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Application of next generation sequencing to detect targetable mutations: A case report of good response to everolimus in salivary duct carcinoma

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Abstract
Salivary gland tumors are rare set of cancers accounting for less than 5% of all head and neck cancers. Of the various histologies salivary duct carcinomas are aggressive tumors with no standard of care management protocol. Several phase 1 and phase 2 studies of systemic therapy and targeted therapy in these tumors show minimal response rate. We present a case of metastatic salivary duct carcinoma, in whom next generation sequencing detected a targetable mutation in AKT1 gene and was started on everolimus with a stable disease over next 5 months.

Keywords: salivary duct carcinoma, AKT1 gene, everolimus

Introduction
Salivary gland tumor comprise of less than 5% of all head and neck tumors and they are amongst the most heterogenous group of tumors in the human body [1]. Salivary duct carcinomas [SDC] are amongst the most aggressive malignancies and comprise of approximately 6% of all salivary gland cancers [2]. Histologically speaking SDC's resemble ductal carcinomas of breast and like breast cancers may express HER2 [3-5]. Major salivary glands are affected in 96% of cases and usual presentation is rapidly enlarging parotid mass with facial nerve involvement. Being the aggressive malignancy that it is, 65% patients don't survive beyond 48 months [6]. SDC is a rare malignancy so due to lack of phase 3 trials there is no standard of care treatment and its aggressive nature confers a very poor response to systemic chemotherapy. Many phase 2 studies have evaluated systemic therapy in salivary gland tumors and have shown very modest responses. With the revolution in molecular studies we have pandoras box for targeted therapies. We report a case of metastatic SDC with mutation in AKT1 gene detected by next generation sequencing and is targeted with am TOR inhibitor.

Case report
Patient is a 67year old hypertensive male who presented with history of swelling in the parotid region for the past one and half years. Subsequent MRI of face and neck revealed a 4.3cm *3.5cm *2.4cm mass with solid and cystic component involving superficial lobe of the parotid gland, abutting the deep lobe with enlargement of bilateral upper deep cervical and submandibular lymphnodes. He underwent total parotidectomy and SND with histopathologic analysis showing a picture of salivary duct carcinoma with a second component of osteoclastoma. Post surgery patient underwent adjuvant RT and was kept on follow up. After 3 years patient presented with a enlarged pre-auricular lymphnode subsequent PET CT scan showed metabolically active right upper deep cervical lymphnode with right lung nodule in upper lobe and a solitary rib lesion suggestive of a metastatic disease. Patient then choose to undergoe next generation sequencing which revealed a missense mutation in AKT1 gene - 41G>A (Glu17Lys), on chromosome no 14 and a missense mutation in TP53 gene on chromosome no 17. Based on the report patient was started on Everolimus based oral targeted therapy in the dose of 5mg per day. Patient tolerated the therapy well and after 4 months a repeat PET CT scan is suggestive of a stable disease by RECIST as well as PERCISt criteria. (Fig 1 and 2)

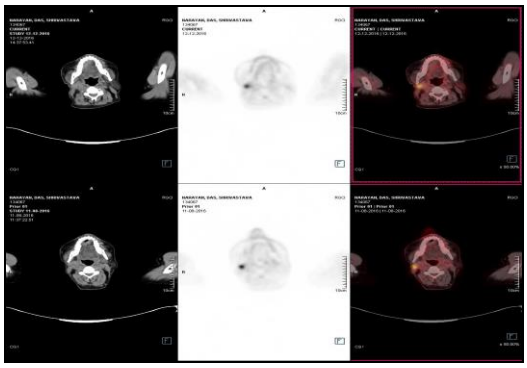

Fig 1: Parotid swelling before and after 4 months of everolimus therapy

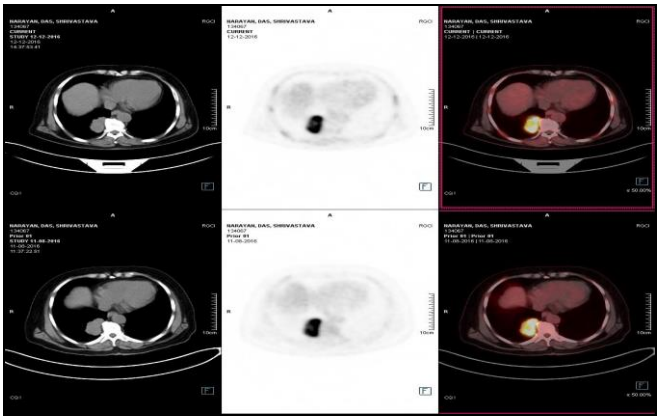

Fig 2: Lung nodules before and after 4 months of everolimus therapy

Discussion

Three most common histologic subtypes of salivary gland cancers are (1) adenoid cystic carcinoma (ACC), (2)adenocarcinoma (ADC) and (3) mucoepidermoid carcinoma (MEC). Salivary duct cancers (SDC) are rare tumors and thus there is insufficient literature for treating metastatic disease. Several phase 2 studies are done in the commoner subtypes and in SDC at best these results can be extrapolated. Appropriate patients can be treated like adenocarcinomas and modest responses have been seen with single agent vinorelbine, paclitaxel [7, 8]. Combination chemotherapy like CAP (Cyclophosphamide/Doxorubicin/ Cisplatin) [9-14] and PAF (Cisplatin/Doxorubicin/5FU) [15] have been tried but with increased toxicity and no survival benefit in Salivary gland cancers.

Modest response rates can be achieved with cytotoxic chemotherapy (~4% to 27%) [8, 13, 16] and no drugs are approved by the Food and Drug Administration (FDA) specifically for salivary gland tumors.

The understanding of the underlying molecular changes in malignant SGC has led to the identification of several potential therapeutic targets. These therapies are the most promising strategies against these rare and aggressive malignancies. Several possible biological targets in salivary gland tumors have been reported: c-Kit [17] (positive protein expression by immunohistochemistry but no exon 11 or 17 mutations); EGFR [18], HER2 [19, 20], androgen, estrogen and progesterone receptor protein expression by immunohistochemistry [21]; and *PIK3CA* [22] and *BRAF* mutations [22].

There are few phase II trials evaluating these agents, and the data are too preliminary to recommend their routine use and moreover the patients in these trial were largely unselected thus conclusions cannot be derived from these studies

But when patients were selected for the presence of *ERBB2*/HER2 or PIK3CA aberrations and were treated with appropriate targeting agents (trastuzumab and lapatinib [23] or mTOR inhibitors [24], respectively), anecdotal remarkable responses have been described.

Kato *et al.* in there study used next generation sequencing and found that the most common molecular abnormalities involved the *TP53* gene (36/117 [30.8% of patients]), cyclin pathway (*CCND1*, *CDK4/6* or *CDKN2A/B*) (31/117 [26.5%]) and PI3K pathway (*PIK3CA*, *PIK3R1*, *PTEN* or *AKT1/3*) (28/117 [23.9%]) [25].

In our patient, after molecular analysis we found an aberration in the PI3 kinase/AKT/mTOR pathway that consisted of a missense mutation in AKT1 gene. Patient has not progressed for the last 4 months achieving a stable disease. He tolerated the dose of 5mg per day of everolimus very well with grade 1 fatigue and grade 1 mucositis. Similar case report by Piha-Paul SA et.al. reported two cases with mutations in the PI3K/AKT/mTOR pathway showing a 25% respose to temsirolimus based targeted therapy [24]. A phase 2 study of everolimus in progressive unresectable adenoid cystic carcinoma showed partial metabolic response to therapy, however no patient achieved a CR or PR but 80% of patients had a stable disease and mOS was 23.7 months [26].

Targeting a molecular target appears to be the way to go forward in these aggressive salivary gland tumors. Correct selection of patients, identifying the targets and further development of new drugs would be the future goals, further studies are required to standardize these therapies in salivary gland cancers.

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