

## Case Report

### Giant Carcinoma Ex-Pleomorphic Adenoma with Distant Metastasis: A Case Report with Review of Literature

Supriya Kheur, Yashwant Ingle, Meena Kulkarni, Tushar Patil

#### Abstract

Pleomorphic adenoma, though essentially benign can undergo malignant transformation. Here, a case of a female patient with a giant size tumor of parotid weighing 1.6 kgs has been presented. The tumor was diagnosed as carcinoma ex-pleomorphic adenoma which showed breast and lung metastasis. The various parameters which can predict malignant transformation in Pleomorphic adenoma have also been discussed in this paper. The understanding of the underlying complications of Pleomorphic adenoma makes us better equipped in rendering optimal treatment to the patient.

**Key words:** Neoplasms;Complex and Mixed;Adenoma;Pleomorphic;Mixed;Malignant;Salivary Gland Tumor;Carcinoma;Giant Size;Metastasis;Malignant Transformation.

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#### Introduction

Pleomorphic Adenoma (PA) is a benign salivary gland neoplasm. It represents 45 – 74% of all salivary gland tumors and more than 50% of them occur in parotid gland. This tumor is plagued with recurrences, malignant transformation and metastasis<sup>1</sup>. The rate of recurrence is high due to their pseudo capsule and inadequate resection as well as the predominance of myxoid and hyalinised material. The malignant transformation generally occurs about 10 years after the benign pleomorphic adenoma<sup>2</sup>. Malignancies arising in PA encompass of 3 entities: 1) carcinoma ex-pleomorphic adenoma (CXPA), 2) carcinosarcoma and 3) metastasizing benign pleomorphic adenoma.<sup>2,3</sup> There are only 2 cases of CXPA reported with extensive lung metastasis reported in the literature.<sup>4,5</sup> We report a case of CXPA showing all the classical features with abnormally increased size along with breast and lung metastasis. A complete review of this malignant mixed tumor is done with special emphasis on the pathogenic mechanism that leads to transformation of PA to CXPA.

#### Case Report

A 63 year old female patient reported to our Out Patient Department with a large neck mass. The patient gave a history of the lesion being present since past 21 years which had gradually increased to the present size. She also gave a history of surgical removal of the growth after which the

increase in size was tremendous. On examination the mass was soft to firm, lobulated, nodular and variegated in consistency. It was covered with stretched skin with superficial distended veins prominently seen in some areas. The lesion extended anteriorly from the lobule of the ear, with the pinna being lifted to the level of the occipital prominences posteriorly. The lesion was extended laterally along the length of the neck up to the supraclavicular notch (Fig 1a).

The patient also presented with a single small nontender, nodular mass in the left breast. The axial computed tomography scan of the lesion revealed well defined predominantly cystic mass, 14.2 X 14.1 cm with innumerable internal septae. The mass was seen extending superiorly from the level of infra-auricular region. Medially the lesion had a poor plane of differentiation with the left parotid gland. The lesion was also indenting the left submandibular salivary gland with invagination into the plane adjacent to the left para-pharyngeal space. The left carotid sheath and its content were displaced medially. Few borderlines enlarged left jugular and submandibular nodes were present. A 1.1 cm parenchymal nodule was found on the right upper lobe of the lung (Fig 1b).

Further chest radiographs revealed typical cannon-ball appearance. Multiple variable radiolucencies seen in both lungs were

suggestive of metastasis. Aspiration performed from 3 - 4 different sites of the mass revealed an abundance of mucoid material with few cells showing myoepithelial differentiation and mitotic activity. The cells were in clusters and sheets with round to polygonal shape, high nuclear/cytoplasmic ratio, prominent nucleoli, irregular outlines, acinuous formation at places. The background revealed abundant pink, vacuolated, myxoid ground substance. A provisional diagnosis of adenocarcinoma was made with differential diagnosis of CXPA (Fig 2a).

After obtaining the patient's informed consent, complete (wide) surgical excision of the lesion was performed using the cervical trans-parotid approach, preserving the facial nerve. The facial nerve was dislocated laterally by the tumor and gently dissected from the deep lobe of the parotid and following which the tumor was completely removed. Many different approaches of large parotid mass removal have been discussed in the literature. All authors agree on the need to perform surgery with adequate exposure, so that the vital structures are protected along with a complete removal of tumor mass.

On gross examination the excised lesion revealed an irregular lobulated mass, covered with superficial skin. In cut sections, the tissue showed solid and cystic areas, of 4 x 2 cm to 1 x 1 cm, consisting of mucoid material. Solid areas showed glistening, shiny, translucent appearance and it was firm to hard in consistency. Few areas of necrosis and hemorrhage were also seen with areas of fibrosis and calcifications.

The histopathological assessment of lesional tissue showed biphasic areas. The epithelial component revealed nests and sheets of round to oval cells with high nuclear / cytoplasmic ratio, vesicular nuclei with irregular borders and prominent nucleoli. In few areas immature cartilage foci were noted. Background showed abundant chondromyxoid ground substance with floating epithelial islands. Perinuclear invasion and lymphovascular emboli were evident. There were no keratin pearls or spindle cells. (Fig 2b) A diagnosis of Carcinoma Ex-Pleomorphic Adenoma was made. Sections from breast nodule revealed the same histology as above against breast tissue in background.

## Discussion

CXPA is a rare, aggressive, poorly understood malignancy that usually develops in a primary or recurrent PA.<sup>6</sup> The pathogenesis has not been well understood. CXPA accounts for 3.6% of all salivary neoplasms and for 11.7% of salivary malignancies.<sup>7</sup> The main requirement of histologic diagnosis of CXPA is the presence of PA and a carcinoma. Sometimes the origin can only be inferred from history. Histopathological features of CXPA are: the capsule invasion, hemorrhage, necrosis alternating with areas presenting classical features of pleomorphic adenoma.<sup>8</sup> CXPA shows a wide morphological spectrum with mainly epithelial, myoepithelial cells forming a variety of patterns in mucoid, myxoid and chondroid matrix. These tumors predominantly show epithelial component exhibiting malignant transformation as opposed to carcinosarcomas that have both epithelial and connective tissue malignant components.<sup>9,10</sup>

Recent studies have shown that the most frequently encountered histological types in a CXPA are highly malignant adenocarcinoma or undifferentiated carcinoma, although many other types were found such as squamous cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, papillary carcinoma and terminal duct carcinoma.<sup>7</sup>

Malignant transformation can occur in 1.9 - 23.3% of cases.<sup>12</sup> The risk of malignant transformation in PA increases with time interval, recurrences, advanced age of the patient and location in the major salivary gland.<sup>7</sup> Some authors have postulated 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.<sup>12,13</sup> In the present case also, the lesion was present since 21 years and rapid growth was noticed in the past two years, after surgery. CXPA rarely occurs before age of 20 years.<sup>11</sup> It usually presents as a mass with a long evolution that shows a sudden increase in size. In 12 - 55% of cases this rapid increase in size may be accompanied by pain, facial nerve palsy and fixation to the surrounding soft tissue. A small percentage of patients may have tumors with rapid growth, without any symptoms.<sup>1</sup>

There are many studies which have been done to determine the microscopic features

which could predict malignant transformation in an otherwise benign PA. Auclair & Ellis evaluated atypical features of PA like hypercellularity, capsular violation, hyalinization, necrosis and cellular anaplasia. They concluded that benign mixed tumors that showed prominent zones of hyalinization and moderate mitotic activity were more likely to undergo malignant changes than those that did not.<sup>14,15</sup> Most of the cases report metastasis to regional lymph nodes. Few cases of gigantic PA metastasizing to mediastinal lymph nodes have also been reported.<sup>16</sup> An analysis of 73 cases treated at Mayo Clinic done by Lewis et al have revealed that the most significant features for prognosis in CXPA include tumor stage, grade and proportion of

carcinoma, extent of invasion and proliferation index determined by digital image analysis of feulgen and MIB-1 stained sections respectively.<sup>17</sup> But, using interpretation of cellular atypia, increased mitotic index and lack of encapsulization as signs of malignant transformation remains controversial, because these signs can also be seen in ordinary PA.<sup>1,7</sup> In most cases, it is generalized as an imbalance between apoptosis and proliferation of transformed cells. Proliferation of the benign epithelial component can be due to activation of oncogenes and/or loss of tumor suppressor genes. Retinoblastoma (pRb) protein is the key cell cycle regulator at G1-S phase. The p53 also plays a central role as tumor suppressor.

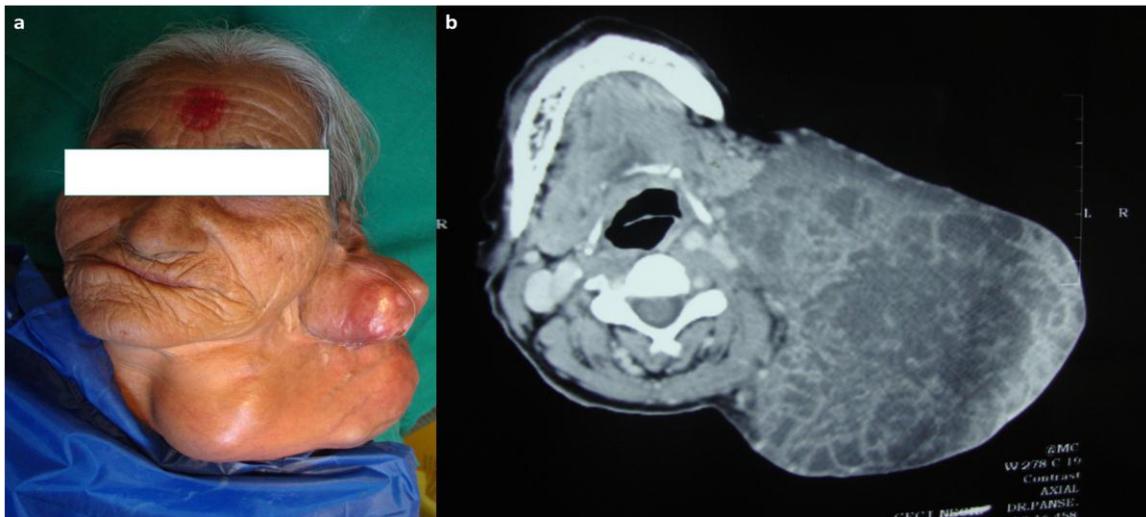


Figure 1: The clinical photograph of the patient exhibiting the huge parotid mass (a). The computed tomography scan of the lesion exhibiting its cystic nature and septae with well demarcated boundaries (b).

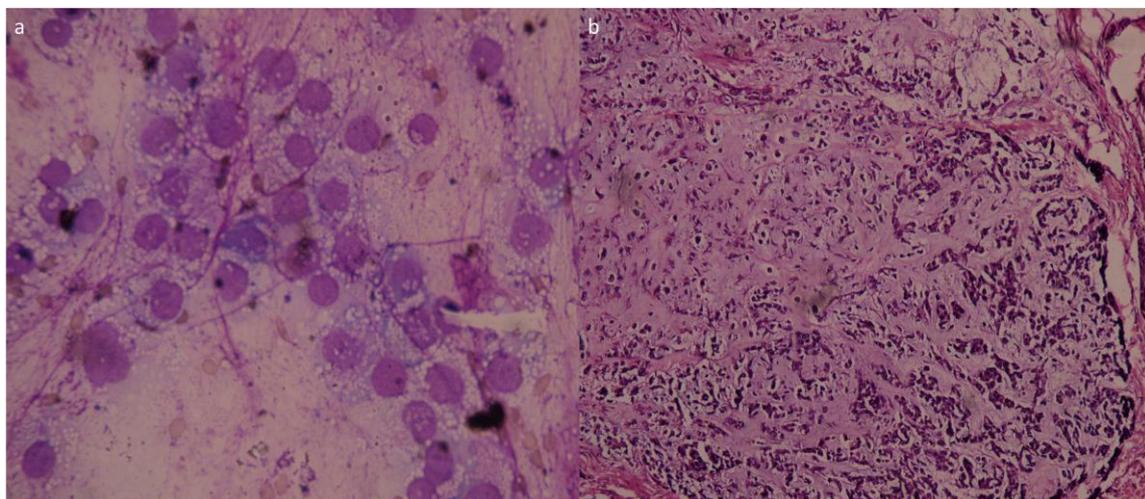


Figure 2: The fine needle aspiration cytology aspirate shows round to polyhedral myoepithelial cells in a pinkish mucoid background (a). The histopathology revealed Islands of epithelial cells in the background of abundant chondro-myxoid areas and few areas showed mitotic figures.



Tarakji had evaluated the expression of p53 and pRb expression in PA and CXPA, revealed that p53 cannot be used as a reliable indicator for malignant transformation. They found that, p53 aberrant expression in tumor duct cells is more frequent than in the myxochondroid tissue, indicative of the fact that epithelial component is responsible for malignant progression.<sup>18</sup> But, expression of pRb increases significantly in CXPA (77.8%) as compared to 6.8% of PA cases studied.<sup>19</sup> In addition to the grading, Ki 67, or other proliferation markers, are useful prognostic indicators while p53 and E-cadherin appear to be of limited value.<sup>20</sup>

The study conducted by Martin MT et al on maspin expression in CXPA revealed that maspin, which is a member of serpin family of proteinase inhibitor, is consistently associated with myoepithelial cells. When only epithelial cells undergo transformation in PA, maspin expression is downregulated whereas when myoepithelial cells are also transformed, high maspin expression is seen. This is in turn related to increase in tumor suppressor activity. A correlation of immunohistochemical markers to that of histology of CXPA revealed that clinical behavior of these tumors is closely related to the carcinomatous component.<sup>21</sup> Thus we now have various molecular markers which could predict malignant transformation in PA. Detailed histopathological examination and application of these biomarkers to PA should enable us discriminate lesions with high risk of malignant transformation from those with low risk.

### Conclusion

Giant Parotid PA's or its malignant counterpart, CXPA are very rarely documented in the recent literature. Lack of information on the part of the patient, low socio-economic status and fear of surgery seem to be the most important factors for these long standing lesions. Our case also showed lung and breast metastasis. The various histological parameters that can predict carcinomatous changes in benign pleomorphic adenomas were also evaluated. All the clinicians and surgeons need to be aware of its diverse presentation as it may influence the treatment protocol and outcome for the patient.

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