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Original Article

Dentistry Section

p63 as an Ideal Diagnostic Marker for Pleomorphic Adenoma: An Immunohistochemical Study

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ABSTRACT

Introduction: Pleomorphic Adenoma (PA) histopathologically represents a heterogeneous lesion with a varying proportion of epithelial and mesenchymal components. Due to its morphological diversity, a diagnostic dilemma often arises when identifying its various patterns. This diverse morphology is considered to be a function of the neoplastic myoepithelium. Tumor protein 63 (p63) is expressed in stratified epithelia and in the basal cells of salivary glands.

Aim: To investigate the immunoreactivity of p63 as a reliable myoepithelial marker in PA.

Materials and Methods: A cross-sectional study was performed in the Department of Oral and Maxillofacial Pathology at PGIDS, Rohtak, Haryana, India. The duration of the study was 14 months, from March 2015 to April 2016. A total of 15 tissue blocks of histopathologically diagnosed cases of PA were included from departmental archives and subjected to Immunohistochemistry (IHC) using a monoclonal p63 antibody. The myoepithelium was classified as myoepithelial-like (abluminal and spindled), modified myoepithelium (myxoid and chondroid), and transformed myoepithelium (solid epithelioid, squamous, and basaloid cribriform). IHC for p63 was assessed in each myoepithelial component, as well as in non neoplastic Myoepithelial Cells (MEC) and inner tubular epithelial cells. Only nuclear staining for p63 was considered positive. The obtained data were subjected to statistical analysis, and the Chi-square test was applied.

Results: The PA samples subjected to IHC showed 100% p63 reactivity. Transformed MEC, abluminal, and modified MEC revealed variable immunostaining with a significant difference (p=0.049). There was no immunostaining in luminal/inner layer cells in all cases of PA. p63 was also expressed in the nuclei of MEC of acini and intercalated ducts of normal salivary gland tissue.

Conclusion: p63 is a sensitive and specific myoepithelial marker to identify MEC in PA. Additionally, the expression of MEC-associated markers in acini and intercalated ducts of normal salivary glands has confirmed their role in the histogenesis of this tumour.

Keywords: Myoepithelial cells, Nuclear staining, Salivary gland neoplasm, Tumor protein 63

INTRODUCTION

The PA is a benign salivary gland epithelial neoplasm, characterised by a great diversity of morphological aspects, as a result of cytological differentiations and growing patterns [1]. This morphological plasticity has been attributed to the MEC, which, together with epithelial cells, represents the proliferative component of PA [2]. The basic cellular components of this kind of tumour have been represented by two distinctive cellular populations: a luminal one (represented especially by the ductal luminal cell) and an abluminal one (represented by the MEC and the myoepithelial-like cells derived from it) [1]. These two major types of tumour cells may play a potential role in the morphological diversity of salivary gland tumours. Therefore, PA and other salivary gland tumours often have similar histopathological features [3].

The MEC are ectodermal in origin and are wedged between luminal acinar and intercalated duct cells and the basal lamina in normal salivary glands [4]. They have also been seen in mammary glands, sweat glands, and various other glands of the body [5]. The argument that PA does not arise in the exocrine pancreas, where MEC are absent, seems to reinforce the concept of neoplastic MEC [6]. Earlier, it was thought that contractile function was attributed to MEC in normal physiology; however, these cells are now recognised to be involved in embryonic development, extracellular matrix synthesis and remodeling, and paracrine signaling. In the breast, the MEC inhibits proliferation, angiogenesis, and tumour cell invasion. A tumour-suppressor function has also been suggested for MEC [2]. Indeed, several studies have demonstrated the role of MEC in the development and progression of certain salivary gland tumours [7-11].

Immunohistochemistry has gained popularity regarding the much-improved microscopic diagnosis of neoplasms and also a more exact realisation of histopathologic features, histogenesis, and pathogenesis of those lesions. In everyday pathology practice, the identification of neoplastic MEC in PA is difficult by routine Haematoxylin and Eosin (H&E) staining and also by special techniques. However, several IHC markers have been proposed for the identification of these cells and hence improved differential diagnosis. MEC show variable affinity for different antibodies as these cells are present in different stages of differentiation, especially when present in normal salivary glands [4].

The variability or loss of immunoreactivity for some markers, most notably that of Cytokeratin (CK) 14, and the expression of other markers generally absent in the normal myoepithelium (S100 protein, Glial Fibrillary Acidic Protein (GFAP), Vimentin (VIM)), is unique to neoplastic MEC [2]. Recently, Devi A et al., also reported this variability, revealing loss of the adhesion molecule E-cadherin and expression of mesenchymal markers like VIM and Smooth Muscle Actin (SMA) in PA [12]. Hence, several IHC markers like SMA, VIM, calponin, CK14, p63, and p40 are being used for MEC in PA [1-2,4,7,12-20]. However, these markers have a wide range of specificity and sensitivity, and potential errors in interpretation [2,3,7]. A recent study by Teixeria LN et al., proved p63 immunostaining, being intense nuclear, as superior to the often weak and vague cytoplasmic staining with other myoepithelial markers in PA, making its interpretation easier [7]. The authors investigated the immunohistochemical expression and distribution pattern of the MEC-related immunomarker (p63) in normal salivary gland tissue and PA in order to further support published literature considering its possible role in the development of PA and further improved diagnosis.

Neoplastic myoepithelium is considered a key cellular participant in the morphogenetic processes responsible for the variable histologic appearances of PA. However, controversy still exists concerning the

extent of its activities in salivary gland tumours. The present study, however, may have been able to establish the relative roles played by the myoepithelium.

MATERIALS AND METHODS

A cross-sectional study was performed in the Department of Oral Pathology at PGIDS, Rohtak, Haryana, India. The duration of the study was 14 months, from March 2015 to April 2016. The study was done after obtaining informed consent from the patients and ethical clearance from the Institutional Ethical Committee (PGIDS/IEC/2016/58).

Inclusion criteria: Histopathologically diagnosed cases of PA and normal salivary gland tissue were included in the study.

Exclusion criteria: Tissue sections from patients with a history/symptoms of having any systemic illness and those were not willing to undergo the biopsy procedure or failing to sign the consent form were excluded from the study.

Study Procedure

A convenient sample of 15 cases of PA was selected from the paraffin wax processed tissue archives from 2014 to 2016. From each case of PA and normal salivary gland (n=5), two sections were cut for H&E and immunohistochemical staining. For IHC, authors used the DAKO LSAB® 2 system, Horseradish Peroxidase (HRP) technique for p63. Three to four micrometer thick sections were dewaxed in xylene and hydrated with graded alcohol. All sections were washed twice in Phosphate Buffered Saline (PBS) and incubated for 15 minutes in 4% H_2O_2 to block endogenous peroxidase. After incubation with the primary antibody p63 for one hour at room temperature, the sections were washed twice in PBS and bound peroxidase was developed with 0.02% 3,3-diaminobenzidine in 0.1 mol/L Tris buffer, pH 7.6, in 0.005% H_2O_2 for six minutes, and counterstaining was then performed with Mayer's haematoxylin. The sections were air-dried, cleared, and mounted [3].

The evaluation of the immunohistochemical reaction was independently made by two investigators, and in cases of inconsistencies, they were reinvestigated until a consensus was reached. The number of immunoreactive cells was semiquantitatively measured as follows: >75% positive cells, 50-75% positive cells, 25-50% positive cells, <25% positive cells, negative staining/nil [12]. The interpretation criteria to determine the intensity of the nuclear immunostaining reaction were as follows: Intense staining (+++), moderate staining (++), mild/weak staining (+), negative staining (-) [12].

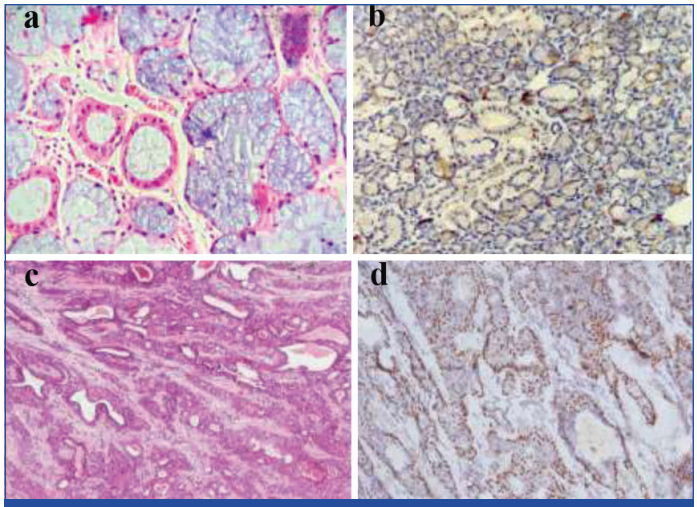
STATISTICAL ANALYSIS

The data were analysed using the Statistical Package for Social Sciences version 12.0, and the Chi-square test was applied. Statistical significance was inferred at $p<0.05$.

RESULTS

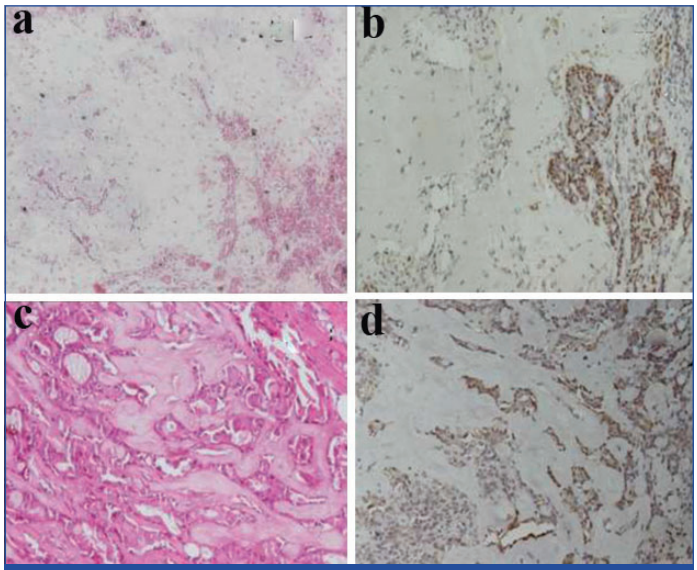
Normal salivary gland: The H&E stained section shows normal salivary gland acini and ducts [Table/Fig-1a]. In all five cases of normal salivary gland tissue, p63 uniformly stained myoepithelial and basal cells lining the acini and ducts. The luminal acinar and ductal cells were not highlighted by p63 [Table/Fig-1b].

Pleomorphic Adenoma (PA): Histopathology: The H&E stained section of PA consisted of both the mesenchymal and epithelial components arranged in the form of cellular proliferative areas and two-layered ductal structures in which myoepithelium-like cells (abluminal cells) were present exterior to inner luminal cells [Table/Fig-1c]. The epithelial cells outside the abluminal cells radiate from the mantle, melting into the sea of chondromyxoid stroma referred to as modified MEC. Myxoid regions contained stellate or spindle-shaped MEC. Chondroid regions showed lacuna and non lacuna cells embedded in a homogeneous basophilic matrix [Table/Fig-2a]. Hyaline areas comprised non cellular homogeneous matrix, which were seen



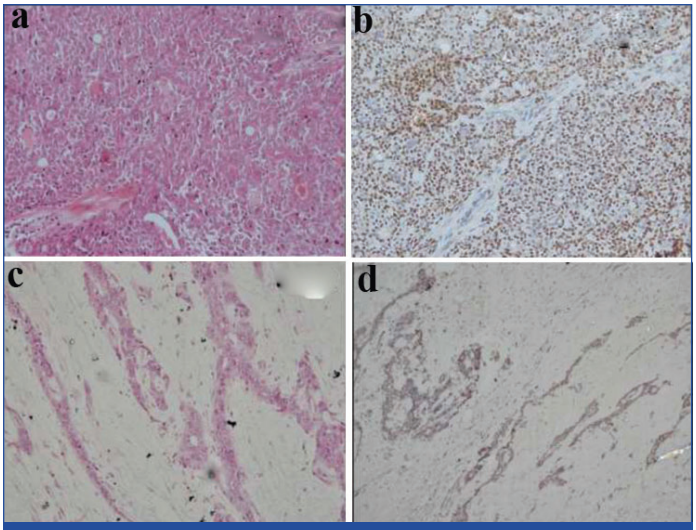
[Table/Fig-1]: (a) H&E image showing normal salivary gland acini and ducts (20x); (b) p63 staining in Myoepithelial Cells (MEC) and basal cells of normal salivary gland (10x); (c) H&E image of luminal and abluminal differentiation in PA (10x); (d) Immunoexpression of p63 in abluminal MEC and absence of staining in luminal epithelial cells (10x).

between small tubular structures or intermingled with epithelial cords [Table/Fig-2b]. Cellular proliferative areas with sheets [Table/Fig-3a] or cords [Table/Fig-3c] of basaloid, epitheloid cells were noted in H&E stained sections. Cribriform areas and squamous islands termed as transformed myoepithelium were also evident in PA [Table/Fig-4a-d].

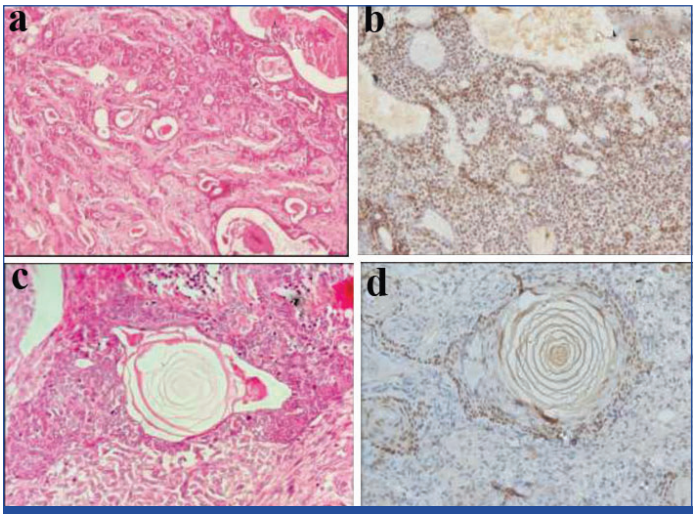


[Table/Fig-2]: (a) H&E staining shows chondromyxoid and hylinised areas (10x); (b) Immunoexpression of p63 in Myoepithelial Cells (MEC) in chondromyxoid areas (10x); (c) H&E staining shows chondromyxoid and hylinised areas (20x); (d) Myoepithelial cells surrounding hylinised areas in PA (20x).

Immunohistochemistry: [Table/Fig-5] depicts the detailed immunohistochemical expression of p63 in different cell types of PA. There was no immunostaining (-) in luminal/inner layer cells in all cases of PA. At the level of myoepithelium-like/abluminal cells, 12 (80%) cases showed intense (+++) immunostaining, while 3 (20%) cases presented with moderate (++) staining with the tumoural mass being covered ranging from >75% to 25% [Table/Fig-1d]. At the level of modified MEC in chondromyxoid areas [Table/Fig-2b] and hyalinised areas [Table/Fig-2d], A total of 11 (73.3%) of cases revealed intense (+++) immunostaining, 3 (20%) cases revealed moderate staining intensity involving a varying degree of the tumoural zone depending on the case, and 1 (6.6%) revealed mild/weak (+) immunostaining. At the level of epithelial proliferative areas (transformed MEC) in the form of sheets [Table/Fig-3b] or cords of epitheloid cells [Table/Fig-3d], cribriform/basaloid areas [Table/Fig-4d], and squamous islands [Table/Fig-4d], 8 (53.3%) cases revealed intense (+++) immunostaining, 6 (40%) revealed moderate (++) staining intensity involving a varying amount of tumour mass, and 1 (6.6%) case revealed mild/weak (+) immunostaining.



[Table/Fig-3]: a) Myoepithelial Cells (MEC) arranged in sheets and cords (H&E, 10x); (b) Immunoexpression of p63 in the proliferative areas showing sheets and cords of Myoepithelial Cells (MEC) of PA (10x) c) Myoepithelial cells arranged in sheets and cords (H&E, 20x); d) Immunoexpression of p63 in the proliferative areas showing sheets and cords of MEC of PA (20x).



[Table/Fig-4]: a) Cribriform and squamous metaplastic areas (H&E,10x); b) Showing p63 immunoexpression in Myoepithelial Cells (MEC) in the cribriform and squamous metaplastic areas of PA (10x); c) Cribriform and squamous metaplastic areas (H&E, 20x); d) Shows p63 immunoexpression in MEC in the cribriform and squamous metaplastic areas of PA (20x).

Cell types	Intense staining (+++) n (%)	Moderate staining (++) n (%)	Mild/weak staining (+) n (%)	Negative staining (-) n (%)	Total
Solid proliferative areas/transformed MEC	8 (53.3)	6 (40)	1 (6.66)	0	15
Abluminal/ myoepithelium like cells	12 (80)	3 (20)	0	0	15
Modified MEC	11 (73.3)	3 (20)	0	1 (6.66)	15

[Table/Fig-5]: Immunohistochemical expression of p63 in different cell types of PA. Chi-square test; p=0.046; MEC: Myoepithelial cells

DISCUSSION

Neoplastic myoepithelium plays a crucial role in the development of various histologic appearances in many salivary gland tumours. Mixed tumours, for example, do not occur in tissues where MEC are absent [21,22]. However, selecting a specific marker to identify neoplastic myoepithelial cells in salivary gland tumours can be challenging, as these cells often do not exhibit a well-differentiated phenotype like their normal salivary gland counterparts [7].

Several markers, such as S-100, CK14, VIM, GFAP, Maspin, SMA, calponin, and acidic calcium-binding protein, have been studied for myoepithelial cells in PA. However, these markers have shown variable expression and cytoplasmic immunostaining. In contrast, p63 has been found to be located in the nuclei of basal/peripheral cells of normal salivary glands as well as in salivary gland neoplasms [2,3,7,23,24]. Additionally, p63 has been identified as a sensitive marker for lung squamous cell carcinomas and has been used for assessing breast lesions due to its differential expression in the luminal, basal, and myoepithelial cells of breast tissue [23].

Therefore, in the present study, authors investigated the immunohistochemical expression and distribution pattern of p63 in PA to further support previous studies suggesting p63 as an ideal myoepithelial marker [7,23,25].

The p63 gene belongs to the p53 family and has been used as a selective histochemical marker for myoepithelial cells and basal/stem cells of stratified epithelium. It plays a crucial role in the morphogenesis of the epidermis and limb development. The p63 gene encodes three isoforms: p63α, p63β, and p63γ, and is located on chromosome 3q27-29. Amplification of the 3q27 region has been observed in several tumours, suggesting its role as an oncogene rather than a tumour suppressor gene. However, the direct role of p63 in tumour formation has not been demonstrated [23]. Myoepithelial cells in PA can be detected as the outer component of ductal structures, which rarely exhibit a well-differentiated phenotype, or as polygonal and modified cells (hyaline and plasmacytoid) [2,7].

In the present study, all 15 samples of PA were positive for p63 antibody, consistent with the results of previous studies by Wato M et al., Genelhu MCS et al., and Ladeji AM et al., [3,21,23]. Immunostaining for p63 was observed in the myoepithelial-like (abluminal) cells in all cases, with intense immunoreactivity in 12 cases and moderate staining intensity in three cases, covering the tumour mass ranging from 75% to 25%. These positive abluminal cells were seen merging with the peripheral stroma, similar to a study by Edward PC et al., [26]. Ladeji AM et al., also found p63 positivity in the myoepithelial-like (abluminal) cells in all 24 studied PA tissue samples, with a range of weak (45.8%) to moderate (50%) positivity [23].

In the present study, almost all non luminal cells, including polygonal, spindle-shaped, hyaline, and plasmacytoid cells, showed concentrated p63 immunostaining, similar to reports by Wato M et al., where p63 was found to be concentrated in the nuclei of modified and transformed myoepithelial cells. The authors stated that p63 was a more sensitive marker than calponin [3]. At the level of modified myoepithelial cells, 11 cases showed intense immunoreactivity, three cases showed moderate staining, and one case showed negative expression, involving a varying degree of tumour mass depending on the case. Intense reactivity was also observed in myoepithelial cells in myxoid and chondroid stromal areas. These findings in the present study are supported by the reports of Nagao T et al., Alves FA et al., Bilal H et al., and Rooper L et al., [27-30]. Additionally, in the present study, myoepithelial cells surrounding the hyalinised areas also showed strong immunoreactivity.

Immunoreactivity of p63 in the solid proliferative (transformed) areas was observed in almost all cases, with varying degrees of intensity, which is supported by studies conducted by Gerald Langman G et al., and Teixeira LN et al., [2,7]. Intense immunoreactivity was detected in squamous islands and keratin pearls. However, staining in epithelioid sheets was patchy. Langman G et al., compared the molecular marker WT1 with p63 for myoepithelial cells in PA and suggested that WT1 may be a better myoepithelial marker than other markers targeting structural constituents of cells. However, WT1 immunopositivity in squamous islands was patchy and limited to peripheral cells, while p63 stained the entire squamous islands, consistent with the results of the present study [2].

In a recent study by Teixeira LN et al., (2018), the expression pattern of four myoepithelial markers, namely Smooth Muscle Actin (SMA), Vimentin (VIM), p63, and p40, was studied in PA. It was found that p40 expression followed p63, but the labeling was heterogeneous and scattered. VIM and SMA expression were not observed in squamous

metaplastic areas. However, both VIM and p63 were considered good markers for myoepithelial cells with different phenotypes, although p63 was easier to identify due to its nuclear immunolabelling [7].

The present study demonstrates that neoplastic myoepithelial cells expressing the p63 protein play a major role in the development of PA. These cells were observed to be organised in ductal structures, strands, and sheets, and were also present in hyalinised, myxoid, and chondroid areas of PA. Furthermore, the nuclear accumulation of this protein makes it easier to identify, suggesting that p63 may be a better marker for diagnosing PA compared to other markers that show vague cytoplasmic expression.

Limitation(s)

The major limitation of the present study was the smaller sample size. To further enhance the understanding of the value of nuclear positivity of p63 in PA, conducting double immunostaining using other myoepithelial markers would be of great help.

CONCLUSION(S)

In the present study, authors found strong nuclear expression of p63 in neoplastic MEC in the chondromyxoid and hyalinised areas, as well as in various architectural patterns such as solid sheets/nests, strands, cribriform, and squamous metaplastic areas of PA. These findings suggest that neoplastic myoepithelium may play a crucial role in the morphogenetic processes responsible for the variation in histologic features observed in PA. Additionally, p63 immunostaining may be highly valuable in identifying MEC in challenging cases of PA, leading to improved diagnosis and facilitating appropriate treatment planning.

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