Case Report

Extensive squamous metaplasia with cystic change in pleomorphic adenoma: A potential diagnostic pitfall in fine needle aspiration cytology

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ABSTRACT

Pleomorphic adenoma (PA) is the most common salivary gland tumor, frequently affects the parotid gland. Histological diversities are common as PA may show mucous, sebaceous, oncocytic cells, and squamous metaplastic cells. Squamous metaplasia rarely results in formation of extensive keratin-filled cyst lined by squamous epithelium. This can be mistaken for malignancy, like squamous cell carcinoma and mucoepidermoid carcinoma on cytological interpretation, due to limited and selective sampling. Here, we report a case of slowly enlarging parotid mass in a 70-year-old male. Cytological smears revealed moderately atypical squamous cells, clumps of keratin material, necrosis, inflammatory cells and macrophages along with bland epithelial and myoepithelial cell in fibromyxoid stroma. Cytological diagnosis of squamous cell carcinoma ex-pleomorphic adenoma was suspected. Subsequent resection showed pleomorphic adenoma, with extensive squamous metaplasia and cystic change on histology. There was no evidence of squamous cell carcinoma. The cytopathology findings are probably related to ischemic infarction, which mimic malignancy. This case emphasizes the need for a cautious and systematic approach in the cytological interpretation of cystic pleomorphic adenoma with metaplastic epithelial changes. We discuss the pitfall in the cytological diagnosis including differential diagnosis of this uncommon presentation.

Key words: Cystic change, fine needle aspiration cytology, pleomorphic adenoma, squamous metaplasia, squamous cell carcinoma

INTRODUCTION

Pleomorphic adenoma (PA) is the most common benign tumor of major or minor salivary glands.[1-3] Fine needle aspiration cytology (FNAC) is an accurate tool for the diagnosis of PA, with a reported reliability of 80-95%.[4,5] PA is characterized by biphasic pattern of epithelial/myoepithelial cells and fibromyxochondroid stroma.[1,4] However, morphological variations cause difficulty in the cytodiagnosis.[1,5] PA rarely presents with extensive keratin-filed cyst lined by squamous epithelium. Such microscopic findings may represent a diagnostic dilemma for pathologists and misinterpreted as squamous cell carcinoma or mucoepidermoid carcinoma on cytology.[1-9] We report a case of PA with extensive squamous metaplasia and cystic changes in a 70-year-old male. The cytopathological picture showed a puzzling mixture of necrosis, keratin, inflammation, and moderately atypical squamous cells with bland epithelial and myoepithelial cells in fibromyxochondroid stroma, simulating squamous cell carcinoma in preexisting PA. On subsequent parotidectomy squamous cell carcinoma was not found on extensive histological sampling. Infarction-induced striking atypia of metaplastic cells closely stimulate malignancy. This case highlights the difficulty of making a correct cytological diagnosis and discusses various differential diagnoses of such unusual entity.

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CASE REPORT

A 70-year-old male presented with complaint of slow growing painless mass over the right parotid region since

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5 years. Physical examination showed 5 × 4-cm sized, firm, mobile swelling with normal overlying skin. Radiological findings revealed solid-cystic lesion with high vascularity in the superficial lobe of the right parotid gland. Clinical and radiological findings suggest benign salivary gland neoplasm.

FNAC was done using a 23-G needle attached to a 10-cc syringe. FNAC yielded whitish cheesy aspirate mixed with blood. Smears were fixed in 95% ethanol and stained with Hematoxylin-Eosin (H and E) stain. Cellular smears revealed many clusters and dispersed keratinized squamous cells intermingled with bland epithelial and myoepithelial cells, fibrillary chondromyxoid matrix, and hyaline globules. Few clusters of overcrowded squamous cells showed moderate to marked pleomorphism, hyperchromatic nuclei, prominent nucleoli, and moderate cytoplasm. Many dispersed tadpole-like squamous cells showed hyperchromatic and irregular nuclei with keratinized cytoplasm. Keratin flakes, necrosis, inflammatory cells, macrophages, and histiocytes were evident in background [Figure 1]. A diagnosis of squamous cell carcinoma ex-pleomorphic adenoma was suspected.

In view of suspected malignancy, a nerve-sparing parotidectomy was performed. The mass was not adhered to the surrounding tissues. Grossly tumor was well encapsulated, grayish-white, and measured 5 × 4 × 4 cm. The cut surface was predominantly cystic and filled with yellowish necrotic material. Adjacent whitish firm area was evident near capsule [Figure 2]. Histology showed an encapsulated tumor mass with approximately 70% of the tumor volume composed of necrosis and keratin filled multicystic spaces, lined by metaplastic squamous epithelium with papillary finger-like fronds of squamous cells. Few solid sheets and nests of squamous cells were intermingled with fibrous stroma and inflammatory cells. Occasional foci of residual chondromyxoid matrix with ductal structures lined by bland cuboidal cells were seen. The cystic spaces containing eosinophilic amorphous material were lined by metaplastic squamous cells and cuboidal cells with granular cytoplasm. The rest of the areas showed fibrosclerotic and inflammatory response. On extensive multiple sampling, mucoid or malignant cells were not found [Figure 3]. A diagnosis of pleomorphic adenoma with extensive squamous metaplasia and cystic changes was made.

The postoperative course was uneventful. Patient had been reviewed regularly, without evidence of recurrence after a period of 3 years of excision.

DISCUSSION

Pleomorphic adenoma (PA) is the most common salivary gland neoplasm.[1-3] PA usually appears as a solitary,

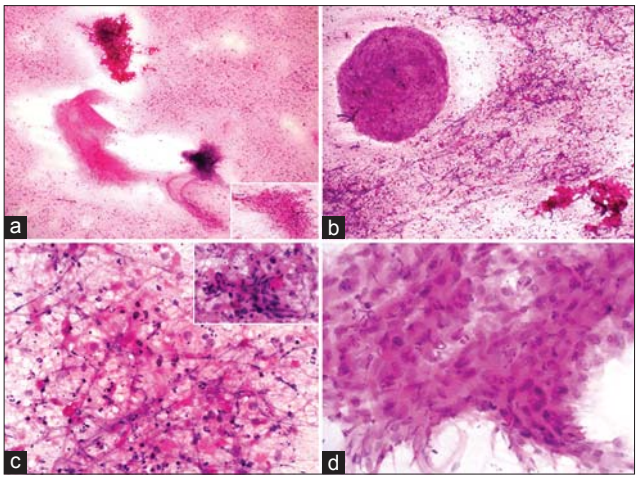

Figure 1: H and E stain: (a) Clusters and dispersed squamous cells admix with keratin, necrosis and chondromyxoid matrix (×40) (Inset figure × 200); (b) Bland epithelial cells are embedded in eosinophilic hyaline globule, with adjacent cluster of keratinized squamous cells in inflammatory and necrotic background (×100); (c) Markedly atypical tadpole-shaped keratinized squamous cells show hyperchromatic, irregular nuclei, and keratinized cytoplasm (×200) (Inset figure × 400); (d) Squamous cells show moderate to marked pleomorphism, vesicular nuclei, prominent nucleoli, and scant to moderate cytoplasm (×400)

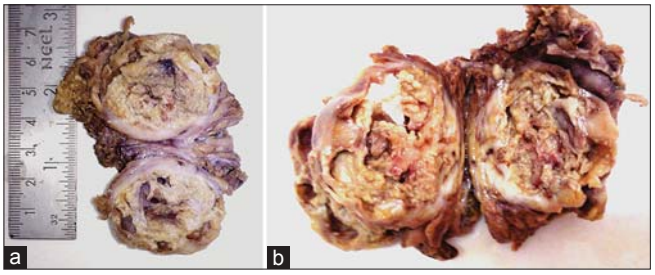

Figure 2: (a) Grossly well-encapsulated grayish-white tumor measures 5 × 4 × 4 cm. (b) The cut surface shows predominant cystic area, filled with yellowish necrotic material. Whitish firm area is evident near capsular margin

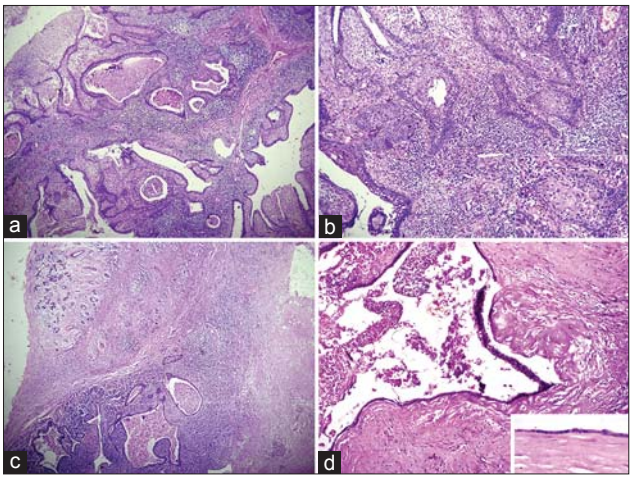

Figure 3: H and E stain: (a) Necrosis and keratin-filled multicystic spaces are lined by metaplastic squamous cells with papillary finger-like fronds (×100); (b) Sheets and nests of squamous cells show mild atypia and keratinization with moderate inflammatory cells (×200) (Inset figure ×400); (c) Foci of chondromyxoid matrix with bland cuboidal cell-lined ducts, along with few metaplastic squamous cells lined cystic spaces (×40); (d) Necrotic and eosinophilic material-filled cystic space is lined by cuboidal cells with granular cytoplasm, with adjacent fibrosclerotic tissue (×100) (Inset figure ×400)

slowly growing, painless rubbery mass.[2,3] Histological diversities are the hallmark of PA as its name implies.[1-4] The proportion between epithelial and chondromyxoid elements are variable.[3] In addition, PA is characterized by wide spectrum of morphological patterns, including squamous cells, mucous cells, oncocytes, sebaceous cells, bone, adipose tissue, and crystalline materials.[1-3]

Focal squamous metaplasia is found in about 25% of PA.[1-4] Rarely extensive squamous metaplasia with cystic changes are reported.[1-8] Squamous metaplasia is commonly associated with ischemia, repair following infarction, and necrosis of the salivary gland.[1,2,9] Squamous metaplasia is also evident in non-neoplastic entities like chronic sialadenitis, necrotizing sialometaplasia, lymphoepithelial cysts, salivary duct cyst and in neoplastic lesion like Warthin tumor.[1,2,7,10] The tumor may be misdiagnosed as a squamous cell carcinoma when squamous metaplasia is extensive and shows nuclear atypia.[2] Adenexal differentiation in the form of extensive keratin-filled cysts, reminiscent of trichoepitheliomatous differentiation is also reported in literature.[3,4] Stromal changes, such as chondroid, osseous, myxoid or mucoid changes are variable in PA. However, scanty or absence of stroma is an unusual finding.[3] Extensive squamous metaplasia with cystic changes in PA, especially in scanty or absent stroma, can lead to a misdiagnosis of benign condition like keratocystoma or malignancy including mucoepidermoid carcinoma and squamous cell carcinoma, due to limited and selective sampling by FNAC and incisional biopsy.[1-9] Morphological diversities are often not a problem in histopathology, where the whole tumor is available for examination.[4] Cyst formation might originate from the squamous metaplasia of tumor cells, enlargement of duct-like structures by secretion from tumor cells or salivary gland tissue, hemorrhagic infraction and necrosis in the malignant tumor.[11] In our case, extensive necrosis-filled cystic spaces and moderately atypical metaplastic squamous cells are probably related to the ischemia, necrosis, and reparative process. These changes on cytology mislead for squamous cell carcinoma in preexisting PA.

Keratocystoma, dermoid cyst, squamous cell carcinoma, and mucoepidermoid carcinoma (MEC) are the important differential diagnosis of this common benign entity with unusual presentation.[1,3,5,7,10,12-14] Keratocystoma, previously known as choristoma, is a benign salivary gland tumor resembling a trichoadenoma. It shows keratotic lamellae-filled multi-cystic spaces, lined by multilayered stratified squamous epithelium. It also exhibits solid squamous cell islands surrounded by basement membrane within the collagenous stroma, keratinized masses outside the cysts with multinucleated giant cells and focal calcification. The keratinized squamous cells without granular layers are the unique feature of keratocystoma.[3,12] Goulart MC *et al.*, believes that the PA and keratocystoma may constitute related lesions, representing different stages in the evolution of a specific type of salivary gland tumor.[3] Our case shows many features of keratocystoma. However, keratocystoma lacks the myxochondromatous, myoepithelial, or glandular components that are demonstrated in our case. Moreover, the cystic spaces are lined by squamous epithelium with a granular cell layer in our case, which is absent in keratocystoma. FNAC of dermoid cyst of the parotid gland show anucleated and nucleated squamous epithelium, keratin debris, and skin adnexal structures. Histopathology confirms the diagnosis, by revealing a cyst wall with keratinization of the squamous epithelium and the presence of skin annexes (hair follicles, sweat glands, sebaceous glands).[12,13] Anucleated squamous cells and skin appendages are not seen in our case. The features favoring squamous cell carcinoma in our case are the presence of atypical keratinized squamous cells, necrosis, keratin, inflammation, and cystic changes. Cytologic atypia in metaplastic squamous cells are the main culprit for the misdiagnosis. However, presence of fibrous capsule and absence of invasion are against the squamous cell carcinoma on histology.[1,3,5,7,10] MEC show mucous, intermediate, and squamoid cells. Unlike our case, multi-cystic spaces of MEC are usually lined by mucous cells. Prominent keratinization and epidermoid cells are rare in MEC. Potential for misdiagnosis of PA as MEC on cytology include squamous and basaloid cells mimicking squamous and intermediate cells of MEC, presence of sebaceous/mucinous metaplastic cells, vacuolated histiocytic cells, mucoid material and absence of chondromyxoid matrix.[1,3,4] To avoid misinterpretation of PA with squamous metaplasia as squamous cell carcinoma or MEC on FNAC, a close scrutiny for chondromyxoid stroma, a characteristic feature of pleomorphic adenoma, is important. However, even if the stroma of PA is identified, the differential diagnosis may still include a squamous cell carcinoma or MEC arising in a preexisting PA. However, these are exceedingly rare.[1,3,4,6]

Wide local excision is the treatment of choice.[3] PA has a low proliferative rate. Interestingly, the epithelial lining of the large keratin-filled cyst shows a higher proliferative index than the other areas. It may signify that the squamous metaplasia resulting in the large keratin-filled cyst in PA may be clinically significant, probably related to an important growth potential.[3]

CONCLUSIONS

PA with extensive squamous metaplasia and cystic changes can pose significant diagnostic challenge on cytology. Careful cytological evaluation of such case is mandatory, as it would otherwise mislead to squamous cell carcinoma

or MEC in pre-existing PA. Atypical metaplastic squamous cells should be evaluated with great caution. It is important to be aware of this rare benign entity, a mimicker of malignant lesion, to avoid unnecessary aggressive therapy.

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