

Massive metastasising Carcinoma ex pleomorphic adenoma of submandibular gland presenting as a neck mass: a clinical mimicker of a thyroid malignancy

Dr. Malini Goswami¹

¹Senior resident, Department of oncology, Yenepoya medical college, Mangalore

*Corresponding author

Dr. Malini Goswami

Email: sunny.manwani12@gmail.com

Abstract: Carcinoma ex-pleomorphic adenoma (CXPA) is a rare, destructive, poorly understood malignancy of the salivary gland. CXPA is described as a carcinoma arising from a primary (de novo) or recurrent benign pleomorphic adenoma (PA). It is most likely to occur within the major salivary glands, mostly parotid gland and usually occurs in patients in the 6th– 8th decades of life, approximately one decade later than patients with pleomorphic adenoma. Malignant changes in PA have been related with long tumor duration, tumor recurrence, radiation therapy, advanced age, a large tumor size and location in major salivary glands. It often poses a diagnostic challenge to clinicians as well as pathologists. Treatment for Ca ex PA frequently involves an ablative surgical procedure which may be followed by radiotherapy. Overall, patients with Ca ex PA have a bad prognosis. Accurate diagnosis and aggressive surgical management can however increase their survival rates. I present this case to highlight its clinical relevance and diagnostic challenges it posed when FNAC was used as a primary investigative modality.

Keywords: Massive, metastasising, carcinoma ex pleomorphic adenoma, submandibular gland

INTRODUCTION

Carcinoma ex pleomorphic adenoma (CXPA) is described as a carcinoma arising from a primary (de novo) or recurrent benign pleomorphic adenoma (PA) [1, 2]. It has been designated as carcinoma ex mixed tumour, carcinoma ex adenoma, and carcinoma ex benign pleomorphic adenoma [1-3]. It is an uncommon malignancy, as it has a prevalence rate of 5.6 cases per 100,000 malignant neoplasms and a yearly incidence rate of 0.17 tumours per 1 million persons [4]. I present this case to highlight its clinical relevance and diagnostic challenges it posed when FNAC was used as a primary investigative modality.

CASE REPORT

A 65 year old lady presented with swelling in the neck since 20 years which has gradually and progressively increasing in size. She had felt pain over the swelling since 4 months which was throbbing in nature, moderate in intensity with no radiation. On examination, (Figure 1) the swelling was located in the central and left part of her neck arising from left submandibular region reaching up to her clavicle. It was well defined, firm in consistency, non-mobile, non-tender and did not move with deglutition. Fine needle aspiration cytology (Figure 2) was done and revealed neoplastic cells arranged in loosely cohesive clusters and scattered singly in a dirty background. The cells were mildly to moderately pleomorphic, with moderate cytoplasm, centrally placed ovoid nucleus, fine chromatin and inconspicuous nucleoli. Some of these cell clusters exhibited crowding and nuclear grooves. A

diagnosis of carcinoma thyroid TBSRTC category IV was given. Subsequently a CT scan (Figure 3) was done which revealed a large heterogeneous mass lesion measuring 17 X12 X8.3 cm with areas of macrocalcification involving the left anterolateral aspect of neck and face with probable origin from submandibular gland. The lesion was seen to cause effacement of ipsilateral submandibular fat and abut the myelohyoid muscle with loss of fat planes. The deep lobe of submandibular gland could not be visualised separately. The lesion was seen to compress the left lobe of thyroid. Multiple subcentimetric enhancing lymph nodes were noted in the left carotid space, bilateral upper jugulodigastric and right parotid space, largest measuring 13X8 mm. The mass along with thyroid gland and cervical lymphnodes were excised and sent for histopathological examination. Gross examination (Figure 4) revealed a large mass weighing 1.2 kg and measuring 19.5 X 15 X 9 cms. External surface was bosselated, shiny with a thin capsule. Cut surface was solid nodular, yellow white to reddish pink, firm to hard in consistency. A small cystic area was seen measuring 1 X5 cms. The thyroid gland was grossly unremarkable. Microscopic examination (Figure 5) showed a partially circumscribed lobulated tumor composed of a mixed population of cells. One component was malignant –characterised by nests, cords and trabeculae of neoplastic cells with moderate eosinophilic cytoplasm, pleomorphic nuclei, vesicular chromatin and prominent nucleoli. Another component was benign-characterised by nests, diffuse sheets and acini composed of cells with clear to eosinophilic

cytoplasm, ovoid monomorphic nuclei, fine chromatin and inconspicuous nucleoli. Also noted were oncocyctic, plasmacytoid and squamoid cells. A prominent stromal component was seen which was chondromyxoid to hyaline with bland stellate to spindle cells embedded within it. One focus showed cartilage. Numerous dilated vessels were noted. Areas of necrosis were seen. Calcification was noted. Mitotic activity was variable (scant in the benign element and brisk in the malignant

element). Perineural invasion was not seen. The tumor infiltrated the adjacent soft tissue focally. Left submandibular gland sent separately showed origin of the tumor. 9 out of 17 cervical lymph nodes exhibited metastatic tumor deposits. Adjacent skeletal muscle and fat also showed tumor infiltration. A final opinion of Carcinoma ex pleomorphic adenoma submandibular gland with lymph nodal metastasis was rendered.



Fig-1: Clinical examination revealed a large swelling located in the central and left part of her neck arising from left submandibular region reaching up to her clavicle.

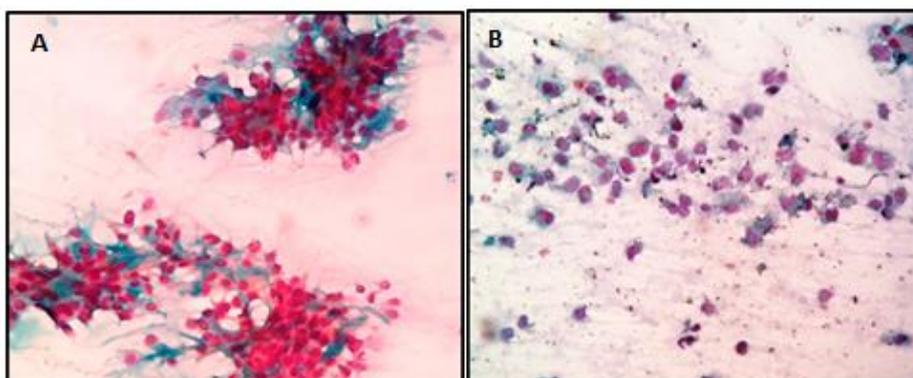


Fig-2(A, B): FNAC revealed neoplastic cells arranged in loosely cohesive clusters and scattered singly in a dirty background. The cells were mildly to moderately pleomorphic, with moderate cytoplasm, centrally placed ovoid nucleus, fine chromatin and inconspicuous nucleoli

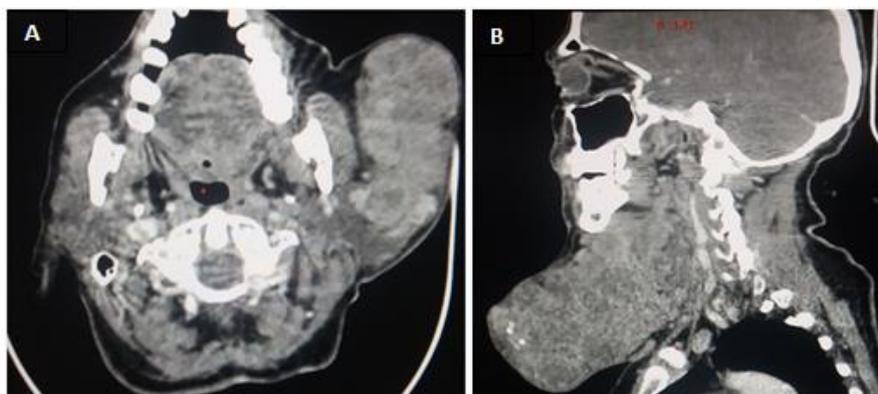


Fig-3(A, B): CT scan revealed a large heterogeneous mass lesion measuring 17 X 12 X 8.3 cm with areas of macrocalcification involving the left anterolateral aspect of neck and face with probable origin from submandibular gland.

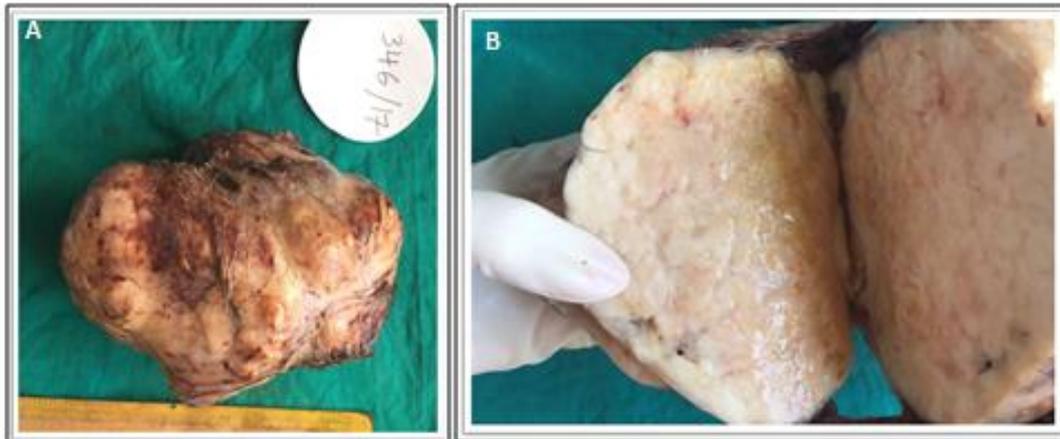


Fig-4(A,B): Gross examination revealed a large mass weighing 1.2 kg and measuring 19.5 X 15 X 9 cms. External was bosselated, shiny with a thin capsule. Cut surface was solid nodular, yellow white to reddish pink, firm to hard in consistency.

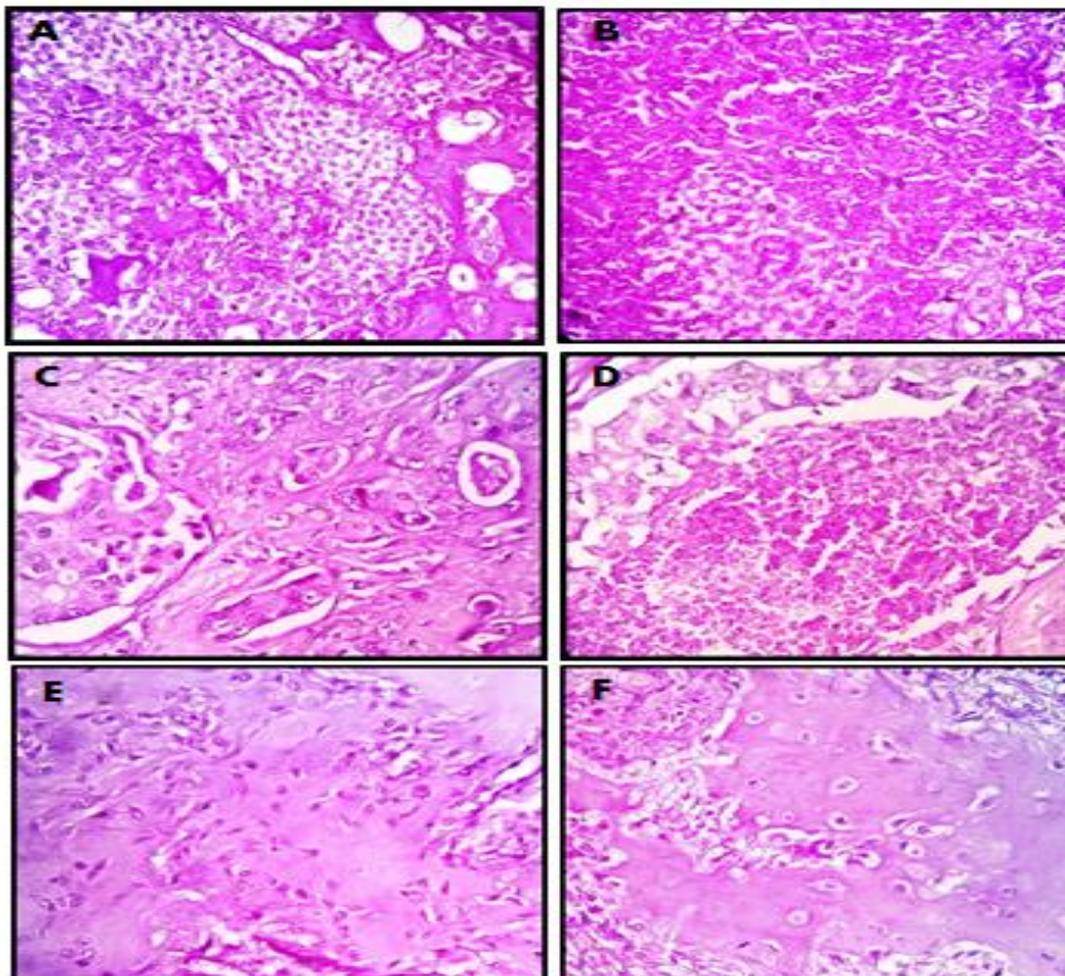


Fig-5:A-B: benign component characterised by nests, diffuse sheets and acini composed of cells with clear to eosinophilic cytoplasm, ovoid monomorphic nuclei, fine chromatin and inconspicuous nucleoli

C: Malignant component characterised by nests, cords and trabeculae of neoplastic cells with moderate eosinophilic cytoplasm, pleomorphic nuclei, vesicular chromatin and prominent nucleoli.

D: Areas of necrosis were seen.

E: A prominent stromal component was seen which was chondromyxoid to hyaline with bland stellate to spindled cells embedded within it.

F: One focus showed cartilage

DISCUSSION

Pleomorphic adenoma (PA) is a common benign neoplasm of the salivary glands that may undergo malignant transformation. Malignant changes in PA which occurs in 5 to 25% untreated patients, usually after 15-20 years of the primary lesion, arise through carcinomatous transformation and are congregated into three categories: carcinoma ex pleomorphic adenoma (CXPA), true malignant mixed tumor (carcinosarcoma), and metastasizing pleomorphic adenoma (mPA) [5, 6]. While carcinoma ex pleomorphic adenoma entails the malignant transformation of only epithelial component, carcinosarcoma is composed of a mixture of both carcinomatous and sarcomatous elements. Metastasizing pleomorphic adenoma is a histologically benign pleomorphic adenoma that curiously manifests local or distant metastasis [7]. In the present case, only the epithelial component was malignant; while the stromal elements were benign, compelling a diagnosis of Carcinoma Ex pleomorphic adenoma to be rendered. Malignant changes in PA have been related with a long tumor duration, tumor recurrence, radiation therapy, advanced age, a large tumor size and location in major salivary glands [5, 8]. Some authors have claimed that the risk of malignant transformation in PA increases from around 1.6% in tumors less than 5 years of evolution, to 9.5% for those presenting for more than 15 years [8]. The present case had a long tumor duration (20 years), advanced age (65 years), a massive size (19.5 X 15 X 9 cms) and submandibular location. CXPA is most likely to occur within the major salivary glands, mostly parotid gland and usually occurs in patients in the 6th– 8th decades of life, approximately one decade later than patients with pleomorphic adenoma [9]. The archetypal clinical history is that of a long-standing mass with rapid growth over the previous few months [7]. Patients frequently complain of a painless mass; but pain, facial nerve palsy, and skin fixation may also occur towards the later part [7]. Grossly, CXPAs are usually poorly circumscribed with some being extensively infiltrative [7]. Based on the presence and extent of invasion of the carcinomatous component outside the fibrous capsule, CXPA can be subcharacterised into non-invasive CXPA, minimally invasive CXPA, and invasive CXPA. This division has clinical relevance because the first two groups usually have an excellent prognosis while the latter has a more guarded prognosis [7]. When the malignant component undergoes lesser than 1.5 mm penetration into extracapsular tissue, it is classified as minimally invasive CXPA and when the invasion is greater than 1.5 mm, it is defined as invasive CXPA [4]. The present case was frankly invasive (>1.5 mm) with involvement of adjacent skeletal muscle and fat. FNAC is commonly used pre-operatively to diagnosis CXPA, however it has a low sensitivity, related to sampling error. The proportion of benign versus malignant components as well as stromal component can be quite variable in different regions of the tumor. Occasionally, extensive

sampling is necessary to find the benign component and in rare cases, a benign remnant might not be found; thereby significantly downplaying the role of FNAC in diagnosing these tumors. In the present case; this drawback was highlighted by the misdiagnosis of this tumor as thyroid carcinoma; during initial evaluation by FNAC. Clinical and radiological picture with thorough histopathological examination determines the diagnosis of CXPA. To fulfil the definition of CXPA, at least a focus of benign pleomorphic adenoma must be identified along with carcinoma or a previous benign pleomorphic adenoma must have been excised from a site in which recurrent tumor is carcinomatous [10]. The malignant component of CXPA is most frequently adenocarcinoma not otherwise specified. Sometimes, the component may be adenoid cystic carcinoma, mucoepidermoid carcinoma, or salivary duct carcinoma. The other less common histological subtypes include acinic cell carcinoma, epithelial-myoeplithelial carcinoma, basal cell carcinoma, myoeplithelial carcinoma, squamous cell carcinoma and clear cell carcinoma [4]. In most occasions, 75% of the luminal epithelial cells undergo malignant change, in 19% of cases; a dual epithelial/myoeplithelial differentiated carcinoma is seen. Pure myoeplithelial malignant change is seen in only 6% of cases [10]. In the present case although no immunohistochemistry was attempted, morphology favoured an adenocarcinoma NOS. The exact pathogenesis of CXPA remains debatable. Gerughty *et al*, held a belief that these tumors were malignant from the onset, as 60% of the patients in their series were primarily seen without a history of a pre-existing tumor [11]. Behars *et al*, proposed that a carcinomatous transformation of a benign mixed tumor resulted in this malignancy because the median age of onset for a benign mixed tumor was 10 years younger than that for CXPA, and most patients were initially seen with a history of a mass present for many years (average duration, 23.3 years), with a sudden growth and new symptoms [11]. Eneroth and Zetterberg perceived that mixed tumors that had been present for longer than five years showed a tetraploid population of cells, similar to that found in CXPA. This suggested that as mixed tumors developed, the cells could undergo a transformation that could induce a carcinomatous component [11]. The development of CXPA follows the multi-step model of carcinogenesis signifying progressive loss of heterozygosity (LOH) at chromosomal arms 8q, then 12q, and finally 17p. The malignant transformation of a PA to CXPA can be credited to the 12q genes, HMGIC, HMGA2 and MDM2 [4]. In general, the suggested therapy for CXPA is wide local excision with contiguous lymph node dissection.[7] Adjuvant radiation therapy is recommended for widely invasive tumours, high grade disease, in cases of questionable resection adequacy and for lymph node and peri-neural invasion [4,7]. The present case was widely invasive and showed lymph nodal metastasis, so surgery was followed with radiation therapy. CXPAs are susceptible

to frequent recurrence and metastasis. These tumors are associated with a 5-year survival rate of about 50% [9]. The prognosis depends on pathological staging parameters like the extent of invasion, lymph node involvement, local or distant metastasis, tumour size and grade [4, 8]. Other significant prognostic factors, as studied by Lewis et al, in Mayo clinic; are proportion of carcinoma and proliferation index determined by digital image analysis of feulgen and MIB-1 stained sections [8].

CONCLUSION

CXPA is an uncommon entity with significant clinical and pathological relevance. This type of tumor is difficult to diagnose, as the mixed tumor component is often small and overlooked, and the malignant component may be difficult to classify. When such tumors present with a giant neck mass; as in the present case, the diagnostic challenges upsurge; more so when FNAC is used as a primary investigative modality. In conclusion I wish to state that a thorough histopathological examination complemented by clinicoradiological correlation is crucial for diagnosing and prognosticating this uncommon neoplasm.

Abbreviations:

- PA: Pleomorphic adenoma.
- CXPA: Carcinoma Ex pleomorphic adenoma.
- FNAC: Fine needle aspiration cytology.
- TBSRTC: The Bethesda System for Reporting Thyroid Cytopathology.
- CT: Computed tomography.
- mPA: Metastasising pleomorphic adenoma.
- LOH: Loss of heterozygosity.
- HMGIC: high-mobility-group protein gene.
- HMGA2: High-mobility group AT-hook 2.
- MDM2: Mouse doubles minute 2 homolog.

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