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Case Report

The Rare Entity of Metastasizing Pleomorphic Adenoma: A Case Report and Review of Literature

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Abstract

Pleomorphic Adenoma is the most common benign lesion of the major salivary glands, but it can also exhibit malignant potential without transformation into Carcinoma Ex Pleomorphic and Carcinosarcoma. Metastasizing Pleomorphic Adenoma (MPA) had the ability to metastasize to bones, lungs and lymph nodes and is associated with poor prognosis. Though some authors consider it to be a benign neoplasia, 2015 World Health Organisation (WHO) classification of head and neck cancers, stamps it as a malignant tumor of epithelial origin.

We report a rare case of MPA of the parotid gland with nodal metastasis and present a bibliographic review of the English literature.

Keywords: Metastasizing; Pleomorphic Adenoma; Immunohistochemistry; Frey's Syndrome; Surgical Management

Introduction

Metastasizing Pleomorphic Adenoma (MPA) is defined as the presence of one or more metastatic foci of histologically benign pleomorphic adenoma. According to the World Health Organisation (WHO) 2015 classification of head and neck tumors, the MPA is considered to be a malignant tumor of epithelial origin. The International Classification of Diseases for Oncology termed MPA as "/1" which describes a neoplasia of uncertain and unknown behavior [13].

A MPA can undergo malignant transformation in 3 ways, namely the MPA, Carcinoma Ex Pleomorphic Adenoma and True Malignant Mixed Tumor (Carcinosarcoma). Pleomorphic Adenoma, though being overtly benign, can rarely metastasize without a histological malignant transformation, especially when surgical excision is incomplete.

A review of the English-language literature since 1942 revealed only 287 confirmed cases of MPA till date [Table 1].

Though the etiopathogenesis of MPA still remains unclear, a number of theories have been postulated, the most popular being hematogenous or lymphatic spread of the tumor cells as a result of iatrogenic manipulation during a surgical procedure. Wermuth., *et al* [12] postulated that pulmonary metastasis can occur due to aspiration of tumor cells into the pharynx whereas Marioni., et al [2] suggested multiple genomic alterations as the cause of the metastatic nature of the disease.

Most cases of Pleomorphic Adenoma occur in patients who have undergone surgery once or twice, with the time of appearance of nodal or distant metastasis being between 1.5 and 55 years after surgery [7]. Metastasis occurs primarily to the bone (50%), lymph nodes (30%), lung (30%) and less commonly to the liver, kidney, retroperitoneum, central nervous system and the skin [13]. According to Nouraei., *et al*. the most common primary site was the primary gland (74%) followed by the minor salivary glands (17%) and the submandibular gland (10%). In the reported cases, the distribution of MPA cases were equal among males and females with average age of incidence being the 6th and the 3rd decade respectively [7,13].

Clinically, there may be a slow growing painless recurrent growth at the primary site or signs and symptoms associated with the site of metastasis such as a head and neck mass, multiple cranial nerve palsies, lower back pain, pathological fractures or an abdominal mass [13].

A whole body FDG-18 PET CT scan still remains the gold standard for detecting multiple organ and nodal metastasis in cases of recurrent or longstanding Pleomorphic Adenoma [8].

Histologically, the diagnosis of MPA should fulfill 2 important criteria: 1. The primary and metastasizing tumors should not have features of malignancy and 2. The primary site should be separate from the metastatic site , but both sites should show evidence of biphasic benign pleomorphic adenoma [13].

The most appropriate treatment option for MPA is surgical that is a Total Conservative Parotidectomy +/- Neck Dissection depending upon nodal metastasis followed by Adjuvant Radiotherapy if indicated in the post-op histopathological examination report.

Although MPA has a bland pathology and is a rare complication of Pleomorhic Adenoma, it is occasionally associated with poor prognosis. The 5-year disease-specific and disease-free survival rates are 58% and 50% respectively.

Case Presentation

A 52-year-old male patient presented to our Head and Neck Oncosurgery outpatient department with a gradually progressive swelling in front and below the left pinna since 3 years associated with intermittent pain. His co-morbidities included Hypertension for which he was not on regular treatment and had no personal habits. On enquiring about his past surgical history we found out that the patient had undergone a Left Superficial Parotidectomy under General Anaesthesia (GA) 23 years back at a teaching hospital in Kolkata. His post-operative HPE report showed Pleomorphic Adenoma with no evidence of malignancy.

A preliminary clinical examination revealed a firm, mobile, non-tender, nodular parotid gland swelling occupying the left preauricular and infra-auricular region with an approximate size of 2 x 2 cm dimension. The growth was mobile on asking the patient to clench his teeth indicating its non-fixity to the underlying muscles or bone. There was no facial nerve palsy (FNP). Examination of the neck revealed a hard, fixed matted lymph node mass at left level II of size 4.3 x 2.8 cm. The oral cavity revealed no abnormality and there was no trismus.

A fine needle aspiration cytology (FNAC) was done from the left parotid growth, which revealed "Recurrent salivary gland neoplasm". A contrast enhanced MRI (CEMRI) of the left parotid region and neck was done to know the site, size and extent of the lesion along with nodal metastasis. The CEMRI showed a well circumscribed altered signal intensity lesion measuring 2.4 x 2.2 x 1.4 cm involving the posterior part of superficial lobe of left parotid gland. The lesion appeared hyperintense on T2W with surrounding hypointense rim s/o fibrous capsule and hypointense on T1W with avid post contrast enhancement along with pre-parotid and level 2 lymph nodes, greatest dimension of 4 x 2 cm – likely metastatic.

The patient was electively prepared for a left sided Total Conservative Parotidectomy and left Type III Modified Radical Neck Dissection (MRND) (I-V) under GA. Routine investigations as a part of the pre-operative work-up, including haematology results and chest X-ray, were unremarkable. After undertaking proper aseptic measures, the patient was positioned supine with the neck extended. A modified Blair's incision (Figure 1) was made with an anterior extension and flaps were retracted superiorly and inferiorly.

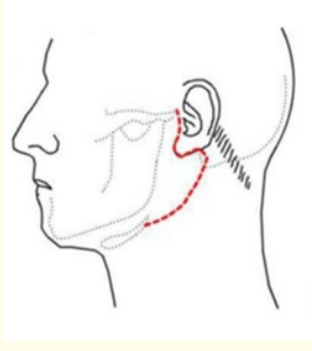

Figure 1

The left facial nerve trunk and its branches were identified. Perioperatively the tumour was found to be extensively adherent to the surrounding structures and encasing the facial nerve. The superficial lobe was removed preserving the temporal, zygomatic and buccal branches. The inferior marginal mandibular nerve could not be preserved and was primarily sutured with 5-0 Ethilon. This was followed by the removal of the deep lobe of the parotid gland. A Type III MRND was done from left level IB to V in usual steps preserving the Left Sternocleidomastoid muscle, Internal Jugular Vein and Spinal Accessory nerve. After achieving haemostasis, a surgical drain was inserted and a 2 layer suturing was done for clo-

sure of the wound. Post-operatively, the patient had a Grade I Left sided marginal mandibular nerve palsy which was evident from the drooping of the left angle of lip, the other branches remained intact. The excised lesion and the dissected lymph nodes were sent separately for HPE.

The HPE report (Figure 2) revealed a multifocal pleomorphic adenoma of the parotid gland with 14 out of 20 lymph nodes showing metastasis. One of the metastatic nodes showed dedifferentiation of the tumour, composed of spindle cells in fascicles, the cells had moderately pleomorphic nuclei but showed no evidence of necrosis or brisk mitotic activity.

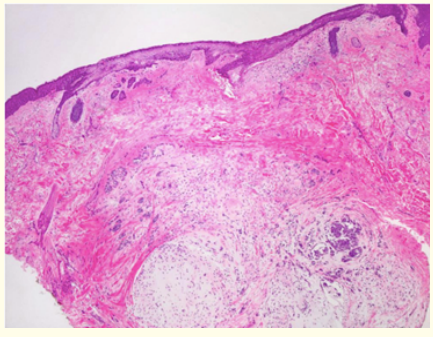

Figure 2

The pathologist suggested an Immunohistochemical (IHC) study of the suspicious lymph node with Ki67, p63, CK, Calponin and Vimentin stains to rule out malignant transformation and subtyping. Unfortunately the patient refused to get the IHC done because of financial constraints. Based on the HPE report, the patient received Adjuvant External Beam Radiotherapy (Adj.RT) (60 Gy/30 fractions x 7 weeks).

One year after the completion of Adj. RT, the patient developed left sided gustatory sweating or Frey's Syndrome, regarding which the patient was counselled and is being managed conservatively with topical Glycopyrrolate . The patient attends regular follow-up and till date has a residual Grade I Facial nerve palsy but has no locoregional or nodal recurrence (Figure 3,4).

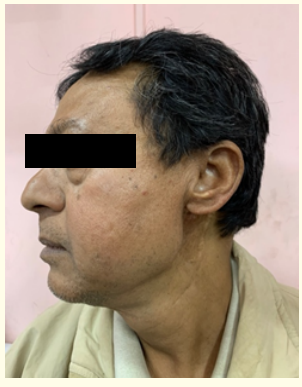

Figure 3

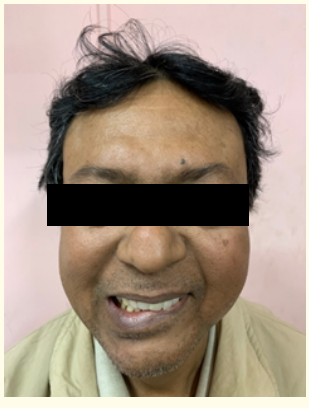

Figure 4

Discussion

Salivary gland tumours comprise approximately 3% of all head and neck tumours. About 70-80% of these tumours occur in the major salivary glands, of which the parotid is the most affected gland. Pleomorphic adenoma is the most common benign neoplasm of the salivary gland [7]. Although a pleomorphic adenoma can undergo malignant transformation to carcinoma ex pleomorphic adenoma, metastasizing pleomorphic adenoma is a rare and unique entity. MPA is a salivary gland neoplasm that histologically corresponds to the features of pleomorphic adenoma, but has the inherent ability of nodal and distant metastasis.

The exact number of cases of MPA is questionable among reviewing authors, some investigators have questioned the very existence of the entity whereas others have supported its existence depending upon some diagnostic criteria. In review of the recent English-language literature, we found out that there were only 287 diagnosed cases of MPA. The total number of cases, their reviewing authors and the period of review are indexed in Table 1.

The Etiopathogenesis is not clearly understood but complete

Authors	Period of Review	No. of Cases
Nouraei., *et al*.	1953 - 2005	42
Marioni., *et al*.	1942 - 2003	60
Knight., *et al*.	1942 - 2014	80
McGarry., *et al*.	1957 - 2007	52
LiVolsi., *et al*.	1977	47
Soteldo., *et al*.	2017	1
Koyama., *et al*.	2018	1
Santaliz-Ruiz., *et al*.	2012	1
Young., *et al*.	2015	1
Rodriguez., *et al*.	2008	1
Singhal., *et al*.	2010	1

Table 1

surgical resection of the primary lesion sometimes becomes difficult due to the involvement of the facial nerve and the presence of pseudopods. This iatrogenic manipulation, as in our case also may have led to haematogenous or lymphatic metastasis.

MPA usually occurs in patients who have previously undergone a surgery, with the time of appearance of metastasis being between 1.5 to 55 years, as in our case the patient developed a recurrence at same primary site with nodal recurrence, 23 years after his first surgery.

HPE plays an important role in the diagnosis of MPA. Usually the primary and pleomorphic adenomas have similar histological appearance, but the ratio between epithelial/myoepithelial components to stromal components may be different. Till date, no histological parameters have been found that can predict the ability of the original tumour to metastasize [13].

IHC studies with p16 and Bcl-2 have proved to be of some value but lacks sensitivity and specificity due to small sample size. Santaliz-Ruiz., *et al*. have stated in their study that overexpression of p16 in the cytoplasm and decreased expression in the nucleus along with Bcl-2 positive immunoreactivity play an important role in the evolution of malignant transformation [11]. As in our case the HPE report showed multifocal pleomorphic adenoma with no evidence of brisk mitotic activity or necrosis and one of the metastatic nodes showed dedifferentiation of the tumour. An IHC analysis with Ki67, p63, CK, Calponin and Vimentin was advised but could not be carried out due to financial constraints.

Koyama., *et al*. suggested that Magnetic resonance imaging is useful in identifying and pre-operative planning of recurrent pleomorphic adenomas , as they have high T2-weighted signal intensity but it was not practical in the follow-up period to detect distant metastasis. They concluded that an FDG-PET/CT scan was an important tool in the follow up period to identify MPA cases with osseous metastasis [8]. As in our case, a pre-operative CEMRI of the left parotid gland and neck showed a well circumscribed lesion which appeared hyperintense on T2W and hypointense on T1W along with nodal metastasis, confirming Koyama's findings. An FDG-PET/CT scan is planned in the subsequent follow-ups to detect any recurrence and nodal or distant metastasis.

An upfront surgery still remains the mainstay of treatment of MPA followed by adjuvant radiotherapy to eliminate occult recurrence that could eventually metastasize to distant sites. Primary chemotherapy or radiotherapy were not very effective, as evidenced by Nouraei., *et al* [1]. As in our case, the patient underwent a left total conservative parotidectomy with a Type III MRND (I-V) followed by Adj.RT. The patient developed a Grade 1 left sided facial nerve palsy in the immediate post-op period as the marginal mandibular branch had to be sacrificed due to tumour encasement. The patient also developed Frey's syndrome one year after completion of RT which is being managed conservatively.

The entity MPA is associated with poor prognosis with 5-year disease-specific rate of 58% and disease-free survival rate being 50%. According to World Health Organisation (WHO) reports, 40%

of the patients die with the disease, 47% live free of disease and 13% live with it. As in our case, the patient has a Karnofsky score of 100 and is on regular follow up every 6 months.

Conclusion

Although, the number of confirmed cases of MPA are few, the incidence is steadily increasing and needs to be further investigated. Pleomorphic Adenoma, though being an indolent benign salivary gland neoplasm, has the potential to behave like a malignant lesion in the form of MPA, thus a proper staging system has to be reinstated with adequate treatment protocols. With the promising work of investigators like Santaliz-Ruiz., *et al*. immunohistochemical analysis may help us to predict the metastasizing capability of this otherwise benign lesion in the future.

Informed Consent

Written informed consent was obtained from patient who participated in this study.

Conflict of Interest

Authors have no conflicts of interest to declare.

Financial Disclosure

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