Carcinoma ex pleomorphic adenoma: a case report and review of literature

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Abstract:
Background: Carcinoma ex pleomorphic adenoma (CA-ex-PA) is extremely unusual in minor salivary glands of oral cavity. CA-ex-PA is a carcinomatous change as a primary or as a recurrence of pleomorphic adenoma.
Objective: Due to resemblance of clinical symptoms of Ca ex PA and benign pleomorphic adenoma, it is mandatory for surgeons to keep high degree of clinical alertness, considering the peculiarity of this tumor.
Case Report: 54-year-old male presented with swelling on left side in the pre-auricular region from the middle of zygomatic arch to mastoid process and from tragus of the ear up to angle of mandible. Fine needle aspiration cytology revealed a mixture of benign and malignant components. Total left parotidectomy with left radical neck dissection followed by reconstruction with cervicodeltopectoral flap was performed. Combination of chemotherapy and radiotherapy were given to patient. Histologic examination and pre-operative fine needle aspiration cytology confirmed the diagnosis of Carcinoma ex pleomorphic adenoma (CA-ex-PA). Two-year follow-up of patient showed no recurrence of the lesion.
Conclusion: Due to the similarity in the clinical symptoms of CA-ex-PA and benign pleomorphic adenoma, it is vital that clinicians maintain a high degree of clinical vigilance, considering the oddity of this malignancy.
Keywords: Carcinoma ex pleomorphic adenoma, Fine needle aspiration cytology, parotidectomy.
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Introduction
Malignancies of parotid gland are relatively rare and account for 1-3 % of all tumors of head.¹ The most common benign salivary gland tumour is Pleomorphic adenoma (PA). It is mostly found in parotid glands and is usually managed successfully by surgical resection.² Unfortunately around 6% of these tumours transform into Carcinoma ex pleomorphic adenoma. (Ca-ex-PA).²³ Ca-ex-PA is defined as a carcinoma originating from a primary (de novo) or recurrent benign pleomorphic ade-
noma. Its incidence is about 5 to 25% of parotid carcinomas. The exact pathogenesis of Ca-ex-PA is not clear. One school of thought is that they are malignant from the onset whereas some believe it to be a carcinomatous transformation of a mixed tumor. Histopathological examinations is important aid diagnosis. The objective in presenting this particular case is to present pathological and clinical features of Ca-ex-PA.

Case report

A 54-year-old male patient reported to our institution with a swelling on left side of the pre-auricular region extending anteroposteriorly from midpart of zygomatic arch to mastoid process and superoinferiorly from tragus of the ear to the angle of mandible (Figure 1).

The patient also had enlarged level IIB lymph nodes. The skin over the swelling was fixed; on palpation, the lesion was hard and firm in consistency. Intra-oraly, the uvula and tonsil were shifted towards the right side. Fine needle aspiration cytology showed combination of cells having benign and malignant elements (Figure 2); benign epithelial component appeared as small to round cells with bland oval nuclei while malignant component appeared as large cells with large pleomorphic nuclei showing granular chromatin and high nucleus: cytoplasmic ratio (Figure 3).

Fluorodeoxyglucose (FDG) positron emission tomography depicted a high uptake in the left parotid region and in the neck nodes at level IIB, III and IV. Ultrasonography of neck was done for mapping of nodes which showed metastatic disease at level IIB and III. Treatment decision taken in our case was total parotidectomy of the left side with left radical neck dissection followed by cervicodeltopectoral flap (Figure 4).
Most crucial part of management was resectibility of the lymph nodes as they were totally fixed on vital structures like common carotid artery and for that particular reason radical neck dissection was carried out first. Fixed skin over the lymph node was marked separately and upper cervical incision was joined to the marked skin. Second incision was a vertical incision which was dropped from primary incision at 90 degrees to 1-1.5 cm above clavicle sub-platsymal flaps were raised till identification of greater auricular nerve. Clearance was done from level IA to
IB till level V, nodes at level IIB were completely fixed to the carotid sheath however a plane could be formed over the carotid sheath to remove the nodes, Level IIB nodes were excised in total with overlying skin. XI nerve, SCM was sacrificed. Once radical neck dissection was finished primary tumor was approached with a lazy S pre-auricular (Blair’s incision), flap was raised in subplatysmal plane anteriorly till anterior border of parotid gland. Dissection was deepened in pre-auricular tragus region for identification of facial nerve main trunk which could not be found so dissection was continued till the styloid process posteriorly, medially tumor was free from posterior border of ramus of mandible so it was not sacrificed however of the deep portion of gland and base of skull were blunt dissection was done with a gloved finger. External carotid artery was ligated at deeper level to medial surface of deep lobe of parotid gland and whole tumor was removed in toto. Cervicodeltopectoral flap marking was done by extending lower vertical incision till tip of acromion process of scapula continuing inferomedially towards xiphisternum medial to nipple of chest. Haemostasis was achieved and no.16 drains were placed and suturing done in layers patient healed uneventfully, drains removed after 12 days. Patient was sent for adjuvant radiotherapy and chemotherapy with a boost of radiation at level IIB. Histopathology of the resected tumor revealed undifferentiated carcinoma ex pleomorphic adenoma suggested by pleomorphic tumor cells with focally vacuolated cytoplasm seen infiltrating into the benign pleomorphic adenoma. Foci showing infiltrating carcinoma composed of cells arranged in nests, sheets, cords and vague glandular pattern noted (Figure 5). Histopathological examination showed areas of pleomorphic adenoma composed of biphasic population of cells in chondromyxoid matrix. Duct like structures lined by inner epithelial and outer myoepithelial cells (Figure 6).

**Fig.5** Areas of pleomorphic adenoma (Black arrow) with infiltrating foci of carcinoma (grey arrow) – H&E stain-10 X

**Fig 6:** Pleomorphic adenoma composed of biphasic population of cells in chondromyxoid matrix-H&E stain-10 X
The cells are highly pleomorphic with moderate amount of eosinophilic cytoplasm, round nuclei with irregular nuclear borders, coarsely clumped chromatin with some showing prominent nucleoli (Figure 7). Post-operative immunohistochemistry and fluorescence in situ hybridization for HMGA-2 gene was positive (Figure 8). Recall after 24 months showed the absence of any recurrence (Figure 9). The overall picture was suggestive of Carcinoma ex pleomorphic adenoma (CA-ex-PA).

**Fig 7:** Foci of carcinoma composed of pleomorphic cells arranged in nests and vague glandular pattern- H & E stain-40 X

**Fig. 8:** Immunostain for HMGA-2 gene
Discussion

CA-ex-PA known carcinoma in a mixed tumour or carcinoma ex mixed tumour typically found in the gland arising from pleomorphic adenoma. CA-ex-PA encompass about 6.2% of all mixed tumors, 3.6% of all tumors of salivary glands salivary tumors, 12% of all salivary malignancies. CA-ex-PA which is an uncommon malignant tumor of salivary gland, has a prevalence rate of 5.6% cases/100,000 malignant tumors. The incidence rate of CA-ex-PA is 0.17% tumors/1 million persons.

Livolsi.V and Perzin.K in 1977 introduced the term non-invasive carcinoma ex pleomorphic adenoma and concept of malignant tumour arising in mixed tumour. This was supported by Spiro et al., but with the observation that histological indications demonstrate pre-existing salivary gland tumour. CA-ex-PA is a carcinomatous conversion inside a primary (de novo) or recurrent pleomorphic adenoma.

CA-ex-PA is mostly observed as a firm mass present in parotid gland. It has also been found to originate in sub-mandibular gland and at times in minor salivary glands in the region of hard and soft palate. Tumors at these sites are smaller in size compared to those arising from the major salivary glands. CA-ex-PA have also been identified in lacrimal glands, nasal cavities, trachea and breast. Literature on CA-ex-PA in different areas of head and neck region are added in a tabulated format indicating area of carcinoma, case reported with relevant information (Table 1).
CA-ex-PA has more predilection for females compared to males and is frequently seen during sixth to seventh decade of life. Based on extent of carcinomatous component outside the fibrous capsule, CA-ex-PA can be sub-classified as i) non-invasive ii) minimally invasive (<1.5 mm penetration of malignant element into extra capsular tissue) and, iii) invasive (greater than 1.5 mm invasion from tumor capsule into to neighbouring tissues).

Invasive type has non-defined infiltrative margins. There is very high nuclear pleomorphism with prominent nucleoli. There is adjacent perivascular and perineural infiltration with haemorrhagic and necrotic foci. Where as in Non-invasive type has well-defined borders with very little pleomorphic nuclei. Small quantity of myxoid area is seen. Mix of Cellular and acellular areas are observed in low foci. As per the histological results, our case is an...
example of invasive type. As per WHO classification published in 2005 for malignant changes of pleomorphic adenoma, CA-ex-PA is the one which is most frequently encountered in comparison to metastasizing PA and carcinosarcoma. In our case, four important clues to arrive at a diagnosis were 1) location of swelling in the parotid region, 2) Fine needle aspiration cytology showing mixture of benign and malignant cells 3) Fluorodeoxyglucose (FDG) positron emission tomography showed an increased uptake in left parotid region, neck and 4) Ultra-sonography of neck for mapping of lymph nodes showing metastasis. On this basis, we arrived at the diagnosis of Carcinoma ex pleomorphic adenoma. Adjuvant pre-treatment fine needle aspiration cytology, fluorodeoxyglucose (FDG) positron emission tomography and ultrasonography aid in making preliminary diagnosis and extent of metastasis. Pre-operative diagnosis of tumor of parotid gland is established on basis of history, clinical findings, FNA findings, histologic picture. FNAC is frequently used preoperatively for diagnosis of CA-ex-PA. The sensitivity is still low mainly associated with error in sampling, cytomorphological variability and less experience. Lesions salivary glands with suspected carcinoma, it is important to have aspiration from multiple sites. CA-ex-PA can be misdiagnosed as some other malignant salivary gland tumor or mistaken with PA. Abundant atypical cells, coarsely clumped chromatin with prominent nucleoli and necrosis are key features in distinguishing PA from malignant tumors including CA-ex-PA.

In majority of cases of PA, most common malignancy observed is adenocarcinoma NOS (not otherwise specified). The other unusual malignancies which can be seen in relation to PA are that can arise in setting of PA are myoepithelial carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, adenoid cystic carcinoma and sarcomatoid carcinoma. In our case, it was adenocarcinoma NOS developing in setting of PA.

Treatment often involves a surgical procedure(parotidectomy), which may be followed by radiotherapy. Superficial parotidectomy is done in cases of minimally invasive CA-ex-PA whereas complete or radical parotidectomy is done for frankly invasive CA-ex-PA. A related neck dissection is also undertaken if cervical lymph nodes presents with evidence of metastases. Neck dissection may be functional, modified, or radical as per the indications. The surgical technique to eliminate the neoplasm could be followed by reconstructive surgery. A soft tissue reconstruction like radial free flap or a cervical rotation flap is accomplished in various cases for repair of the defect. In our case the reconstruction was facilitated by cervico-deltopectoral flap. Patients can be given with options of combination of chemotherapy and radiotherapy. Post-operative radiotherapy is normally used in cases of high grade disease or questionable resection adequacy, and for invasion of perineural tissues and lymph nodes. In this case, both radiotherapy and chemotherapy with a boost of radiation at level IIIB was given as per the treatment plan. Multiple factors like type of invasion, lymph node and local or distant metastasis, tumor grade and size and total removal of tumor does dictate prognosis of CA-ex-PA. Survival rates of these patients may be increased by prefect diagnosis of CA-ex-PA along with complete surgical and radiological treatment of these patients.

Recent molecular investigations of CA-ex-PA has provided with new insights on its carcinogenesis. It is seen that there is a progressive loss of heterozygosity (LOH) at chromosomal arms 8q, 12q, and 17p. Role of p53 gene has been suspected in pathogenesis of CA-ex-PA. Righi et al first reported with point mutation of p53 in CA-ex-PA. Patel et al found better immunohistochemical staining for p16 proteins and cyclin D1 with malignant components of CA-ex-PA compared to normal stromal and epithelial components. Also with progression of CA-ex-PA, expression of p21 gene may increase, linking to its role in progression of disease. Levels of COX-2 are sufficiently lower in PA compared to CA-ex-PA suggestive of increased expression of COX-2 could be an relevant as an early stage event in the pathogenesis of the this disease. Epidermal growth factor receptor (EGFR), HGF-A (scatter factor) and c-Met (a proto-oncogene) (45), Transforming growth factor alpha (TGF α), Fibroblast growth factors (FGF)-2 45 have been investigated to have a role in progression and invasion of CA-ex-PA. There was increased expression of E-cadherin expression in cases of CA-ex-PA with comparatively less reactivity in comparison to benign tumours. Thus, along with clinical, histological findings, these specific candidate genes which have been associated with the development and progression of CA-ex-PA should be considered as a vital diagnostic aid for confirmation of lesion.

**Conclusion**

Ca ex PA is an uncommon aggressive malignancy. Quite often it is associated with regional metastasis which invariably leads to mortality. It also poses a difficulty in diagnosis, as the mixed tumour component is usually minute.
and is easily overlooked, and the malignant component may be difficult to classify. Preoperative diagnosis of salivary gland tumours is quite challenging because of the overlap in histopathological characteristics. Due to the similarity of clinical symptoms of Ca ex PA and benign pleomorphic adenoma, it is vital that clinicians maintain a high degree of clinical vigilance, considering the oddity of this malignancy and performs postoperative immuno-histochemistry and fluorescence in situ hybridization for HMGA-2 gene to confirm the diagnosis. In conclusion, early and prompt diagnosis followed by aggressive surgical intervention of patients with Carcinoma ex pleomorphic adenoma can enhance their survival rates.

Conflict of interest
None declared.

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