASMS WITH EXTENSIVE LYMPHOID COMPONENT

Mucocellular Carcinoma

Mucocellular carcinomas are the most common malignant neoplasm in adults and children; the mean age for presentation is within the fourth decade, with a slight female predilection. The parotid gland and the palate are the 2 most common sites of involvement with this tumor. Many of these tumors present as a painless slow growing mass, occasionally with a recent significant increase in size. A tumor associated with pain, skin fixation, or ear drainage may suggest a more aggressive lesion. Lower-grade tumors are more commonly associated with a cystic component, whereas higher grade lesions are often solid.

These tumors are often challenging dilemmas on both histologic and cytologic specimens. By definition, mucocellular carcinomas are a combination of neoplastic mucinous cells, intermediate cells, and epidermoid cells. The diagnosis in low-grade tumors requires confirmation that intermediate cells are present. These small-sized to medium-sized cells often have intermediate to high nuclear-cytoplasmic ratios. The cytoplasm of intermediate cells is often dense and homogenous, resembling squamous metaplastic cells. The oval to round nuclei may appear deceptively bland in low-grade tumors, in contrast to the irregular and pleomorphic nuclei in high-grade carcinomas. Lower grade lesions are often characterized by a higher proportion of mucinous and intermediate cells as compared with higher grade lesions that are composed primarily of intermediate and epidermoid cells.

Mucinous cells are also an important component to recognize when making a diagnosis of mucocellular carcinoma. Mucinous cells vary in proportion to intermediate cells, depending on the grade of the tumor. The mucinous cells in mucocellular carcinomas may resemble bland, foamy histiocytes and can be misinterpreted as features diagnostic of a benign retention cyst. A clue to the recognition that these cells are epidermal in origin is the clustering or cohesiveness of these histiocyte-like cells on aspiration cytology. The presence of “foam cells” intercalated in between intermediate cells is also an important diagnostic clue. Mucinous cells may also present as signet cells, with or without the presence of intracytoplasmic mucin “target vacuoles.” However, the presence of mucinous cells by themselves should not be considered diagnostic of a mucocellular carcinoma, because mucinous metaplasia can be observed in other benign processes including Warthin tumors as previously discussed. In addition, one should realize that the quantity of extracellular and intracellular mucin is not a reliable method to help distinguish mucocellular carcinomas from Warthin tumors either.15

In my experience, the most common misdiagnosis when dealing with a low-grade mucocellular carcinoma is confusing this lesion with a Warthin tumor. Many pathologists are not aware that, in a significant number of cases, lymphoid tissue can be associated with mucocellular carcinomas.16 On histologic specimens, this lymphoid tissue corresponds to a lymphoid host response surrounding the invasive border of tumor, with the center of tumor being devoid of lymphocytes. On aspiration, the population of lymphoid cells is often dispersed in the background, admixed with clusters of mucinous or intermediate cells. The density of lymphoid cells can vary from a relatively sparse to an abundant number of lymphocytes (Figure 9, A and B). The presence of lymphoid cells and relatively bland clusters of intermediate cells in low-grade tumors may lead to the misdiagnosis of a Warthin tumor. A useful clue is to recognize that the intermediate cell cytoplasm of mucocellular carcinomas is dense and homogeneous, in contrast to the granular cytoplasm of oncocyte cells in Warthin tumors (Figure 10). In addition, when examining syncytial groups of intermediate cells with increased contrast, one should note the difficulty in demonstrating the presence of distinct cytoplasmic borders of intermediate cells, in contrast to the well-defined cytoplasmic borders found in clusters of oncocytes in Warthin tumors. Occasionally, the glandular cells of low-grade mucocellular carcinomas may mimic oncocytes. Careful examination of these cells reveals a foamy, histiocyte-like appearance of the cytoplasm of these glandular cells, in contrast to the more densely granular character of oncocyte cytoplasm (Figure 11). The presence of vacuolated mucinous cells within a salivary gland aspirate should suggest the possibility of a mucocellular carcinoma; however, one should keep in mind that scattered metaplastic mucinous cells may be present in a Warthin tumor.

Fortunately, high-grade mucocellular carcinomas are usually not confused with benign neoplasms such as Warthin tumor, because of the obvious malignant nature of the intermediate and epidermoid cells. Higher-grade tumors often have a greater proportion of malignant-appearing epidermoid cells, occasionally with keratinized cytoplasm (Figure 12). The challenge of high-grade tumors with an extensive lymphoid background is not making the diagnosis of malignancy but recognizing the tumor as a mucocellular carcinoma versus a high-grade primary or metastatic carcinoma. The presence of mucin-producing cells favors a mucocellular carcinoma in such a case (Figure 13). The use of mucin-stains such as a mucicarmine stain or periodic acid–Schiff with diastase can help illustrate the rare mucin-producing glandular cells in high-grade tumors. Abundant keratinization and the presence of keratin pearls often favors a squamous cell carcinoma17 and most likely represents a metastatic lesion. In some cases, it is difficult to differentiate between other high-grade primary or metastatic lesions. A diagnosis of a “high-grade non–small cell carcinoma” with a list of diagnostic possibilities should be considered in such a case.

Acinic Cell Carcinoma

Acinic cell carcinomas account for approximately 6% of all salivary gland neoplasms and are the fourth most common salivary malignant neoplasm, following mucoepidermoid carcinomas, adenocarcinoma not otherwise specified, and adenoid cystic carcinoma. The majority of acinic cell carcinomas are found in the parotid gland (84%), followed by the submandibular gland, buccal mucosa, lip, and palate. There is a slight predilection for women with an average age of presentation of 44 years. The tumor often presents as slowly enlarging mass within the parotid...
gland for months to even years. Intermittent pain or tenderness is present in about 30% of patients.

By definition, acinic cell carcinomas recapitulate serous differentiation, at least focally. Clear cells and nonspecific ductal-like cells can also be observed. Aspirates are often hypercellular, comprised of variably sized aggregates of bland-appearing acinar cells with finely granular cytoplasm. The cytoplasm of the tumor cells is often very fragile during smear preparation. This feature of acinar cells often results in the presence of scattered bare tumor nuclei in a finely granular background. These bare nuclei should not be confused with lymphoid cells. The groups of tumor cells are devoid of the adipose tissue and ductal structures associated with normal salivary gland acinar groups. In addition, the distribution of the acinar tumor groups is generally haphazard as compared with normal salivary gland; however, microacinar groups and rosettelike structures may be present. The groups of tumor can be intimately associated with thin-walled blood vessels in a perivascular pattern. Acinar cell cytoplasm is usually finely granular, light green to gray on Papanicolaou stain and pink to light magenta on air-dried preparations. The cytoplasm of the tumor cells may be dense, resembling oncocytes. The nuclei are often eccentrically located, usually with relatively low nuclear-cytoplasmic ratios with mild anisonucleosis. Occasionally the cells have a foamy, clear cell appearance.

A real diagnostic challenge occurs when acinic cell carcinomas are associated with lymphoid cells (Figure 14). A recent study found that lymphoid cells are present in approximately one third of cases, with a predominant lymphoid pattern in 10% of cases. Auclair mentions that the presence of a lymphoid host response is so frequent in acinic cell and mucoepidermoid carcinomas in the parotid that perhaps it could be considered an expected finding. When abundant lymphoid cells are present, and the acinar cells present have dense cytoplasm, a misdiagnosis of Warthin tumor can be made. Acinic cell carcinomas generally do not have the distinct cytoplasmic borders of true oncocytes within a Warthin tumor; however, focal honeycomb areas are sometimes seen. Acinic cells can be distinguished from oncocytes by the presence of azurophilic granules with air-dried stains; however, the presence of these granules, especially with Papanicolaou stain, can be deceptively subtle. The cytoplasm of acinic cell neoplasms often show a more foamy, clear cell appearance with Papanicolaou stain as compared with oncocytes within a Warthin tumor. In addition, the granules within the acinic cells are often periodic acid–Schiff–diastase resistant, in contrast to the oncocyic cytoplasm of Warthin tumors.

Cases of chronic sialadenitis can mimic acinic cell carcinomas, especially when acinar cell groups are present with lymphoid cells; however, a misdiagnosis can be
Lymphoepithelial Carcinoma

Lymphoepithelial carcinoma is a rare lesion that affects those of Chinese, Eskimo, and Greenlander decent, much higher than Caucasians,19,20 and is often associated with the presence of Epstein-Barr virus infection,21,22 especially where Epstein-Barr virus is endemic. The tumor only comprises 0.4% of salivary gland neoplasms in nonendemic areas.7,23 The mean age of presentation is approximately 45 years,24 with no male or female predominance. The lesion is most commonly found within the parotid gland (82% of cases), followed by the submandibular gland, and often presents as a painless swelling, from 1 to 10 cm in size.7 In advanced cases, skin or underlying tissue fixation may occur; associated pain or discomfort is common, and nerve palsy occurs in approximately 20% of patients. Lymphoepithelial carcinoma is associated with regional node involvement in approximately 40% of cases. Despite this statistic, this tumor has the best prognosis among undifferentiated carcinomas with survival figures of approximately 75% to 85% with combined radiation and chemotherapy.24 Recent studies also indicate that there is no association between benign lymphoepithelial lesions and lymphoepithelial carcinomas.

Lymphoepithelial carcinomas of the salivary glands morphologically mimic lymphoepithelial carcinomas in other parts of the body, especially sinonasal undifferentiated carcinoma.25 The presence of metastatic lymphoepithelial carcinomas to the intrasalivary and perisalivary gland lymph nodes is a more frequent occurrence than a lymphoepithelial salivary gland primary. Distinction between primary and metastatic lesions may depend on clinical and radiographic findings.

Although the tumor may present as a circumscribed mass, most lesions are infiltrative into surrounding salivary gland, soft tissue, or skin.7 Aspirates from these lesions are characterized by the presence of single and clusters of high-grade neoplastic cells admixed with a mature...
lymphoid population. The tumor cells often have high nuclear-cytoplasmic ratios, granular chromatin patterns, with single prominent nucleoli. The cytoplasmic borders of the neoplastic cells can be indistinct when in groups, similar to intermediate cells of mucoepidermoid carcinoma. The tumor cells can occasionally be spindle-shaped (Figure 16). The lymphoid cells are present in the background and can be intimately associated with groups of tumor cells as well (Figure 17). Areas of necrosis are common, as are the presence of mitotic figures.

Other salivary gland neoplasms associated with lymphoid stroma such as Warthin tumors and acinic cell carcinomas can be distinguished from cases of lymphoepithelial carcinoma by the fact that the epithelial component of the 2 former neoplasms are composed of large neoplastic cells without high-grade nuclei. Distinction from high-grade cases of mucoepidermoid carcinoma can be difficult, especially if the epidermoid component of the mucoepidermoid carcinoma is not obvious and/or if a squamous component of a lymphoepithelial carcinoma is present.

Sebaceous Lymphadenocarcinoma

Sebaceous lymphadenocarcinomas are very rare malignant tumors of the salivary glands. The most common sites of presentation have included the parotid gland and the periparotid lymph nodes. The rare cases of these tumors have been reported in those between the fifth and seventh decades. Metastatic tumors to the salivary glands account for approximately 10% of malignant tumors reviewed at the Armed Forces Institute of Pathology. Metastatic squamous carcinomas and melanomas are the most common head and neck metastatic neoplasms to the major salivary glands, whereas metastatic carcinomas of the lung, breast, and kidneys are the most frequent infraclavicular primaries. The majority of metastatic neoplasms involve the intraparotid and perisubmandibular nodes. The peak in-
Incidence of metastatic tumors within the salivary glands is within the seventh decade; however, the age of presentation parallels the age of presentation of the types of primary tumors within the various age groups. Metastatic tumors can mimic primary salivary gland neoplasms as if they were involved lymph node enlarges.

Metastatic tumors can accompany a significant population of lymphoid cells on aspiration, especially when the metastatic lesion partially replaces an intraparotid or paraparotid lymph node. The cytologic features of the metastatic tumor often mimic the neoplasm at its primary source. Spindle cell neoplasms such as spindle cell melanomas and squamous cell carcinomas can be diagnostic challenges (Figure 19, A and B). The use of immunoperoxidase stains including cytokeratins, S100, HMB-45, and Melan-A may be necessary to distinguish these tumors. Because primary squamous cell carcinomas and adenocarcinomas of the salivary gland are rarer than their metastatic counterparts, reference to previous material for comparison and the use of appropriate panels of immunoperoxidase stains may be helpful in sorting out a primary versus metastatic lesion. High-grade mucoepidermoid carcinomas can be mistaken for metastatic non-small cell carcinomas from the lung, for example. Although TTF-1 stains may be particularly useful in this situation, one should keep in mind that primary squamous cell carcinomas of the lung may be TTF-1 negative. However, a squamous carcinoma with extensive keratinization favors a metastatic lesion rather than a high-grade primary mucoepidermoid carcinoma, usually arising from the upper aerodigestive tract or skin, respectively. Other diagnostic challenges may include clear cell neoplasms such as metastatic renal cell carcinomas, which can mimic a primary lymphoid-rich acinic cell carcinoma.

**SUMMARY AND CONCLUSIONS**

Diagnosis of salivary gland lesions by FNA can present a challenging task for pathologists. The recognition of cytologic architectural patterns at low to intermediate magnification can aid the observer in approaching a correct diagnosis. This article presented one such pattern in salivary gland cytology: epithelioid cell clusters with an extensive lymphoid background. Nonneoplastic and neoplastic entities that fall under this architectural pattern were discussed, including the unique cellular characteristics that distinguish these lesions.

**References**