Low Grade Carcinoma Ex-Pleomorphic Adenoma: Diagnosis and Diagnostic Challenges Caused by Fine Needle Aspiration: Report of Three Cases and Review of Literature

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Abstract Low grade carcinoma ex pleomorphic adenoma (LG CXPA) is a rare low grade malignant neoplasm arising from preexisting pleomorphic adenoma (PA). LG CXPA demonstrates no overt cytological atypia, and can be difficult to distinguish from cellular PA. Invasive growth is one of the hallmarks of LG CXPA, e.g., tumor extends beyond the capsule and into adjacent non-neoplastic tissue. However, it is known that capsular and vascular invasion, as well as the presence of stroma-rich PA in soft tissue without a capsule (pseudopodia) can be seen in PA. These histological findings have no prognostic significance and are not diagnostic of malignancy. In addition, recurrent PA typically presents as numerous nodules extending into soft tissue and skeletal muscle, which again are not considered malignant features. Thus, “infiltrative growth” of LG CXPA is difficult to define and diagnosis is challenging to many practicing pathologists. In this study, we report three cases of LG CXPA. We review the diagnostic criteria for LG CXPA, and discuss the diagnostic challenges caused by fine needle aspiration (FNA) changes. FNA is widely used as a cost-effective, quick and accurate method for diagnosing salivary gland lesions. Histological changes post-FNA are usually focal and mild, and are not causes of diagnostic difficulties. According to our knowledge, this is the first report of LG CXPA complicated with FNA changes.

Keywords Salivary gland neoplasm · Pleomorphic adenoma · Low-grade carcinoma ex pleomorphic adenoma · Pleomorphic adenoma malignant transformation

Introduction

CXPAs are rare malignant salivary neoplasms arising from pleomorphic adenoma (PA) [1]. The majority of CXPA are high grade (HG CXPA) with obvious malignant features such as infiltrative growth, severe nuclear pleomorphism, increased mitotic activity, and necrosis. Only a minority of CXPA are low grade. LG CXPA is further classified into specific types of salivary gland neoplasms, such as epithelial-myoepithelial carcinoma, basal cell adenocarcinoma, myoepithelial carcinoma, etc. Accurate diagnosis of HG CXPA, LG CXPA, and PA is very important as the prognosis and treatment is different for each of these neoplasms. PA is a benign neoplasm and complete surgical resection is associated with excellent prognosis, while HG CXPA is usually associated with dismal prognosis and neoadjuvant therapy is necessary for the majority of patients. Compared with PA, LG CXPA is associated with increased local recurrence and distal metastasis, and neoadjuvant therapy is applied to a subset of patients, depending on the histological finding and stage of the cancer [2].

The diagnosis of LG CXPA can be very challenging, with the major differential diagnosis being cellular PA. By definition, LG CXPA is low grade malignant transformation of a pre- or co-existing PA, and both low grade salivary gland carcinoma and PA are present in the same neoplasm [2]. The carcinoma component is defined on basis of recognition of a specific type of salivary gland carcinoma and/or evidence of infiltrative growth. Both the recognition of a specific type of salivary gland carcinoma and

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recognition of infiltrative growth can be challenging. The epithelial and myoepithelial components of PA can form different architectural patterns, and focal areas of PA can be indistinguishable from other low grade malignant salivary gland neoplasms, such as basal cell adenoma/adenocarcinoma, adenoid cystic carcinoma, polymorphous adenocarcinoma, and myoepithelial carcinoma. The cytologic and focal architectural overlap between PA and these low grade malignancies are well known to practicing pathologists. It is advised that a definitive diagnosis of malignancy should be avoided for small biopsy specimens, as evaluation of the entire lesion is often necessary to distinguish low grade malignant neoplasms from PA [2, 3]. Circumscription/encapsulation is an important feature of PA, while malignant neoplasms typically demonstrate infiltrative growth. Thus evaluating the interface between neoplastic and adjacent normal tissue is of ultimate importance in establishing the correct diagnosis of salivary gland neoplasms. In some cases, however, infiltration is not straightforward, as certain “infiltrative growth” can be seen in PA, including capsular invasion and vascular invasion. In addition, “capsular herniation” or “pseudopodia” can be seen in stroma-rich PA, in which the stromal component of PA projects into adjacent normal tissue without a capsule. All three of these histological findings have been shown to have no prognostic significance, and are not diagnostic of malignancy [4, 5]. Thus distinguishing low-grade CXPA from cellular PA can be difficult and subjective in a considerable subset of cases.

FNA is widely used for diagnosing salivary gland neoplasms. FNA is a safe, cost-effective and accurate method for diagnosing salivary gland lesions. Compared with biopsy, FNA is associated with milder and fewer complications, especially with facial nerve damage. In addition, the diagnostic sensitivity and specificity of FNA are comparable to these of small biopsy and frozen section procedure according to some studies [6]. Histological changes following FNA are usually mild and focal, and include hemorrhage, inflammation, fibrosis, and squamous metaplasia. Rare cases of extensive tumor necrosis, typically seen in oncocyctic neoplasms, have been reported [7]. In general, FNA changes are not causes of diagnostic difficulty in salivary gland neoplasms.

In this study, we report three cases of LG CXPA. All three cases had residual PA from which carcinoma arose from. The first case was diagnosed based on the infiltrative growth of the neoplasm, the second case was diagnosed based on recognition of a specific type of low grade malignant salivary gland neoplasm (myoepithelial carcinoma), and the third one was diagnosed based on both recognition of a specific type of low grade malignant neoplasm (epithelial-myoepithelial carcinoma) and the presence of infiltrative growth. Two of these cases showed post-FNA changes that are potential causes for misinterpretation. We reviewed

the diagnostic criteria for LG CXPA and discussed the FNA-related histological changes in salivary gland that pathologists should be aware of to avoid misdiagnosis, especially for LG CXPA.

Case Presentation

Case 1

A 46-year-old male with no other significant past medical history presented with a right parotid mass of 3 years duration. CT scan showed a well-circumscribed 3.9 cm mass in the superficial lobe of right parotid. FNA was performed. Cytomorphologic features typical for a pleomorphic adenoma, including ductal epithelium, myoepithelial cells, and chondromyxoid stroma components were all present. Subsequently the patient underwent a right parotidectomy 8 days after the FNA.

Gross examination of the resected parotid gland showed a 5.5 cm well-circumscribed firm mass with a heterogeneous cut surface. Microscopically, the tumor was composed of cells forming ducts with islands of squamous differentiation. Focal chondromyxoid stroma was present. In addition, there were areas of necrosis associated with focal mild atypia and an increased mitotic rate. The capsule was entirely submitted for evaluation and showed diffuse edema, lymphocytic infiltrates, and extensive fibroblastic proliferation. The salivary gland surrounding the tumor demonstrated diffuse acinar atrophy and ductal proliferation. Careful inspection of the capsule showed several foci with extension of tumor beyond the fibrous capsule and invasion into normal salivary gland tissue. The area of extension beyond the capsule measured <1.5 mm in the largest focus (Fig. 1). The diffuse reactive/reparative changes made the assessment and measurement of invasion very difficult. After multiple intra-departmental and inter-departmental discussions, a diagnosis of minimally invasive LG CXPA was made.

No additional treatment was done. The patient was doing well at 5 months after the surgery. There was no sign of residual or recurrent disease based on physical and radiologic examination.

Case 2

A 58-year-old female presented with a right parotid mass and facial nerve paralysis. Her past medical history was significant for having pleomorphic adenoma of the right parotid gland that had recurred twice. She had three prior surgeries performed in a foreign country with removal of the masses and both the superficial and deep parotid lobes. MRI examination of the recurrent mass showed

Fig. 1 Case 1 **a** One focus of tumor infiltrates through the capsule and into adjacent salivary gland, which shows extensive reactive post-FNA change (2X). **b** Extension beyond the capsule measures less than 1.5 mm. These invasive tumor cells are bland, with no increased mitotic activity or nuclear pleomorphism. Based on these findings, a

diagnosis of minimally invasive LG CXPA was made (10X). **c** Typical PA area with chondromyxoid stroma, ducts, and myoepithelial cells (10X). **d** Extensive reactive changes also involve normal salivary gland with acini atrophy, ductal proliferation, edema and lymphocytic infiltrates (10X)

a well-circumscribed multi-lobulated 5.8 cm solid mass located at the right parotid gland site. No invasive growth was appreciated. FNA was performed, and a cytologic diagnosis of PA was made with characteristic morphologic findings. The patient underwent resection of the mass 25 days after FNA.

Gross examination of the resected specimen showed a multilobulated solid mass with no necrosis or hemorrhage. Microscopically, the specimen was composed of multiple nodules varying in size from several millimeters up to 3.6 cm. Some areas of the largest nodule showed typical pleomorphic adenoma morphology with epithelial cells forming ducts, chondromyxoid matrix and myoepithelial cells. The nodules at the periphery were hypercellular, and composed of tumor cells with nested growth pattern, clear cytoplasm and mild nuclear pleomorphism. Increased mitotic activity (up to 10/10 high power field (HPF)) was noted in these hypercellular nodules (Fig. 2). Immunohistochemical stains showed that these tumor cells were positive for S100, CK5/6 and p63, and were negative for

CK7, confirming the myoepithelial nature of these cells. The multinodular growth pattern, hypercellularity, and increased mitotic activity were diagnostic of low grade myoepithelial carcinoma [8].

One area within the largest nodule showed necrosis. The necrosis was considered one additional piece of evidence to support a diagnosis of CXPA. However, careful evaluation showed that the necrosis was more likely FNA-related, as other reactive changes including hemorrhage, fibrosis and granulation tissue were seen at the periphery of the necrosis.

The clinical team decided to closely follow-up this patient with no neoadjuvant therapy. She was doing well at 2 month after the surgery.

Case 3

A 46 year old female presented with a right parotid mass for 2 years. CT scan showed a well-circumscribed 3.6 cm mass, radiographically consistent with a benign tumor.

Fig. 2 Case 2 **a** Multinodular growth of low grade myoepithelial carcinoma. Tumor cells with clear cytoplasm are seen (2X). **b** Tumor cells with moderate nuclear pleomorphism, clear cytoplasm and increased mitotic activity. **c** Focal plasmacytoid morphology is seen in some areas. Increased mitotic activity and atopic bodies are seen. **d** Residual PA area with ductal structure, myoepithelial cells,

and minimal stroma. **e** Large areas of necrosis is seen. However, the necrosis is adjacent to areas of hemorrhage, fibrosis, and granulation tissue. This is considered post-FNA change. **f** One focus of necrosis is seen located within the hypercellular myoepithelial-rich area. It is difficult to tell the necrosis is true tumor necrosis or FNA-related change

FNA diagnosis was PA with classic cytomorphic features.

Gross examination of the resected parotid gland showed a 4.0 cm well-circumscribed multilobulated solid mass. The mass was entirely submitted for microscopic examination. Microscopically, the mass was encapsulated with irregular borders and multiple cellular projections and satellite

nodules extending into adjacent salivary gland and soft tissue. These projections and nodules were comprised of bland basaloid cells with intervening basement membrane material. Minimal cytologic atypia was seen, and mitotic activity was up to 3/10 HPF. No necrosis was present. In the center of the mass, there was one large area of hyalinized stroma with focal chondromyxoid feature, corresponding to

the residual PA (Fig. 3). Immunohistochemical stains were performed. These nodules were composed of a two-layered epithelial-myoepithelial epithelium, with ductal cells positive for CK7 and myoepithelial cells positive for S-100 and p63. The tumor cells were negative for beta-catenin. Based on the morphologic and immunohistochemical findings, a diagnosis of epithelial-myoepithelial carcinoma ex PA was made.

No additional surgery or other treatment was done to this patient. She was doing well at 6 months follow-up after the surgery.

Discussion

Salivary gland neoplasms are uncommon tumors, with incidence of less than three per 100,000 people according to data from National Cancer Institute. Despite being rare, these neoplasms represent one of the most heterogeneous groups of neoplasms: the current WHO Classification of

Head and Neck Tumors contains 33 different types of salivary gland neoplasms [9]. Many of these tumors are very rare, demonstrate overlapping histomorphologic features with each other, and diagnosis can be very challenging, especially for nonspecialized pathologists.

LG CXPA is one of the rarest and under recognized salivary gland neoplasms. Despite being completely different from its HG counterpart in terms of clinical presentation, treatment option, prognosis, and histomorphological findings, LG CXPA is not separated from HG CXPA in the vast majority of articles and books, including the current WHO Classification of Head and Neck Tumors [2, 8, 10, 11]. As a consequence, LG CXPA is not well known to many practicing pathologists, surgeons and oncologists.

LG CXPA is defined as low grade salivary gland carcinoma arising from a PA component. The carcinoma component can be any low grade malignant salivary gland neoplasm: low-grade adenocarcinoma NOS, myoepithelial carcinoma, mucoepidermoid carcinoma, polymorphous low-grade adenocarcinoma, acinic cell adenocarcinoma,

Fig. 3 Case 3 **a** Tumor with irregular border. Hypercellular nodules and projections are seen at the periphery of the neoplasm. Although a thick fibrous capsule is present, this is considered infiltrative growth. **b** The tumor cells are bland basaloid cells. Necrosis, nuclear pleomorphism, and increased mitotic activity are not seen. The two types

of epithelial-myoepithelial cells are not readily appreciated on morphology, but is demonstrated by immunohistochemical study. **c, d** Tumor nodules are seen outside of the capsule and grow into the normal salivary gland

epithelial-myoepithelial carcinoma, and adenoid cystic carcinoma [2]. These low grade neoplasms typically do not show overt malignant features. Cytological atypia is typically mild, mitotic activity is low, the ki-67 index is usually less than 5% for these tumors, and necrosis is only very rarely seen. In addition, many of these neoplasms demonstrate overlapping morphology with each other, and with cellular PA. With the PA component, LG CXPA can be mistaken for a cellular PA with multinodular growth pattern.

Histologically, most cases of PAs are encapsulated neoplasms composed of three components: epithelial cells, myoepithelial cells, and chondromyxoid stroma. All three components can demonstrate variable histological morphology, and as a consequence, it is known that “no two PAs look alike”. While the majority of PA are not difficult to diagnose, some problematic cases include cellular PAs with limited stroma, or non-encapsulated tumors that involve minor salivary glands. PAs can also show multinodular growth with pseudopodia extending to adjacent soft tissue and normal salivary gland. These pseudopodia are usually hypocellular comprised of myxoid stroma only. Recurrent PA, in contrast, typically demonstrates “infiltrative growth” presenting as multiple nodules in the soft tissue, skeletal muscle and other normal tissues. These recurrent PAs are usually stroma-rich but not hypercellular [4, 5].

According to Dr. Wenig, extension of tumor cells beyond the capsule into adjacent salivary gland parenchyma and soft tissue is considered invasive growth and diagnostic of malignancy [2]. For recurrent PA and PAs that are un-encapsulated, it is generally accepted that only perineural and intravascular invasion are considered “true” invasive growth and are signs of malignancy. Certain cytomorphologic features are considered atypical but not diagnostic of malignancy, including prominent zones of stromal hyalinization, diffuse cytologic atypia, atypical mitoses and tumor necrosis. While multinodular growth, tumor cells protruding into capsule, and intravascular permeation are considered acceptable for PA. These histologic findings may raise concern but are not diagnostic of malignancy, and not associated with adverse outcome. The same observation applies to findings such as hypercellularity, focally increased mitotic activity, and focal severe cytologic atypia (bizarre cells). For HG CXPA, usually necrosis, invasive growth, and diffuse atypia are all present and the diagnosis is straightforward [10], whereas for LG CXPA, the presence of atypical features in the residual PA could be the first hint for a possible malignant diagnosis [2].

FNA is widely used for diagnosing salivary gland lesions. Compared with biopsy, FNA is simple, fast and much more cost-effective. Minimal patient preparation is required. The entire procedure usually takes no more than

15–20 min. A preliminary diagnosis can be made on-site immediately after the procedure and delivered to the surgeon. Most importantly, FNA causes much less complications including facial nerve damage, tumor implantation, fistula formation, and tissue reaction that make subsequent surgery difficult. FNA is highly accurate in distinguishing nonneoplastic lesions from neoplasms, thus it spares up to one-third of patients from unnecessary surgeries. FNA is also accurate in distinguishing benign from malignant neoplasms, with sensitivity and specificity comparable to these of small biopsies [6]. For patients who are poor surgery candidates, the benign nature of the neoplasm provides assurance that surgery can be avoided or delayed. Post-FNA histological changes include hemorrhage, necrosis, fibrosis, squamous dysplasia, and capsular pseudoinvasion. These changes are usually mild and focal. In this study, we showed one case with extensive post-FNA reactive changes involving the tumor capsule and a second case with extensive post-FNA necrosis. These histologic changes may not cause diagnostic challenges in other types of benign or malignant salivary gland neoplasms. However, for LG CXPA, the diagnosis could be dependent on the presence and absence of capsular invasion, and necrosis is an important diagnostic clue, as necrosis is considered an atypical finding for PA and portends malignant transformation. These post-FNA changes could cause significant diagnostic challenges, as seen in one of the cases in this study. For two of the cases in this report, surgery was performed shortly after FNA (8 and 25 days respectively), and relatively extensive changes were seen. A longer interval between FNA and surgery might be better to avoid the presence of diffuse FNA changes.

Despite their complex histologic presentations, the majority of PAs have characteristic cytomorphologic features and the diagnosis is usually straightforward on FNA material. Cytologic diagnosis of PA is based on the presence of three of these components: epithelial cells, myoepithelial cells, and chondromyxoid stroma. While the epithelial cells and myoepithelial cells, as seen histologically, can have variable morphologies, the chondromyxoid stroma component is unique and demonstrates the same characteristic morphology. The stroma is light blue-green on Papanicolaou stain and purplish-red on Diff-Quick stain. It has fibrillary texture with irregular feathery outlines and has myoepithelial cells embedded in it. These distinctive features of stroma are characteristic enough to distinguish PA from other salivary gland neoplasms. However, LG CXPA cannot be diagnosed and distinguished from PA on FNA biopsy due to the lack of clear-cut cytologic atypia and the presence of the same components as PA. As seen in this study, all three cases of LG CXPA were misdiagnosed as PA on preoperative FNA. Fortunately, LG CXPA is an uncommon neoplasm, and we can still diagnose PA

on FNA with confidence due to the almost negligible incidence of LG CXPA. The other salivary gland lesion with similar chondroid/myxoid stroma as PA is sclerosing polycystic adenosis (SPA). SPA is a very rare non-neoplastic epithelial lesion that resembles fibrocystic change and sclerosing adenosis of breast. Some cases of SPA contain chondroid/myxoid stroma that is indistinguishable from that of PA histologically [12]. Only about 70 cases of SPA have been reported to date with five case reports describing FNA findings of SPA. None of these five reported cases showed the presence of stroma.

With the increasing utilization of FNA in diagnosing salivary gland lesions, frozen section is needed only when FNA diagnosis is inconclusive or to evaluate the margin status of resection specimens. For all three cases in this study, the preoperative FNA diagnosis was benign PA. Nonetheless, a frozen section was submitted for the recurrent PA case (case 2) due to radiologic findings that were suggestive of malignancy. The submitted sections showed a hypercellular neoplasm with bland cytology and limited stroma, with microscopic findings compatible with a cellular PA. Similar to other low grade malignant salivary gland neoplasms, frozen section is of very limited value for LG CXPA diagnosis. Usually evaluation of multiple sections including the entire capsule is required for the correct diagnosis.

Compliance with Ethical Standards

Conflict of interest None of the authors have any conflicts of interest to disclose.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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