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Review Article

Carcinosarcoma of submandibular salivary gland: our experience of a rare tumour with review of literature

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ABSTRACT

Carcinosarcoma arising from the submandibular gland is a very rare pathologic entity. Rarity of tumour makes the treatment recommendations difficult. We share our experience of a 76 year old gentleman who presented with a swelling in right submandibular region which was present since last fifteen years and increased over last one month. Fine needle aspiration cytology was done preoperatively which was suggestive of salivary gland carcinoma. After investigating properly a diagnosis of malignant tumour arising from submandibular gland was made and he underwent submandibular gland fossa clearance with ipsilateral modified radical neck dissection. Post-operative histopathology with immunohistochemistry correlation was suggestive of carcinosarcoma arising from pre-existing pleomorphic adenoma of submandibular gland. He received radiotherapy as adjuvant treatment.

Keywords: Salivary Gland, Submandibular Gland, Carcinosarcoma, Malignant salivary gland tumour, Rare salivary gland tumour

INTRODUCTION

Carcinosarcoma of the salivary glands is a very rare tumour, comprising 0.04% to 0.16% of all salivary gland tumours and 0.4% of all malignant salivary gland neoplasms.[1] Tobacco and smoking are not associated with these however radiation appears to be a risk factor, definitive risk factors for development of this disease are not known. Out of all salivary gland malignancies carcinosarcoma is one of the rarest variants and hence often overlooked in the differential diagnosis. Fine needle aspiration cytology alone may not be enough to diagnose this variant as the presence of dysplastic cells only from carcinoma component often begets mislabelling as salivary gland carcinoma.

Histologic types of salivary gland tumours and effect of the location of lesion on histology

Salivary gland tumours vary considerably in their histological patterns and behaviour. The chances of finding a malignant pathology proportionately increase as we move from largest to the smallest of salivary glands. The most common salivary gland tumour is pleomorphic adenoma which comprises about half of the salivary gland tumours, the most common malignant tumours are mucoepidermoid carcinoma, adenoid cystic carcinoma, polymorphous low grade adenocarcinoma, carcinoma ex pleomorphic adenoma, acinic cell carcinoma and adenocarcinoma. There is an interesting correlation between the histology and the site of origin. About 40% of minor salivary gland tumours in patients involve the palate, by far the most common site; this is also where

almost all of the relatively few benign minor salivary tumours in patients originate. Most minor salivary gland tumours arising in other anatomic sites are almost invariably malignant.[2]

With respect to the distribution of malignant salivary tumours, spiro et al reported that mucoepidermoid carcinoma is the most common diagnosis in the parotid gland, whereas adenoid cystic carcinoma is the malignant tumour most often encountered in submandibular or minor salivary sites.[3] Most of all salivary gland carcinosarcoma occur in the parotid, comprising about two third of the cases, Submandibular gland and minor salivary glands are involved in about 19% and 14% cases respectively.[4] This makes submandibular gland carcinosarcoma a very rare entity.

Origin of nomenclature

Carcinosarcoma of the salivary glands was first described by Kirklin et al in 1951.[5] The term true malignant mixed tumour in the salivary glands was first used by King in 1967.[6] The nomenclature of true malignant mixed tumours is debated and it is suggested that the term *cancer in pleomorphic adenoma* be used. In fact, it is so rare that according to the World Health Organization's histologic classification of salivary gland tumours (second edition), malignant mixed tumour only refers to the carcinoma in pleomorphic adenoma.[7]

Theories of origin of the lesion

Malignant mixed tumour accounts for less than 2% of all mixed tumours of the salivary glands. Some cases, however, seem to arise de novo, in the absence of a previous pleomorphic adenoma.[1,8-10] Two schools of thought exist as to the origin of carcinosarcomas. The convergence hypothesis maintains that multiclonal stem cells of the epithelial and mesenchymal components play a causative role. The divergence hypothesis postulates a monoclonal origin from a single totipotent stem cell with divergent differentiation.[11,12] The latter hypothesis is more favoured. Gotte et al hypothesized that the tumour originates from a myoepithelial cell precursor.[13] Other investigators have postulated that the tumour originates from inner ductal cells or a pluripotent primitive cell.[14,15] A history of exposure to irradiation of pleomorphic adenoma has been reported as a cause.[16,17] The reported interval between the irradiation and the onset of carcinosarcoma varies from 1 to 36 years.

Histopathologic diagnosis with immunohistochemical and electron microscopic findings

The diagnosis is based on the demonstration of true malignant epithelial and mesenchymal components in the tumour. The most common malignant epithelial component is squamous cell carcinoma or adenocarcinoma, whereas the most common malignant mesenchymal component is chondrosarcoma, followed by other sarcoma subtypes.[1] A few cases of carcinosarcoma of parotid gland featuring areas of malignant giant cell tumour resembling giant cell tumour of the bone and soft tissues are reported in literature.[8,18] The spindle cells are cytokeratin immune reactive in the majority but in up to 40% it may be cytokeratin negative.[19-23] Cytokeratin staining may vary from focal to diffuse. Expression of vimentin and various myogenic markers (desmin, actins) have been reported in studies.[21-24] S100 protein and HMB-45 are usually negative. Ultrastructure wise, in the majority of cases, carcinosarcoma show evidence of epithelial derivation, including desmosomes, tonofilaments, and macula adherens.[19-25] Other studies report that markers like smooth muscle actin are undetectable by immunohistochemistry while cytoplasmic myoepithelial structures may be detected by electron microscopy.

Complete deletion of one allele at 17p13.1, 17q21.3, and 18q21.3 was detected by LOH analysis indicating allelic loss in both components of the tumour. Double strand sequencing of the *p53* tumour suppressor gene revealed a wild-type allele favouring the hypothesis of monoclonal origin of salivary gland carcinosarcoma with a common stem cell that could be the myoepithelial cell and an inactivated tumour suppressor gene on chromosome 17 other than *p53*.[13]

Prediction of prognosis

A nomogram with high concordance index of 0.85 was developed to predict the risk of recurrence of malignant salivary gland tumours. The five variables most predictive for recurrence were age, grade, vascular and perineural invasion, and nodal metastasis.[26] The applicability of such a tool to carcinosarcoma is not yet conclusively proved.

Treatment recommendations

The recommended treatment for carcinosarcoma arising from salivary glands is wide excision which may include anatomic dissection of the gland and nodal clearance followed by adjuvant treatment with radiotherapy, the beneficial effects of radiotherapy cannot be conclusively claimed however many authors believe that aggressive nature of disease justifies adjuvant radiotherapy [27]. Several reports in the literature claim that postoperative radiation therapy significantly improves loco-regional control in malignant tumours arising from major salivary glands but suggest that high-tumour grade alone is not a compelling indication for postoperative irradiation.[31] Due to a lack of conclusive data concrete recommendations cannot be made at present.[28-30] About 60% of patients have local and distant recurrence with grave prognosis.

Our experience of this rare tumour

A 76 year old gentleman presented to us in outpatient department with swelling in right submandibular region

which was present since last 15 years however it increased in size over last one month. He did not have any addiction or medical comorbidities. There was no family history of cancer. He had taken treatment for pulmonary tuberculosis about thirty years back. Examination revealed presence of 6x6 cm swelling in right submandibular gland region with restricted mobility and small level II nodes. The examination of the oral cavity, chest and axilla, abdomen, skeletal system was normal. Fine needle aspiration cytology from submandibular gland was suggestive of salivary gland carcinoma. Apart from routine blood investigations, a computed tomographic scan of oral cavity and neck was obtained to evaluate the local extent of tumour and to rule out metastasis from other primary as the cause of submandibular gland enlargement, a chest radiogram was also done. He underwent direct laryngoscopy followed by right submandibular fossa clearance including resection of a part of mylohyoid muscle with resection of digastric muscle anterior belly for soft tissue clearance with type III modified neck dissection. Post-operative histopathology was suggestive of pleomorphic predominantly spindle cell tumour of salivary gland suggestive of Sarcomatoid epidermal tumour? carcinosarcoma, one out of thirty nodes dissected was positive for presence of malignant cells with no perinodal spread (Figure 1). Soft tissue resection margins were negative. Immunohistochemistry was done showing positivity for CK (AE1/AE3) (focal), EMA and CK 8-18, negative for P 63, Desmin, SMA and S-100 protein with final impression of sarcomatoid carcinoma arising as carcinoma ex- pleomorphic adenoma (Figure 2). Postoperative period was uneventful and patient received adjuvant radiotherapy and is disease free for almost a year now.

CONCLUSION

Carcinosarcoma of submandibular gland is a rare tumour hence there is a lack of randomised controlled trials to make definite recommendations about the treatment options. Most of our knowledge of the disease is through individual case studies and retrospective analysis. Hence report of every case occurring contributes significantly to our existing knowledge of the disease. Though rare, carcinosarcoma arising from salivary gland should be regarded **as** an aggressive tumour and adjuvant treatment in form of radiotherapy should be considered, a role of chemotherapy in adjuvant setting is debatable. A long term disease free survival is possible at least in a few cases who receive adequate surgical treatment with adjuvant radiation according to available recommendations for treatment.

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