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Original Article

Estrogen Receptor α Signaling in Salivary Gland Tumors: Lessons Learned from Breast Carcinoma

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ABSTRACT

Introduction

Successful antihormonal therapy in breast cancers has convinced researchers to find hormonal targets in salivary gland tumors (SGTs) due to histological and morphological similarities between the two types of glands and their tumors. The aim of this study was to determine expression of estrogen receptor (ER) α in SGTs in our region to see if the same treatment regimen may be followed in SGTs with some modifications if needed according to breast tumors.

Materials and Methods: This retrospective analysis was carried out on 57 already diagnosed cases of SGTs. Cases were recruited from histopathology labs of Ayub Medical College, Peshawar Medical College and City laboratory Peshawar. All cases were examined immunohistochemically for ER α expression. Assessment was done by Allred scoring.

Results: Among 57 cases of SGTs, positive hormonal expression was found in 54.4% of cases while 45.6% of cases were found negative.

Conclusion: This study concluded that ER α can be considered as an attractive target for antihormonal therapy in the subset of SGTs expressing them in variable proportions.

Key Words: Estrogen receptors α, Salivary gland tumors, breast carcinoma, neoadjuvant therapy

Introduction

Salivary gland tumors (SGTs) constitute 0.3% of all body tumors and 3-6% of head and neck tumors. Parotid gland is the commonest site and pleopmorphic adenoma (PA) is the commonest benign tumor of salivary glands. Malignant tumors are common in minor salivary glands (SGs), highest percentage has been recorded in the palate.[1, 2] Surgical treatment is the usual curative treatment for benign tumors. Chances of malignant changes are more in long standing and recurrent cases of PA. Adjuvant therapies are needed in cases of rapidly progressing and malignant tumors. In cases where tumors are unresectable or patients who can not tolerate surgery, radiation alone is the treatment of choice but the results are variable.[3] Although targeted hormonal therapies in various cancers including breast cancers are in routine practice nowadays, there are only few indications of their effectiveness in case of SGTs.

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Due to increasing potential of antihormonal therapy, trend for clinical interest in finding more targets in SGTs is also on rise.[4-6]

The close histological and morphological resemblance of breast and its tumors to that of salivary glands has convinced the researchers to find molecular targets for the SGTs. As breast tumors have been successfully treated by antihormonal therapy so the same treatment regimen as is followed in breast cancers can be offered to the clinicians which is based on expression of hormone receptors in SGTs.[5, 6]

Estrogen stimulates cellular proliferation and differentiation. ER is expressed physiologically in oral mucosa and salivary glands in addition to other body tissues.[7] The prognostic & therapeutic importance of ER- α in the tumors expressing them and their role in tumerogenesis is already known so their detection in SGTs may help in modification of therapeutic strategies.[8]

Keeping in view the above mentioned points , this study was designed to find percentage expression of ER α in SGTs in our region, to see if it might help clinicians to modify their treatment strategy according to that of breast tumors.

Materials & Methods

This retrospective descriptive study consisted of 57 already diagnosed cases of SGTs. Cases were retrieved from histopathology labs of Peshawar Medical College, Ayub Medical College and City Medical laboratory Peshawar. All those patients who received or were under treatment were excluded from the study.

After histopathological assessment of various types of SGTs, sections with maximum epithelial content were selected for immunohistochemical expression of ER α . slides which were kept for immunohistochemistry (IHC) were divided into 6 batches. One slide of breast carcinoma as positive control was added to each batch followed by immunohistochemical procedure.

During procedure antigen retrieval was done with microwave oven. Primary antibody (monoclonal Rabbit antihuman clone EP1) and secondary antibody (Dako EnVision™ FLEX detection system) were used for immmunohistochemical staining of selected sections . Allred scoring was used for assessment of ER positivity.

Cells with positive nuclear staining represented proportion score (PS). Average staining intensity of all positive tumor cells was taken as intensity score (IS).Total score (TS) ranging from 0, 2-8 was equal to the sum of proportion score and intensity score. (TS = PS + IS). A positive result was defined as total score more than 3, as per guidelines for ER/PR mentioned in pharmDx™ manual. Scoring was done by two histopathologists and study was approved by Institutional review board (IRB).

Results

Table-1:Expression of ER α in salivary gland tumors

Sr. #	Histological type of Tumor	Estrogen Receptors Status		Total
		Positive	Negative	
1	Pleomorphic Adenoma	20 (64.5)	11 (35.5)	31
2	Myoepithelioma	02 (66.6)	01 (33.3)	03
3	Adenoid Cystic Carcinoma	05 (55.5)	04 (44.5)	09
4	Mucoepidermoid Carcinoma	02 (33.3)	04 (66.6)	06
5	Polymorphous Low grade Adenocarcinoma	01 (20)	04 (80)	05
6	Ca arising in pleomorphic adenoma	0.0	02 (100)	02
7	Myoepithelial carcinoma	01 (100)	0.0	01
Total		**31(54.4)**	**26(45.6)**	**57**

Percentage expression of ER α in benign and malignant salivary gland tumors

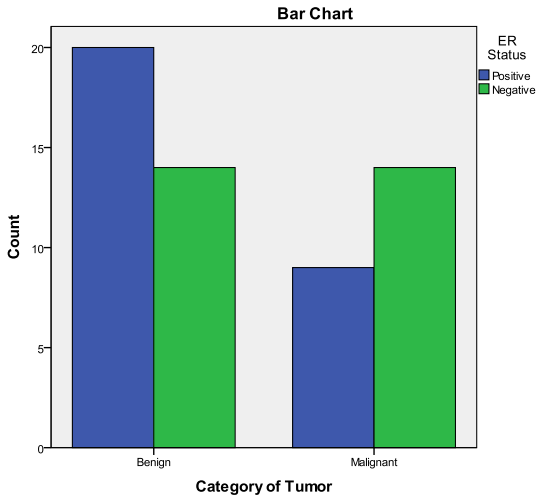

Fig-1: Benign 65% positive, Malignant 39% positive

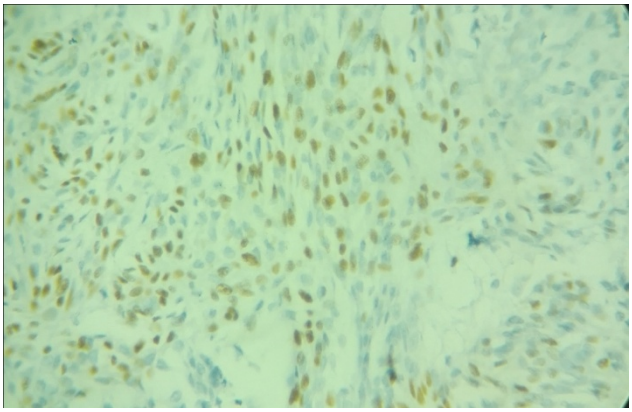

Fig 2: Pleomorphic adenoma (ER α-positive, scoring 6-40×)

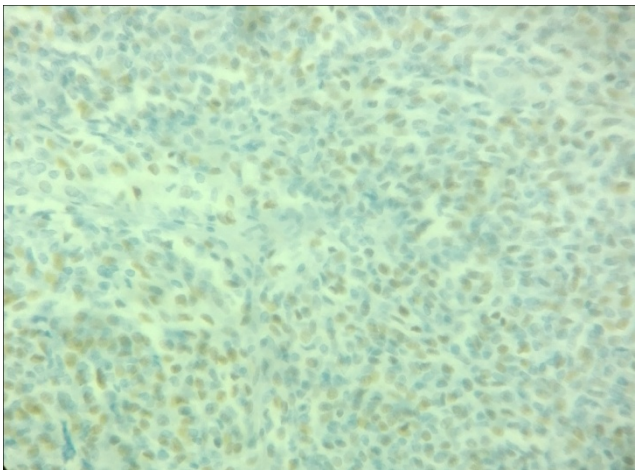

Fig 3: Adenoid cystic carcinoma (ER α-positive, scoring 6-40×)

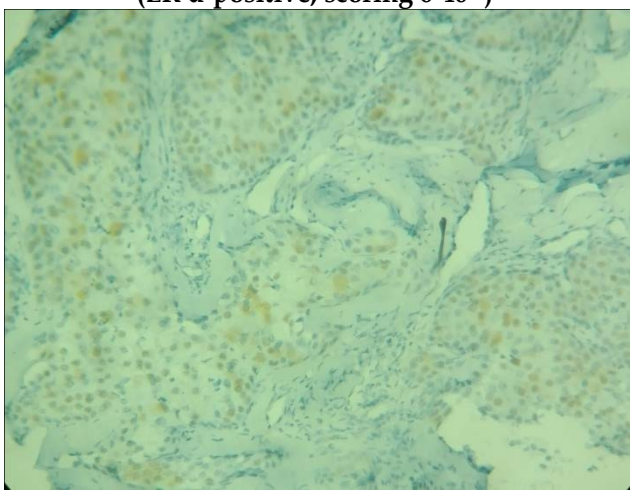

Fig 4: Mucoepidermoid carcinoma (ER α-positive, scoring 6-40×)

All 57 cases included in the study were evaluated for ER α with IHC . Thirty one (54.4%) cases were detected positive for ER α expression while 26/57 (45.6%) cases showed no expression for hormone receptors . Among 34 benign tumors , positivity for receptors was present in 22 (65%) cases while 9 (39%) cases of malignant tumors were found positive for the receptors.

Discussion

This study showed positive expression of ER α in both benign and malignant tumors of salivary glands. Among benign tumors, 64.5% of PAs and 66.6% of myoepitheliomas are positive for hormonal expression. The only treatment of choice for PA is complete removal of the tumor as it can reach to giant proportion if left untreated. Irregular borders, multinodular tumors, and incomplete capsulation are the factors responsible for its high recurrence rate (8%-45%). In case of large tumors it becomes difficult to overcome the challenge of recurrence even with standard surgical procedures and postoperative radiotherapy. Repeated surgeries can lead to higher morbidity, increased risk of facial paralysis along with distortion of local anatomy.[3, 9]

PA can transform to malignant one not only in long standing PA but also in recurrent cases. At times it may behave aggressively and invade blood vessels and lymphatics. Metastasis may also occur to skin, liver lung etc. This raises problem if it occurs in old age or the patient is inoperable.[3, 10] In this study the extent of ER α expression is found to be quite high as compared to literature available.[11, 12] This study detected analogous results to the study on ER α expression in PA of breast. However PA is found rarely in breast but with least complications after surgery in spite of its morphological and histological similarities with PA of SGs.[13]

Adenoid cystic carcinoma (ACC) of salivary glands is histologically similar to ACC of breast and is characterized by sluggish and persistent growth course but prognosis of ACC breast is far better than that of SGs . Even surgical treatment together with radiotherapy of ACC-SG show poor prognosis with time.[8, 14]

Although ACC of breast is characterized by triple negative status, ER expression in ACC breast has also been reported.[15-17] Not only positive expression of ER α has been found in ACC-SGs but response to antihormonal therapy has also been experienced in the past.[18-21] This study also showed 55.5% positivity.

Mucoepidermoid Carcinoma (MEC) of the breast in contrast to that of SGs is a rare tumor but shares same classification of grading and exhibit variable expression of ER-α as in MEC of salivary glands. High grade MEC in both the glands show aggressive clinical behavior. Because of rarity of MEC breast there is no established treatment strategy but importance of hormonal factors affecting tumor biology can not be ruled out.[22-24] This study found positivity of ER α in 33.3% of cases.

Polymorphous low grade adenocarcinoma (PLGA) is malignant neoplasm of rare occurrence predominantly in minor salivary glands.[25] Architecture and cytology of PLGA in SGs is similar to that of breast but clinically it is less aggressive. Furthermore PLGA breast has consistently been found negative for hormone expression.[26]

In this study 1 out of 5 (20%) cases of PLGA revealed positive ER expression in contrast to study of Miller et al who reported negative ER expression in all his five cases. These results can be considered in agreement with each other.[27]

The only case of myoepithelial carcinoma also showed positive expression in this study, although it is quite uncommon.

For all malignant cases of SGTs treatment of choice is surgical excision followed by adjunct radiotherapy. Even ideal surgical treatment can lead to local recurrence and metastasis.[28-30] Role of chemotherapy is controversial as response is very low as compared to its debilitating adverse effects[31] and no other effective therapies are known.[32, 33]

In case of benign tumors, role of radiotherapy should not be neglected as it can cause malignant

transformation[3] so there is need to achieve new therapeutic approaches.

Neo adjuvant therapy has been indicated in ER positive breast cancers. It offers advantages by causing complete remission as it causes tumor shrinkage thus providing a solution to deal with ineffective radio and chemotherapy and converting in operable case to operable one or preventing it from mastectomy.[34, 35] Similar strategy with successful outcome has been reported recently in case of unresectable carcinoma parotid gland.[36] The same platform of treatment (neoadjuvant therapy) may be proposed for all ER α positive inoperable or unresectable SGTs. This can be tailored accordingly to overcome anatomical limitations as has been suggested for ER positive breast cancers. This will help surgeon to make surgery possible for large size tumors (benign and malignant) or where there is metastasis.

Conclusion

Although ER is not highly useful marker as in breast carcinoma to be used for hormonal therapy, subset of SG tumors express ER α in variable proportions. It can be considered an attractive target for hormonal therapy.

Limitations

This study is confined to a single marker so it does not explain its complete relevance to breast tumors with respect to anti hormonal therapy

Recommendation

In addition to ER, other markers used for therapeutic and prognostic purposes in breast cancers such as HER-2 new, Ki 67, Progesterone receptors (PR) and p53 should also be investigated in SGTs. As each receptor has its own therapeutic approach it may help clinician to modify their treatment planning according to their receptor status.

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B. Active Participation in Active Methodology
C. Interpretation/ Analysis and Discussion

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