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Oncocytic Tumors: Oncocytoma, Warthin Tumor, and Acinic Cell Carcinoma

Background

Perhaps more than any other tissues in the body, the salivary glands exhibit a wide range of benign and neoplastic lesions that can have oncocytic or oncocyte-like features. True oncocytes have abundant densely granular eosinophilic cytoplasm due to the presence of numerous mitochrondria. In addition, they have central enlarged round nuclei with a distinct nucleolus. Sometimes the oncocytic features are a primary characteristic of the lesion such as in oncocytoma, and sometimes they are secondary to a process such as oncocytosis, a metaplastic change in the salivary glands of older adults. In the diffuse form of oncocytosis a majority of the salivary gland parenchyma, including ductal and acinar cells, is replaced by oncocytes. This process can even affect the neoplastic cells of many different salivary gland tumors. Radiologically, oncocytes concentrate technetium (99mTc), and therefore, tumors comprised of oncocytes are "hot" by radionuclide scanning. In this chapter, we will discuss the differential diagnosis of salivary gland lesions with true oncocytic features, as well as those that have eosinophilic features that can mimic those of an oncocyte.

Features of Oncocytic Lesions

- Cytoplasmic mitochondria
- May form a primary tumor (e.g., oncocytoma)
- May be a metaplastic process (e.g., oncocytosis)
- Can affect salivary gland neoplasms (e.g., pleomorphic adenoma)
- Detected by radionuclide scanning

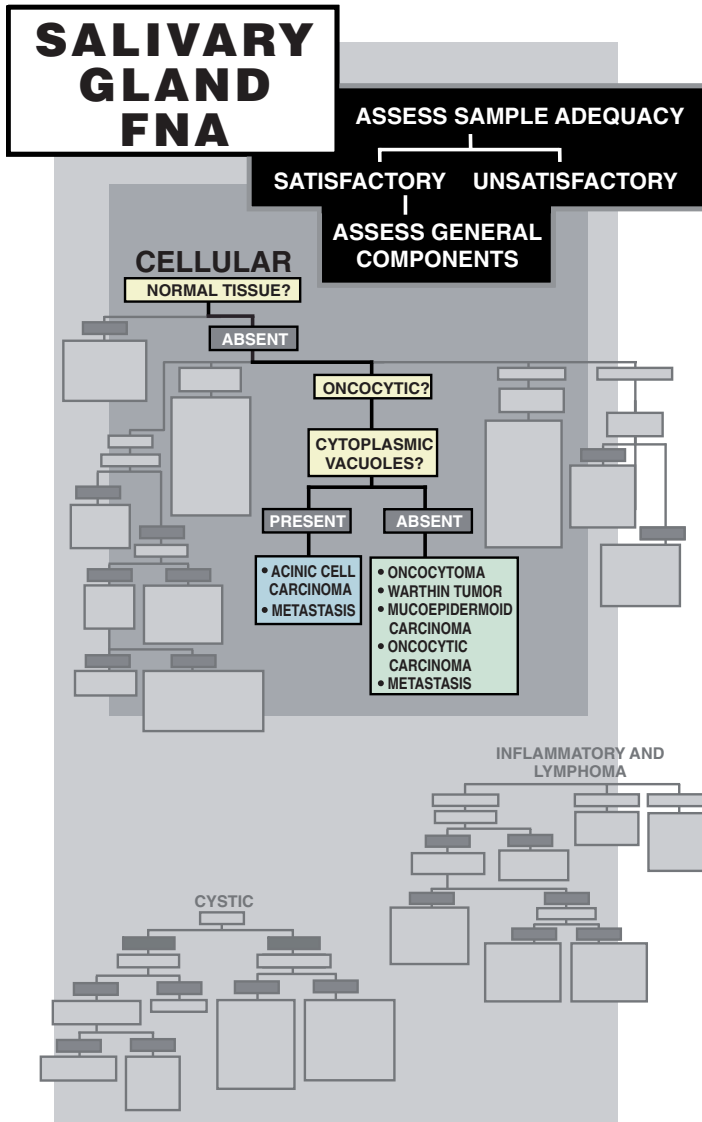

FIG. 8.1. Algorithm for oncocytic salivary gland lesions.

One of the most common diagnostic challenges among salivary gland tumors with an oncocytic microscopic appearance is differentiating the benign tumor, oncocytoma, from the low-grade carcinoma, acinic cell carcinoma. In addition, other tumors or subtypes of tumors with oncocytic features include Warthin tumor, the oncocytic variant of mucoepidermoid carcinoma, pleomorphic adenoma with oncocytic features, oncocytic carcinoma, and metastatic tumors, especially renal cell carcinoma. With the exception of pleomorphic adenoma, the most common salivary gland tumors with oncocytic features lack myoepithelial differentiation.

Salivary gland proliferations of oncocytes include nodular or diffuse hyperplasia (oncocytosis), oncocytoma, and oncocytic carcinoma. Oncocytomas are rare benign salivary gland tumors, representing less than 1% of all salivary gland neoplasms. The majority occur in the parotid gland in older adults with a mean age in the sixth to seventh decade and an equal gender predilection. A small subset of oncocytomas occurs in the submandibular and minor salivary glands. Most present as a slowly enlarging, 3–4 cm, painless mass. Approximately 5% can be multifocal, and even by histologic evaluation, it may very difficult to reliably distinguish a true oncocytoma from a hyperplastic oncocytic nodule in the setting of oncocytosis. On gross examination, oncocytomas are well circumscribed with a characteristic brown-red coloration; microscopically they are encapsulated, while the hyperplastic nodules in oncocytosis are not. Oncocytic carcinomas are clinically expansile, invasive tumors.

Warthin tumor (aka Warthin's tumor) is an interesting neoplasm with a unique pathologic appearance. It is also known by the more complex term papillary cystadenoma lymphomatosum, a name which accurately reflects its histologic appearance. Warthin tumor was first described in 1929 by Aldred Warthin, and it accounts for 5%–15% of all salivary gland tumors. In several large series, it is the second most common salivary gland tumor. Warthin tumor occurs almost exclusively within the parotid gland or rarely within adjacent lymph nodes; 5%–20% of cases can be bilateral or multifocal. While previously cited as more common in men, the ratio of Warthin tumor in women in recent studies is now similar to that in men. It is also more common in caucasians than in other racial groups. Epidemiologically,

Warthin tumor has been associated with cigarette smoking, with an 8-fold increased risk among smokers. There are several hypotheses for the pathogenesis of Warthin tumors; the proliferation of ductal elements developmentally entrapped within parotid-associated lymph nodes seems to be the most logical. This also helps to explain the nearly uniform occurrence within the parotid gland. Clonal and molecular studies indicate that Warthin tumors are not clonal proliferations, and thus are probably developmental lesions rather than true neoplasms, but this remains controversial. Patients, typically in their 5th to 7th decade, present with an enlarging painless mass, of usually less than 4 cm, in the superficial lobe of the parotid gland near the angle of the jaw. Warthin tumors are rare before the age of 40. On clinical examination, palpation of Warthin tumors has a very characteristic "doughy" feel, and aspirates yield a thick green-brown turbid fluid. In very rare cases, synchronous cancers such as squamous cell carcinoma or mucoepidermoid carcinoma, as well as malignant lymphoma can develop within a Warthin tumor. FNA is highly accurate for the diagnosis of Warthin tumors; however, as will be discussed, extensive squamous or mucinous metaplastic changes can present significant diagnostic challenges.

Clinicopathologic Features of Warthin Tumor

- 5%–15% of all salivary gland tumors
- Older adults (5th to 7th decade)
- Primarily within the parotid gland
- 5%–20% are bilateral or multifocal
- 8-fold increased risk among smokers
- Doughy feel on palpation
- FNA is highly accurate except in cases with extensive metaplasia
- Probably developmental, not neoplastic

In many series, acinic cell carcinoma is the second or third most common salivary gland malignancy, representing approximately 6% of all salivary gland tumors and up to 17% of salivary gland malignancies. The exact proportion of acinic cell carcinomas relative to other salivary gland tumors varies, in part due to the classification of some cases as "adenocarcinoma, NOS." Acinic cell carcinoma was first described by Nasse in 1892; it is defined histologically by the presence of at least focal serous acinar differentiation characterized

by PAS+diastase-resistant cytoplasmic zymogen granules. It is generally a low-grade tumor, although high-grade and dedifferentiated forms do occur. Attempts to histologically grade acinic cell carcinomas have met with limited success, and clinical stage is usually the better predictor of clinical outcome. Acinic cell carcinoma characteristically presents as a solitary, well-circumscribed, mobile, slowly growing, 1–3 cm mass which occasionally is painful. The low-grade nature of acinic cell carcinoma is evidenced by the fact that it was previously known as acinic cell tumor, with some patients presenting with a 10 or more year history of a salivary gland mass. Acinic cell carcinoma is more common in women, and there is a broad age range (mean age is 44 years) among patients, from young children to elderly adults. Seventy-five to 90% of cases present in the parotid gland, and most of the remaining cases occur in the intraoral minor salivary glands. A small subset of acinic cell carcinomas is bilateral. Tumors can be solid or cystic, with four histologic types of acinic cell carcinoma recognized: solid, microcystic, papillary-cystic, and follicular. FNA is moderately accurate at detecting acinic cell carcinomas, with approximately 75% of cases being diagnosed as suspicious or malignant. The most difficult cases to detect by FNA are those with a predominance of intercalated duct cells and lacking significant serous acinar differentiation.

Clinicopathologic Features of Acinic Cell Carcinoma

- Second to third most common salivary gland malignancy
- 6% of all salivary gland tumors
- Wide age range, from children to elderly adults
- Primarily within the parotid gland
- At least focal serous acinar differentiation
- Usually low-grade clinical behavior
- Can be solid or cystic

General Diagnostic Approach

The oncocytic arm of the algorithm is characterized by cellular aspirates containing epithelial cells with moderate to abundant eosinophilic cytoplasm (Fig. 8.1). Most cases in the differential diagnosis lack a myoepithelial component. Identifying the presence

or absence of cytoplasmic vacuoles is a very useful feature since their presence favors the diagnosis of acinic cell carcinoma (or a metastasis). Diff-Quik preparations can be used to more readily identify cytoplasmic vacuolization. The distinction between the various differential diagnostic entities in the oncocytic arm of the algorithm is important, since it includes both benign and malignant tumors. A key step is in evaluating the cytoplasmic features of the cells carefully and applying ancillary tests as needed.

Diagnostic Criteria

Oncocytoma

Aspirates of oncocytomas are variably cellular and consist of 2- and 3-dimensional cohesive groups of uniform polygonal cells with moderate to abundant amounts of densely granular eosinophilic cytoplasm (Figs. 8.2–8.3). Occasionally, the cells are arranged in trabeculae, and some single cells can be seen. Intercellular borders are very well-defined. The cytoplasm appears granular in Papanicolaou-stained preparations, and is deep blue and waxy using Diff-Quik stains. Importantly, cytoplasmic vacuoles are absent. The nuclei are centrally placed, uniform, enlarged and round to oval with a small distinct nucleolus. In some cases, the nuclei are more round and pyknotic without a discernible nucleolus. Mitotic activity is absent. The background is clean, lacking debris and lymphocytes. As mentioned previously, oncocytoma and oncocytosis are indistinguishable by FNA and can sometimes be challenging to distinguish even in excisional biopsy specimens. Clinicoradiologic correlation is sometimes helpful, but the distinction does not usually affect the clinical management since both are benign lesions.

Cytologic Features of Oncocytomas

- Cohesive 2- and 3-dimensional groups of uniform polygonal cells
- Moderate to abundant densely granular eosinophilic cytoplasm
- Well-defined intercellular borders
- Absence of cytoplasmic vacuoles
- Enlarged round nucleus with distinct nucleolus
- Clean background without lymphocytes

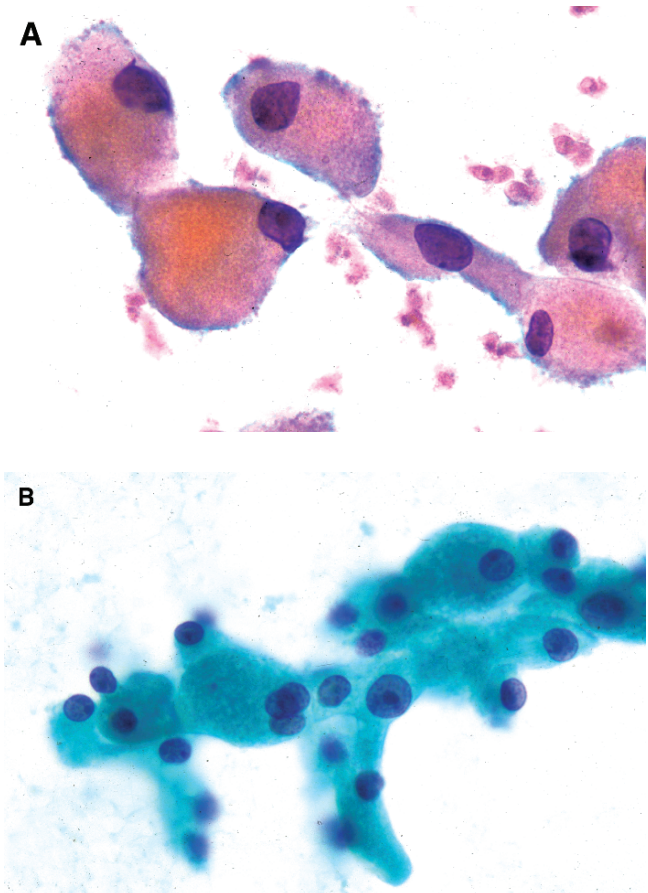

FIG. 8.2. Oncocytoma. (A and B) Cells have abundant evenly granular eosinophilic cytoplasm in a clean background. (Thin-layer preparation, Papanicolaou.)

Warthin Tumor

In addition to its characteristic "doughy" feel on palpation, and the granular opaque green-brown cyst fluid obtained by aspiration, the cytologic features of most Warthin tumors are easily recognized microscopically. There are 3 characteristic cytologic findings in aspirates of Warthin tumor: oncocytes, lymphocytes, and a "dirty"

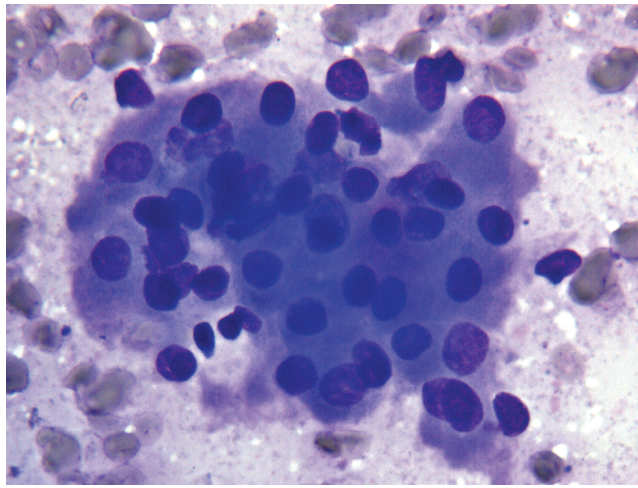

FIG. 8.3. Oncocytoma. The cells are uniform, with moderate amounts of waxy cytoplasm that lacks vacuoles. (Smear, Diff-Quik.)

granular proteinaceous background (Figs. 8.4–8.6). The oncocytes of Warthin tumor are similar to those described for oncocytoma. They are usually present in cohesive 2-dimensional sheets and have well-defined cell borders, giving a pavementing appearance. In some cases, the oncocytes can be arranged in a papillary formation. The cytoplasm is moderate to abundant, granular and eosinophilic owing to the many cytoplasmic mitochondria. The nuclei are enlarged, round to oval and centrally placed, usually with a distinct nucleolus. While the nuclei may appear atypical at first glance, they are very uniform, lacking significant nuclear pleomorphism; mitotic activity is absent. Background lymphocytes consist of a mixed pattern, usually with a predominance of small mature-appearing forms with an admixture of plasma cells, mast cells, tingible body macrophages, and occasional intermediate to larger lymphoid cells. Lymphohistiocytic aggregates representing aspirated fragments of germinal centers are sometimes also seen. The background in Warthin tumors is characteristically cystic, proteinaceous, and granular, sometimes with admixed necrotic cell debris. Occasionally, the background cystic material will contain

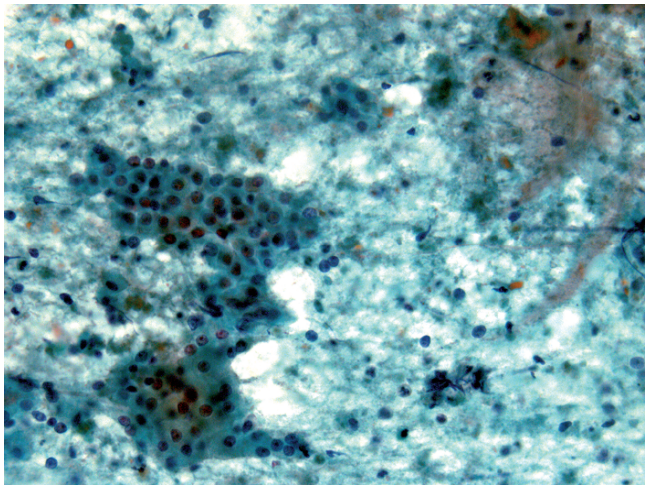

FIG. 8.4. Warthin tumor. The characteristic findings include cohesive flat sheets of oncocytes, lymphocytes, and a granular proteinaceous background. (Smear, Papanicolaou.)

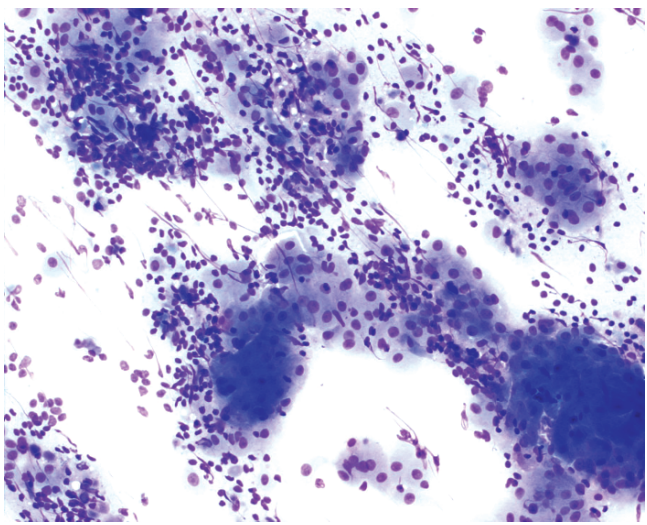

FIG. 8.5. Warthin tumor. The oncocytes have abundant densely granular to waxy cytoplasm in a background of a mixed population of lymhocytes. (Smear, Diff–Quik.)

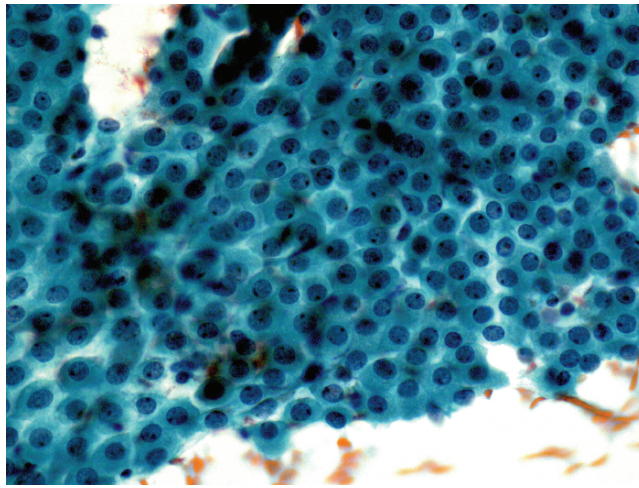

FIG. 8.6. Warthin tumor. The oncocytes form cohesive 2-dimensional groups with distinct cell borders. The cells are uniform, and have enlarged round nuclei with a distinct nucleolus. (Smear, Papanicoloau.)

abundant acute inflammation. It is important not to mistake the background of Warthin tumor for a malignant-associated tumor diathesis.

Cytologic Features of Warthin Tumor

- Cohesive 2- and 3-dimensional groups of oncocytes
- Scattered background lymphocytes
- Lymphohistiocytic aggregates
- Granular cystic background debris
- Squamous and mucinous metaplasia

While over 80% of Warthin tumors exhibit conventional cytologic features by FNA, a subset of Warthin tumors show variations that can lead to diagnostic problems. The predominant cell in most cases is the lymphocyte with occasional scattered groups of oncocytes. However, there is a wide range of cellular findings from cases that are predominantly lymphoid, resembling a lymph node aspirate, to those that have few lymphocytes and are mostly

oncocytes, resembling an oncocytoma. Such variations in cellularity and proportion of lymphocytes to oncocytes can become a diagnostic problem in poorly sampled cases. A careful search for both cell components and good clinicoradiologic correlation are important to avoid a diagnostic pitfall.

Squamous and mucinous metaplastic changes occur in over 30% of Warthin tumors, and in a subset of these, the changes can be extensive. Squamous metaplasia is the best-known change to occur in Warthin tumors (Figs. 8.7–8.8). It can vary from occasional squamoid cells to frank squamous differentiation with keratinization, parkeratotic cells, and even nuclear atypia. Warthin tumors with degenerating squamoid cells or groups of squamous cells within the background debris in the setting of oncocytes and lymphocytes are usually not a diagnostic problem. However, squamous atypia in the absence of the characteristic features of Warthin tumor may make it impossible to exclude a metastatic or primary squamous cell carcinoma. Rare cases of carcinoma arising within Warthin

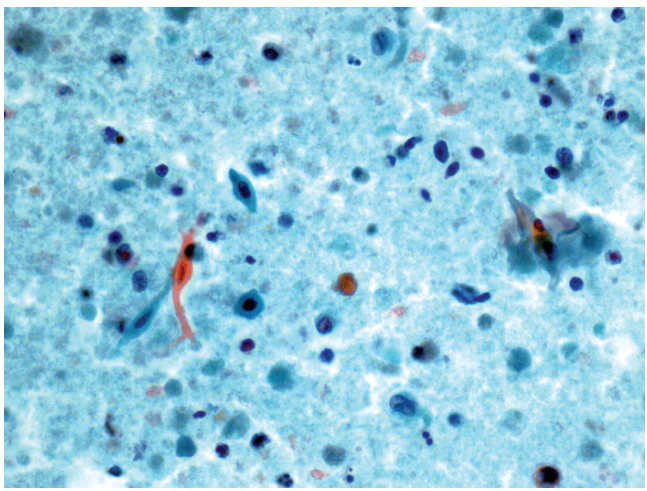

FIG. 8.7. Warthin tumor with squamous metaplastic changes. (Smear, Papanicolaou.) Degenerate squamoid cells are often seen within the background cystic debris of Warthin tumor.

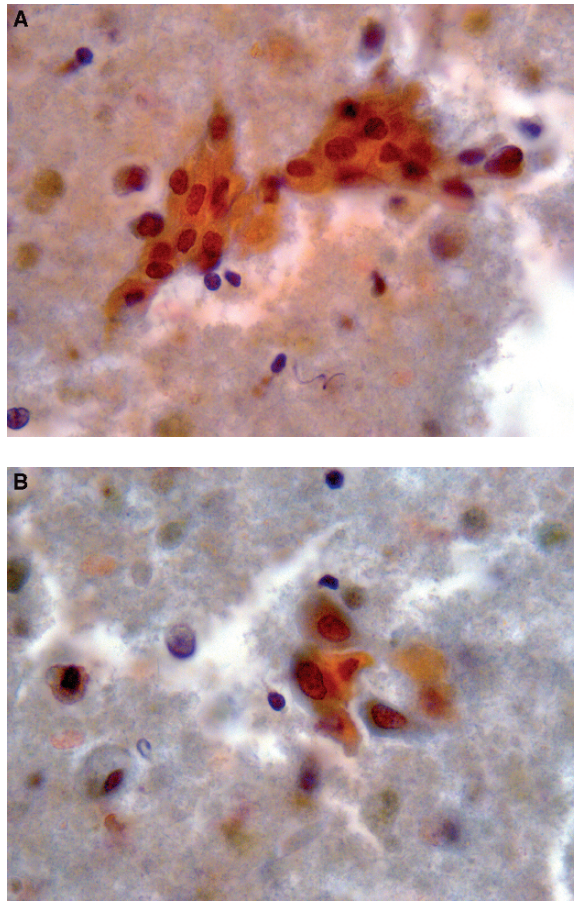

FIG. 8.8. Warthin tumor with squamous metaplastic changes. (A and B) The presence of groups of mildly atypical squamous cells can create a diagnostic problem. (Smear, Papanicolaou.)

tumor have also been reported. Mucinous metaplastic changes also consist of a spectrum from thick background mucoid material to extensive mucin-containing epithelial cells, the latter being a potential mimic of low-grade mucoepidermoid carcinoma (Fig. 8.9). As with squamous metaplasia, mucinous changes, particularly when

presenting as abundant thick background mucin in the context of other conventional features of Warthin tumor, are acceptable. However, when groups of cells with intracellular mucin are present, caution is warranted to avoid a misdiagnosis. Most of these cases will be diagnosed as "atypical," and surgical excision will be necessary to exclude mucoepidermoid carcinoma.

Squamous and mucinous metaplastic changes occur in over 30% of Warthin tumors and can be extensive.

Variants of Warthin Tumor That Can Lead to Diagnostic Difficulties

- Lymphocyte-predominant
- Oncocyte-predominant
- Squamous metaplasia
- Mucinous metaplasia

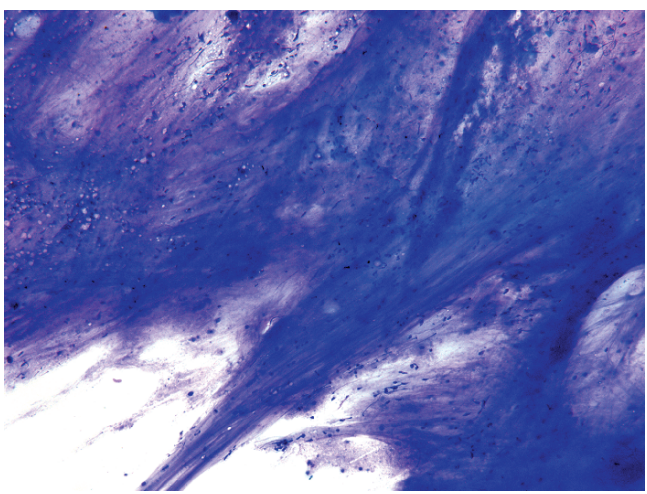

FIG. 8.9. Warthin tumor with mucinous metaplasia. Abundant thick background mucoid material is seen in a subset of Warthin tumors. (Smear, Papanicolaou.)

Acinic Cell Carcinoma

Aspirates of acinic cell carcinoma can contain any of a variety of cell types, including serous acinar, intercalated duct, vacuolated, clear, and nonspecific glandular. The hallmark cytologic and histologic feature, however, is at least focal serous acinar differentiation with its characteristic cytoplasmic zymogen granules. Fortunately, the serous acinar cell is the most common cell type encountered in aspirates of acinic cell carcinoma. In addition to various cell types, the histologic appearance of acinic cell carcinoma can include any of 4 different architectural patterns: solid, microcystic, papillary cystic, and follicular. The solid and microcystic patterns are the most common, and are seen in over 70% of acinic cell carcinomas. In contrast, the follicular pattern is the rarest, present in less than 5% of cases.

At least focal serous acinar differentitation is the hallmark of acinic cell carcinoma.

- Cell types seen in acinic cell carcinomas
  - Serous acinar
  - Intercalated duct
  - Vacuolated
  - Clear
  - Non-specific glandular
- Architectural patterns seen in acinic cell carcinomas
  - Solid
  - Microcystic
  - Papillary cystic
  - Follicular

The classic aspirate of acinic cell carcinoma is cellular and comprised of large polygonal cells with abundant delicate, vacuolated cytoplasm (Fig. 8.10). The cells are haphazardly arranged in 3-dimensional groups, sheets, and as single cells. In some cases, a capillary meshwork or even papillary formations around a fibrovascular core can be seen. The nuclei are cytologically bland, round to oval,

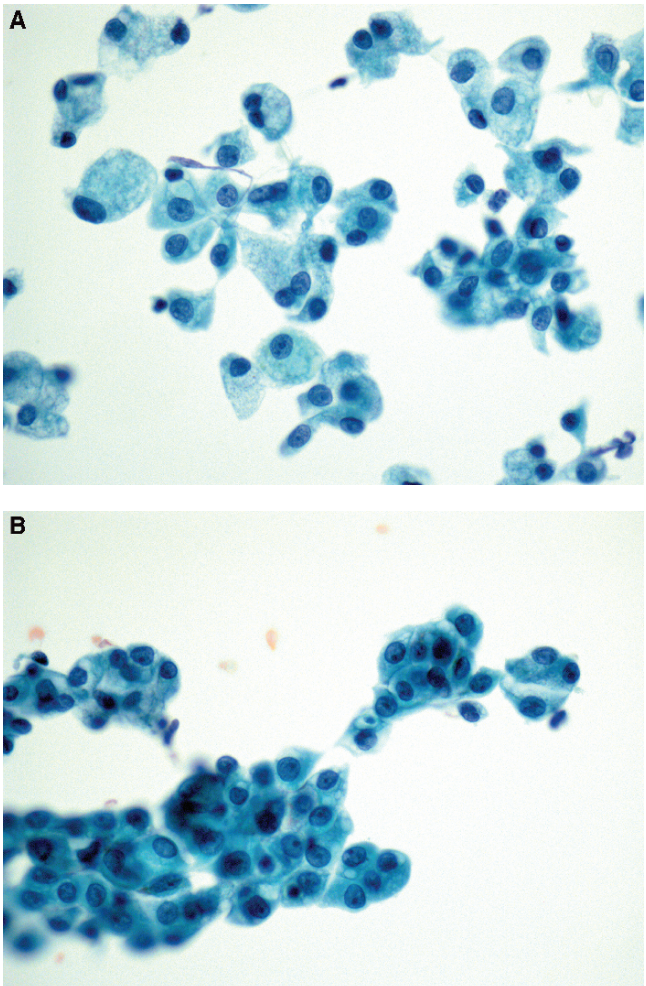

FIG. 8.10. Acinic cell carcinoma. Large polygonal cells with abundant delicate cytoplasm (A) solid subtype; (B) papillary cystic subtype. (Thin-layer preparation, Papanicolaou.)

uniform, and eccentrically placed with small distinct nucleoli. Mitoses are absent to rare. The cytoplasm is the key to the cytologic diagnosis of acinic cell carcinoma. It is abundant, vacuolated, and slightly basophilic to eosinophilic. While the vacuolated nature of

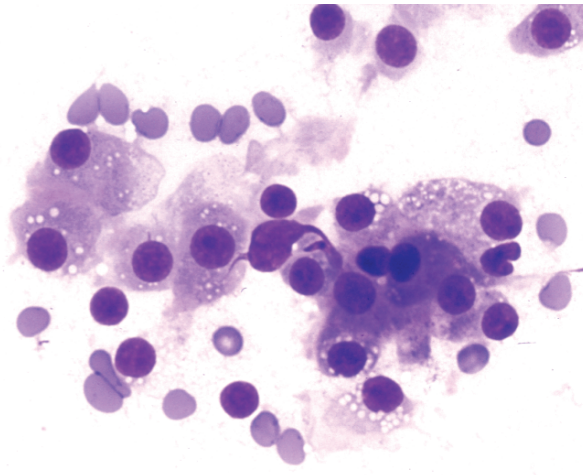

FIG. 8.11. Acinic cell carcinoma. Small cytoplasmic vacuoles are most easily seen in Diff-Quik stained preparations. (Smear, Diff-Quik.)

the cytoplasm can be appreciated using Papanicolau stains, it can be subtle, and the vacuoles are much more visible using Romanowsky stains (Fig. 8.11). Occasional small dark-staining cytoplasmic zymogen granules can often also be seen; while they are sometimes abundant, they are more often sparse and difficult to find (Fig. 8.12). For cases where a cell block is available, staining with PAS + diastase can be used to help demonstrate the presence of cytoplasmic zymogen granules. The background in aspirates of acinic cell carcinoma is clean, but may contain scattered stripped nuclei reflecting the delicate nature of the cytoplasm. Aspirates of the papillary cystic variant will yield a cystic background, and a 10% subset of acinic cell carcinomas will have a mixed lymphoid background, including lymphohistiocytic aggregates. Psammoma bodies can occasionally be found, especially in the papillary cystic variant (Fig. 8.13). Acinic cell carcinomas are also particularly prone to cystic degeneration with associated hemosiderin-laden macrophages. A rare subset of acinic cell carcinomas is dedifferentiated and exhibits high-grade nuclear features that are generally not recognizable by FNA as acinic cell carcinomas.

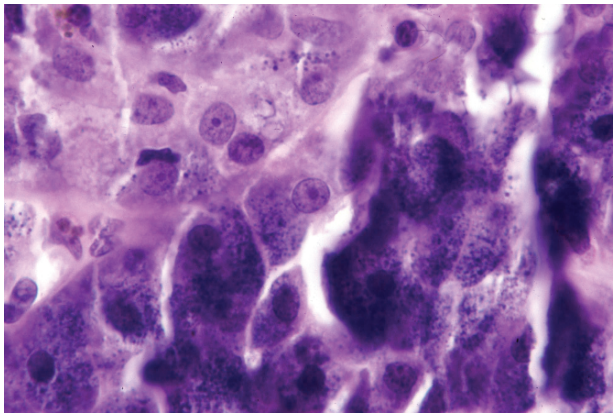

FIG. 8.12. Acinic cell carcinoma. Course basophilic cytoplasmic zymogen granules are the hallmark of serous acinar differentiation. (Cell block, H&E.)

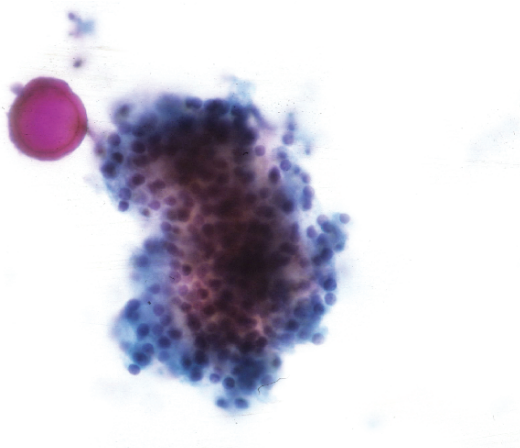

FIG. 8.13. Acinic cell carcinoma. Psammoma bodies are sometimes seen in aspirates of acinic cell carcinoma, especially the papillary cystic subtype. (Smear, Papanicolaou.)

The cytoplasmic vacuoles and zymogen granules are the key to the cytologic diagnosis of acinic cell carcinoma.

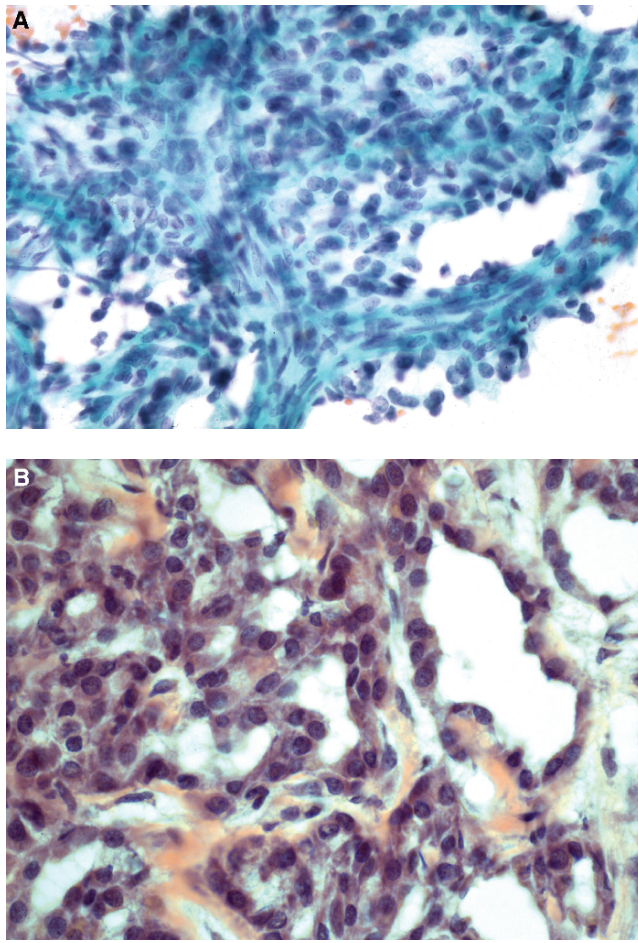

FIG. 8.14. Acinic cell carcinoma. (A and B) A small subset of cases contain a predominance of intercalated duct cells which are cuboidal and lack cytoplasmic zymogen granules. (A, Smear, Papanicolaou; B, Cell block, H&E.)

Cytologic Features of Conventional Acinic Cell Carcinoma

- Large polygonal cells
- Uniform, round eccentric nuclei
- Delicate vacuolated cytoplasm
- PAS-positive, diastase-resistant zymogen granules
- Background stripped nuclei
- Lymphocytes may be present
- Rare psammoma bodies

When acinic cell carcinomas show well-defined features of serous acinar differentiation, a definitive cytologic diagnosis is usually possible. However, a small subset of cases will contain a predominance of cells lacking serous acinar differentiation that can include intercalated duct, vacuolated, clear, and nonspecific glandular types. Of these, the intercalated duct and nonspecific glandular cells pose the greatest diagnostic challenge. While a careful search for focal serous acinar differentiation may be helpful, cases with a predominance of these cell types will usually receive a descriptive diagnosis such as "low-grade glandular neoplasm" with a note and differential diagnosis. Histologically, most cases are recognized as acinic cell carcinoma, but some of these may be classified as adenocarcainoma, NOS. In contrast to serous acinar cells, intercalated duct cells are smaller, cuboidal, have a higher N:C ratio, have centrally placed nuclei, and form cohesive groups (Fig. 8.14). The cytoplasm is more dense and eosinophilic than in serous acinar cells, and it lacks well-defined small vacuoles and zymogen granules. Aspirates of nonspecific glandular cells are similar to intercalated duct cells but more round to polygonal in shape.

Cases with a predominance of intercalated duct cells will usually receive a descriptive diagnosis such as "low-grade glandular neoplasm" with a note and differential diagnosis.

Differential Diagnosis and Pitfalls

The differential diagnosis of salivary gland tumors with oncocytic features includes oncocytoma and oncocytosis, Warthin tumor, acinic cell carcinoma, the oncocytic variant of mucoepidermoid carcinoma, oncocytic carcinoma, and metastatic renal cell carcinoma. Other very rare cystic lesions that can sometimes be considered in the differential diagnosis of oncocytic tumors are cystadenoma, cystadenocarcinoma, and sclerosing polycystic adenosis, which will be discussed in Chapter 9. Among the oncocytic salivary gland tumors, the most common recurring problem in our experience is the distinction between oncocytoma and acinic cell carcinoma (Table 8.1). At low magnification, these two entities appear similar, but at higher magnifaction and using Diff-Quik stains, acinic cells have delicate cytoplasm with small vacuoles, while oncocytomas have densely granular to waxy-appearing cytoplasm without vacuoles. For difficult cases, ancillary studies can be performed using cell block material. While they may be sparse, zymogen granules are present in the cytoplasm of acinic cell carcinomas and can be demonstrated using PAS+ diastase. In addition, phosphotungstic acid-hematoxylin (PTAH), a stain for mitochondria, shows strong positive cytoplasmic staining in oncocytomas, while acinic cell carcinomas are negative or only weakly positive.

The most common recurring problem in our experience is the distinction between oncocytoma and acinic cell carcinoma.

Differential Diagnosis of Oncocytic Salivary Gland Lesions

- Oncocytoma and oncocytosis
- Warthin tumor
- Acinic cell carcinoma
- Oncocytic variant of mucoepidermoid carcinoma
- Oncocytic carcinoma
- Pleomorphic adenoma with oncocytic features
- Metastatic renal cell carcinoma

TABLE 8.1. Comparison of selected differential diagnostic entities.

Feature	Normal Salivary Gland	Oncocytoma	Warthin Tumor	Acinic Cell Carcinoma
Cellularity	Low to moderate	Moderate to high	Variable	Moderate to high
Cells	Acinar and few ductal	Oncocytes	Oncocytes and lymphocytes	Acinar and intercalated duct
Background	Stripped nuclei	Clean	"Dirty" granular debris	Stripped nuclei
Cell Arrangement	Polarized in lobular groups	Sheets and 3-dimensional groups	Sheets and 3- dimensional groups	Haphazard in 2- and 3-dimensional groups
Cell borders	Indistinct	Well defined	Well defined	Indistinct
Atypia	Absent	Absent	Atypical metaplasia	Variable
Cytoplasm	Abundant and vacuolated	Moderate and densely granular	Moderate and densely granular	Abundant and vacuolated
PTAH Stain	Negative	Positive	Positive	Negative
PAS + Diastase	Positive	Negative	Negative	Positive
Electron Microscopy	Zymogen granules	Mitochondria	Mitochondria	Zymogen granules

As mentioned in Chapter 4, an important pitfall to avoid is confusing aspirates of normal acinar cells with those of acinic cell carcinoma. Aspirates of both normal salivary gland tissue and acinic cell carcinoma can look similar when they contain many single cells and stripped acinar cell nuclei within the background. Since individual cells of acinic cell carcinoma can be virtually indistinguishable from normal acinar cells, it is important to search instead for groups of cells. Acinic cell carcinomas contain cells that are crowded together haphazardly, lacking the polarity and ductal elements of normal salivary gland tissue.

As described previously in this chapter, the most common pitfall in the diagnosis of Warthin tumor is related to squamous and mucinous metaplastic changes, which can be extensive. Thorough sampling of the lesion and good clinicoradiologic correlation can be very helpful in avoiding a false positive diagnosis. When the metaplastic changes are present in a background of otherwise normal Warthin tumor components, a correct, definitive diagnosis of Warthin tumor can be made. However, when only metaplastic elements are found, it will not be possible to exclude carcinoma.

The rare oncocytic variant of mucoepidermoid carcinoma (see Chapter 9) is a potential pitfall in the evaluation of oncocytic salivary gland lesions (Fig. 8.15). Most cases are low-grade tumors with minimal nuclear atypia, but an infiltrative growth pattern. Aspirates are cellular and composed predominantly of bland oncocytic cells with scattered mucinous goblet cells and only rare groups of epidermoid and intermediate cells. The background is often partially cystic and mucoid. The oncocytic cytoplasm of the neoplastic cells is positive with PTAH due to the abundant cytoplasmic mitochondria. The key to avoiding misinterpretion of this carcinoma as an oncocytoma or Warthin tumor is to search carefully for the characteristic mucinous goblet cells that are usually a significant component of this tumor combined with the rare epidermoid and intermediate cells. If cell block material is available, stains to confirm intracellular mucin can be performed.

Oncocytic carcinoma is another very rare carcinoma that can pose a potential pitfall in the cytologic diagnosis of oncocytic salivary gland lesions (Fig. 8.16). This is an aggressive salivary gland carcinoma that occurs in older adults (mean age = 62.5 years), and in some cases develops from a pre-existing oncocytoma. Aspirates

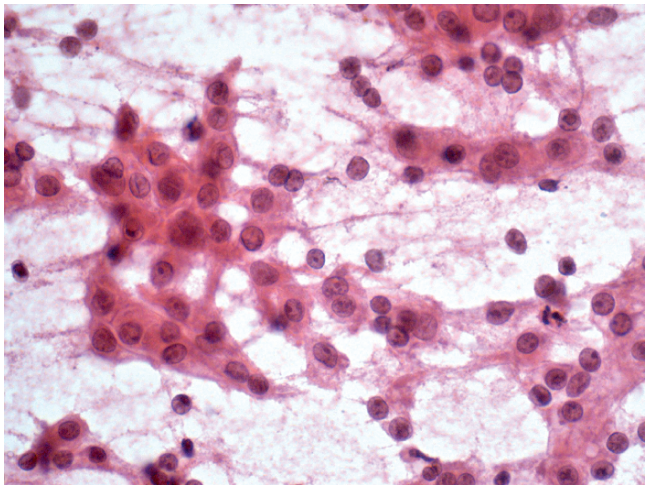

FIG. 8.15. Oncocytic variant of mucoepidermoid carcinoma. A combination of epidermoid and polygonal cells with dense granular oncocytic cytoplasm. (Smear, Papanicolaou.)

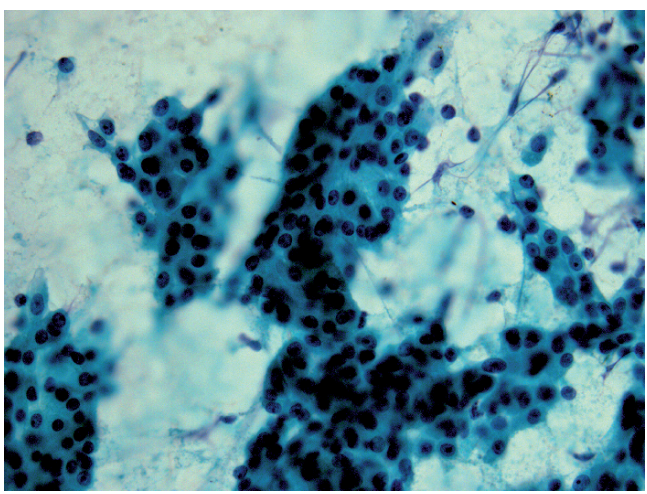

FIG. 8.16. Oncocytic carcinoma. Cells have abundant densely granular cytoplasm, and large nuclei with prominent nucleoli. (Smear, Papanicolaou.)

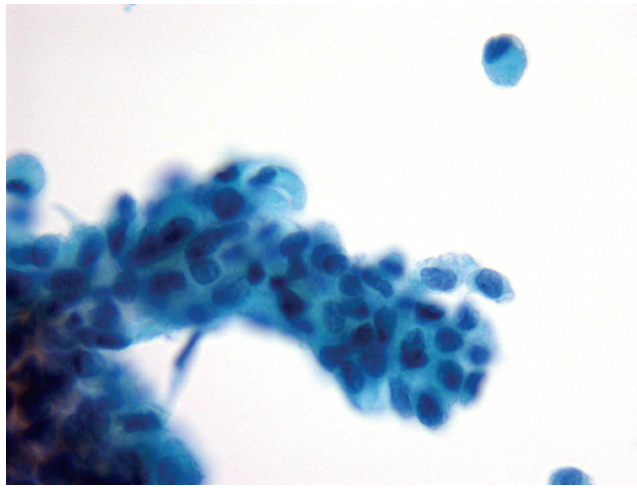

FIG. 8.17. Pleomorphic adenoma with oncocytic features. (Smear, Papanicoloau.)

of oncocytic carcinoma can easily be misinterpreted as an oncocytoma if careful attention is not given to the atypical variation in cell size and shape, and the moderate degree of nuclear pleomorphism. In addition, mitotic activity is often present. and sometimes background necrosis will be found. Tumors are infiltrative and often large - features that are usually appreciated both clinically and radiologically. Therefore, good clinicoradiologic correlation combined with careful microscopic analysis can help to avoid a potential false negative diagnosis.

Oncocytosis is a metaplastic process that occurs in some older adults. It can result in the formation of variably sized nodules of oncocytes that are nearly indistinguishable from true oncocytomas except for their lack of a true fibrous capsule. Oncocytosis can affect various salivary gland tumors; most commonly this has been reported in pleomorphic adenomas (Fig. 8.17). Aspirates of pleomorphic adenoma with oncocytic features will contain many oncocytes, singly and in groups, but thorough sampling will also usually yield characteristic fragments of metachromatic fibrillar matrix material (see Chapter 5). In addition,

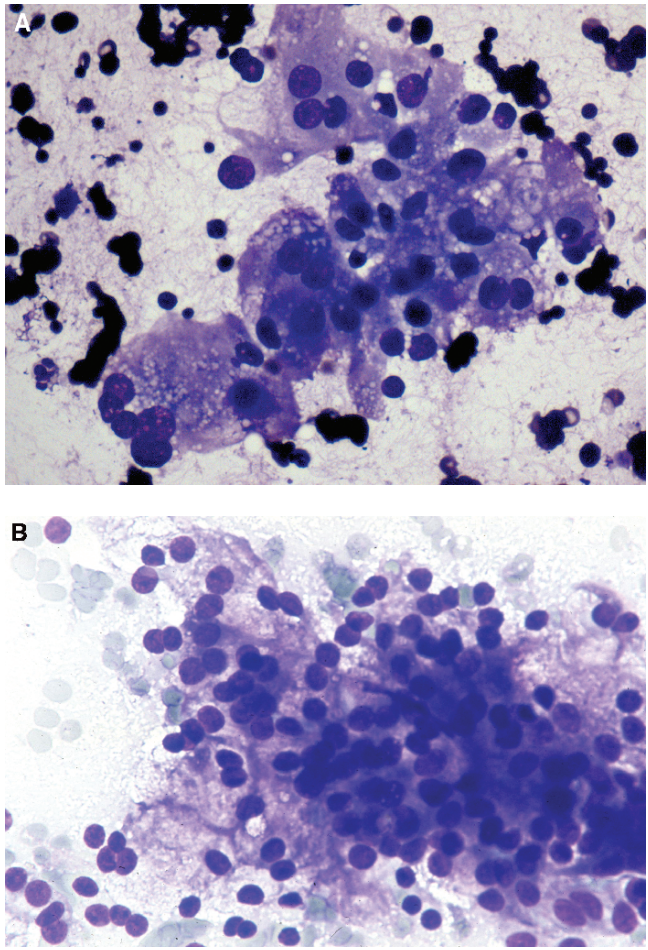

FIG. 8.18. Metastatic renal cell carcinoma (A) can appear very similar to acinic cell carcinoma (B) in salivary gland aspirates. (Smears, Diff–Quik.)

ancillary marker studies such as smooth muscle actin, calponin, and S-100 can be used to demonstrate myoepithelial differentiation, which is not seen in other oncocytic tumors discussed in this chapter.

Metastatic renal cell carcinoma is among the most common distant tumors metastasizing to the major salivary glands, where it can mimic a primary tumor, especially acinic cell carcinoma (Fig. 8.18). Both tumors are characterized by similar abundant delicate eosinophilic cytoplasm and bland nuclear features. The presence of small basophilic cytoplasmic granules favors acinic cell carcinoma. A majority, but not all, patients with metastatic renal cell carcinoma will have a clinical history to alert the cytopathologist to the potential diagnostic pitfall. Applying ancillary immunohistochemical studies using cell block material is the most reliable method for distinguishing renal cell carcinoma and acinic cell carcinoma. In contrast to acinic cell carcinoma, renal cell carcinomas are positive for CD10, renal cell carcinoma marker, and EMA, and negative for cytokeratin 7.

Ancillary Techniques

In assessing an oncocytic lesion of the salivary gland, Diff-Quik stains for identification of cytoplasmic vacuoles should be used in conjunction with standard Papanicolaou stain preparations. In addition, special studies to better define characteristics of the oncocytic cytoplasm can be applied to cell block material. PTAH stains are used for demonstrating cytoplasmic mitochondria, PAS+ diastase will stain zymogen granules, and mucicarmine can be used to demonstrate intra- and extracellular mucin. Although not always an available option, material can also be placed into glutaraldehyde fixative for evaluation by electron microscopy, which is a very sensitive method for distinguishing true oncocytes with abundant cytoplasmic mitochondria from acinar cells with secretory vacuoles and zymogen granules. Immunohistochemical stains are of limited value in the distinction of oncocytic salivary gland tumors. Anti-mitochondrial antibody can be used to help distinguish oncocytoma and acinic cell carcinoma, and a subset of acinic cell carcinomas is positive for amylase. With the exception of pleomorphic adenoma with oncocytic changes, most oncocytic salivary gland tumors, including oncocytoma, Warthin tumor, acinic cell carcinoma, oncocytic mucoepidermoid carcinoma, and oncocytic carcinoma. are immunohistochemically negative for myoepithelial markers (e.g., calponin, smooth muscle actin, S-100).

Most oncocytic salivary gland tumors are immunohistochemically negative for myoepithelial markers.

Clinical Management and Prognosis

The treatment for oncocytoma and Warthin tumor is complete surgical excision, which for parotid-based tumors will most often entail superficial parotidectomy with facial nerve preservation. Local recurrence of either tumor is uncommon. Less than 6% of Warthin tumors recur, and the majority of these are thought to be due to multifocal tumors. Rarely, malignancy can develop within a Warthin tumor, and may originate from either the epithelial (e.g., squamous cell carcinoma, mucoepidermoid carcinoma, oncocytic carcinoma) or the lymphoid component (e.g., small lymphocytic lymphoma, follicular lymphoma, MALT lymphoma). Malignant transformation of oncocytoma to oncocytic carcinoma is also very rare.

Acinic cell carcinomas are treated by complete surgical excision with disease-free resection margins. Postsurgical radiation therapy is usually reserved for cases with positive resection margins or with high-grade or undifferentiated histologic features where the overall prognosis is very poor. The average rate of recurrent acinic cell carcinoma is 33%–44%, and the risk of metastatic disease is 16%–19%. Clinical stage is considered the best predictor of outcome. The least aggressive clinical behaviors are reported for tumors of the minor salivary glands; tumors in the submandibular gland have been reported to have a worse clinical outcome than those arising in the parotid. An unusual feature of acinic cell carcinoma is that local recurrence or metastatic disease can occur decades after the initial diagnosis and resection; therefore, patients treated for acinic cell carcinoma require longterm follow-up.

Suggested Reading

Ali SZ. Acinic-cell carcinoma, papillary-cystic variant: a diagnostic dilemma in salivary gland aspiration. Diagn Cytopathol 2002;27:244–250.

Arida M, Barnes EL, Hunt JL. Molecular assessment of allelic loss in Warthin tumors. Mod Pathol 2005;18:964–968.

Ballo MS, Shin HJC, Sneige N. Sources of diagnostic error in the fine-needle aspiration diagnosis of Warthin tumor and clues to a correct diagnosis. Diagn Cytopathol 1997;17:230–234.

Brandwein MS, Huvos AG. Oncocytic tumors of major salivary glands. A study of 68 cases with follow-up of 44 patients. Am J Surg Pathol 1991;15:514–528.

Chang A, Harawi Sj. Oncocytes, oncocytosis, and oncocytic tumors. Pathol Annu 1992;27:263–304.

Flezar M, Pogacnik A. Warthin's tumor: unusual vs. common morphological findings in fine needle aspiration biopsies. Cytopathol 2002;13:232–241.

Gonzalez-Peramato P, Jimenez-Heffernan JA, Lopez-Ferrer P, Vicandi B, Viguer JM. Fine needle aspiration cytology of dedifferentiated acinic cell carcinoma of the parotid gland: a case report. Acta Cytol 2006;50:105–108.

Jahan-Parwar B, Huberman RM, Donovan DT, Schwartz MR, Ostrowski ML. Oncocytic mucoepidermoid carcinoma of the salivary glands. Am J Surg Pathol 1999;23:523–529.

Klijanienko J, Vielh P. Fine-needle sampling of salivary gland lesions V: Cytology of 22 cases of acinic cell carcinoma with histologic correlation. Diagn Cytopathol 1997;17:347–352.

Parwani AV, Ali SZ. Diagnostic accuracy and pitfalls in fine-needle aspiration interpretation of Warthin tumor. Cancer Cytopathol 2003;99:166–171.

Williamson JD, Simmons BH, El-Naggar A, Medeiros LJ. Mucoepidermoid carcinoma involving Warthin tumor: A report of five cases and review of the literature. Am J Clin Pathol 2000;114:564–570.