

Pleomorphic Adenoma and Histologically Analogous Tumors of Usual and Unusual Sites: An Eight Year Experience in Muzaffarnagar Region

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ABSTRACT

Introduction: Case reports of pleomorphic adenomas of usual and unusual sites form a wonderful data in clinical and pathological literature. Pleomorphic adenoma is a biphasic tumor & characterized by admixture of polygonal epithelial & spindle shaped myoepithelial cells in a variable stromal background. Term "Mixed" benign tumor begets from such architecture.

Aims and Objectives: The aim of the present study was to highlight the various clinicopathological aspects of pleomorphic adenoma and anatomically analogous tumors of various sites in our archives.

Materials and methods: We performed an analysis of clinicopathological features of all "mixed tumors" from our archives.

Observation and Results: In our study we studied 39 cases of pleomorphic adenomas from various sites. A few cases were unusual in terms of locations, size and presentation. Most common site is parotid salivary gland. Extra-parotid sites are submandibular glands, minor salivary glands, skin, external auditory canal and vagina etc. Wide surgical excision is treatment of choice. Histopathological diagnosis is rarely difficult. Immunohistochemistry (IHC) is mandatory, in case of suspicion.

Conclusion: The results from the present study displayed the various presentations, locations and variability on histopathological architecture, thus highlighting the various clinicopathological aspects of pleomorphic adenoma and anatomically analogous tumors. IHC is required in difficult cases.

Keywords: Histopathology, mixed tumor, pleomorphic adenoma, chondroid syringoma.

INTRODUCTION

Pleomorphic adenoma is a benign neoplasm consisting of cells with epithelial (luminal) and myoepithelial (abluminal) differentiation, accompanied by variable amounts of characteristic stroma. The diverse morphology results from amalgamation of cellular and stromal components. The coexistence of apparently epithelial and mesenchymal elements gives rise to the synonym "mixed tumor".

Pleomorphic adenoma is now widely accepted as a pure epithelial tumor with divergent differentiation instead of collision of epithelial and mesenchymal tumors. The monoclonal origin of both the epithelial and mesenchymal elements has also been supported by molecular analysis.¹

Pleomorphic adenoma can occur in various mucosal sites such as nasal cavity, bronchus, skin (chondroid syringoma), breast, and soft tissues.^{2,3,4} Treatment of choice is complete surgical excision. The recurrence rates at 5 and 10 years following complete excision are 3.4% and 6.3% respectively.⁵ Enucleation alone, rupture of protuberances, rupture or spillage of tumor during removal, abundance of chondromyxoid stroma, younger age are associated with higher rate of recurrences. Factors associated with increased risk of malignant transformation are: older age, long standing tumor, submandibular location, large size, prominent zones of hyalinization, and at least moderate mitotic activity.⁶ When the

diagnosis is uncertain, there comes the role of immunohistochemistry to demonstrate the co-existence of glandular and myoepithelial components. The glandular component can be highlighted by EMA, CEA, or c-kit. Myoepithelial and modified myoepithelial cells are positive for cytokeratin, but not EMA and CEA. Currently the most reliable markers for the neoplastic myoepithelial component are p63 and calponin.⁷

AIMS

The aim of the present study was to attempt a clinicopathological study of all cases of pleomorphic adenoma and histologically analogous tumors in our archived cases.

MATERIALS AND METHODS

The material for the present study was collected from the department of pathology, Muzaffarnagar medical college and hospital, Muzaffarnagar. The aim of the present study was to highlight the various clinicopathological aspects of pleomorphic adenoma and anatomically analogous tumors. In the present study 39 cases were studied for eight years from June 2007- July 2015. In the retrospective study all the relevant material like blocks and slides available in Pathology Department, MMCH were studied. In the prospective study, we studied all the relevant new excised lesions for

histopathology from the Department of Surgery, ENT, Dermatology and Gynecology. The relevant clinical history like age of the patient, duration of swelling, any rapid progression, development of pain etc were recorded. Examination included general clinical examination and examination of the swelling proper. After removal of tumor, gross examination was carefully done and represented areas were cut into pieces, processed, blocks made, sections cut and stained with Haematoxylin and Eosin. Stained sections were subjected for histopathological examination. We made our study on a total of 39 cases of pleomorphic adenoma and histologically analogous tumors of various sites. In retrospective study 26 cases were studied and in prospective study 13 cases were studied clinically, their fine needle aspiration cytology was performed as far as possible and biopsies were studied histopathologically.

OBSERVATIONS

Out of 39 cases of pleomorphic adenoma and histologically analogous lesions, twenty seven cases were from parotid gland, 04 cases were from submandibular glands, 02 cases were from minor salivary glands, and 04 cases from skin, one case each were from external auditory canal and vagina respectively. Parotid gland was the commonest site to be involved. Maximum numbers of the cases were in 30-50 years of age group. Mean age is 42.8 years. Twenty two cases were of males (56.41%) and 17 cases were females (43.59%).

There was great variation in size of tumor ranging from few millimeters upto 10 centimeters. FNAC was performed in five prospective cases. FNAC revealed epithelial cells both singly, in groups forming acini, strands, cords, sheets etc. along with fibrillary chondromyxoid ground substance.

Macroscopic examination of excised tissue revealed connective tissue capsule, soft to firm consistency, mucoid, cartilaginous and collagenous areas on cut. On microscopic examination, tumor comprising of epithelial and myoepithelial element in varying patterns and fibrous, mucous, myxochondroid and cartilaginous tissues.

DISCUSSION

Benign mixed tumors (pleomorphic adenoma) are tumors of variable encapsulation characterized microscopically by architectural rather than cellular pleomorphism. Epithelial and myoepithelial elements intermingle most commonly with tissue of mucoid, myxoid or chondroid appearance.⁸

Salivary glands:

Pleomorphic adenoma is the most common neoplasm of the major salivary glands, in particular of the parotid gland. Only occasionally can it be found in the cervicofacial area outside the major and

minor salivary glands of the oral cavity.⁹ Mixed tumor (pleomorphic adenoma) is the most common salivary gland tumor and accounts for about 60% of all salivary gland neoplasms.¹⁰ The mean age of presentation is 46 years but the age ranges from the first to the tenth decades. There is a slight female predominance. About 80% of pleomorphic adenomas arise in the parotid, 10% in the submandibular gland and 10% in the minor salivary glands of the oral cavity, nasal cavity and paranasal sinuses and the upper respiratory and alimentary tracts.¹¹ (FIG.1, 2)

In our study maximum cases were in 30-50 years age group. Mean age is 42.8 years. These findings are in synchrony with the above study. The only point which is in contrast is that in our case there was male predominance. Male: Female ratio being 1.69. The size of the most tumors varies from about 2-5 cm but some reported cases have been massive.¹² In our study the mean size comes to be 5.5 cm, but one of our case was 9.8cm which was from parotid gland. Benign mixed tumors shows a remarkable degree of morphological diversity. The essential components are the capsule, epithelial and myoepithelial cells, and mesenchymal and stromal elements. The capsule varies in thickness and presence. Areas of capsular deficiency were observed, when the tumors were serially sectioned.¹³ In our study capsular diversity was observed in salivary gland tumors. Four cases were devoid of appreciable capsule but on deep serial sections, recognizable capsular tissue was seen in three cases. One case even on deeper sections did not demonstrate capsule. This may be due to subtotal excision of the tumor.

Most tumors show areas where finger-like processes extend into the capsule. The epithelial component shows a wide variety of cell types including cuboidal, basaloid, squamous, spindle cell, plasmacytoid and clear cells. Rarely, mucous, sebaceous and serous acinar cells are seen. These cells are cytologically bland and typically have vacuolated nuclei, without prominent nucleoli, and a low mitotic frequency. The epithelium usually forms sheets or duct-like structures. There is a wide range of epithelial cellularity; sometimes, the epithelial component forms the bulk of the tumor (cellular pleomorphic adenoma).

The mesenchymal-like component is mucoid/myxoid, cartilaginous or hyalinised and sometimes this tissue forms the bulk of the tumor. Cells within the mucoid material are myoepithelial in origin and their cellular periphery tends to blend into the surrounding stroma. The cartilage-like material appears to be true cartilage and is positive for type II collagen and keratan sulphate. Occasionally it is the major component of the tumor. Bone may form within this cartilage or form directly by osseous metaplasia of the stroma. Deposition of homo-

geneous, eosinophilic, hyaline material between tumor cells and within the stroma can be a striking feature of some tumors.⁸

Other extra-salivary sites

Mixed tumors are also been reported in external auditory canal, the nose, and the larynx. etc.⁹ The present article describes eleven cases of benign mixed tumor of extra-parotid sites studied during last eight years. The study includes four cases of submandibular glands, two cases of minor salivary glands, three cases of skin (chondroid syringoma), one case of external auditory canal, one case of vagina.

Chondroid syringoma: Chondroid syringoma is a rare benign skin adenexal tumor of eccrine/apocrine origin. It is also called as mixed tumor of skin because of the presence of both the epithelial and mesenchymal components.¹⁴ Billroth in 1859 described 'mixed tumor of the skin', which was histologically similar to benign mixed tumor of salivary gland. Most cases are benign, few malignant or aggressive forms have also been described.¹⁵ The World Health Organization has defined chondroid syringomas as benign adenexal tumors of skin composed of epithelial and stromal elements with a wide spectrum of patterns histologically analogous to mixed tumors of the salivary gland.¹⁶

The commonest sites are head and neck regions and the extremities. The usual size is less than 3 cm.¹⁷ A total of four cases were taken for study. FNAC was done in two cases. Both the cases were correctly diagnosed by FNAC. Youngest patient was 25 year male, oldest patient was 60 year male. Two cases were from head and neck region, one case was from back and one case was from the upper extremity.

The histological examination picture was more or less similar in the archived cases. It showed a dermal and subcutaneous, well-circumscribed, multilobulated neoplasm characterized by proliferation of clusters of epithelial cells distributed in nests or in tubular structures, lined by two rows of cells, with round to ovoid nuclei. The stroma had myxoid and hyaline degeneration with areas of chondroid metaplasia. However, in one case from back in 25 year male, a focal area with nuclear pleomorphism and a moderate mitotic activity was present.

The commonest sites are head and neck region; particularly, cheek, nose, or lips. Cases have been reported from scalp, orbit, auditory canal, eye lid, hand, foot, axilla, abdominal wall, penis, vulva and scrotum.^{18,19} The optional treatment for chondroid syringoma is surgical excision. Electrodesiccation, dermabrasion, and vaporization with Argon or CO₂ laser have been used as alternative modalities of treatment.²⁰

Because of malignant potential, a wide excision must be done and patient should be followed carefully for both local recurrence and metastasis.²¹

Benign mixed tumor of vagina: Benign mixed tumor of vagina (spindle cell epithelioma) is usually located in or near the hymenal ring. Tumor appears as a well circumscribed, painless sub mucosal mass that is less than 5cm. The mean age at presentation is in the fourth decade and these lesions, which are usually discovered during routine gynecologic examination, are most commonly thought clinically to represent a cyst or polyp.

It is composed of small stromal-type spindle cells intermixed with mature squamous cells and glands lined by mucinous epithelium.²² In our case the patient was of 45 years of age and was clinically diagnosed as a case of vaginal polyp. Histopathological findings were revealing a plexiform pattern of growth composed of small stromal type spindle cells intermixed with mature squamous cell & glands lined by mucinous epithelium. (FIG. 3) Ultrastructural and immunohistochemical studies support an epithelial nature.²³ There is also immune-reactivity for CD34, BCL2, CD99, h-caldesmon and CD10. There is co-expression of keratin and smooth muscle actin suggesting the possibility of myoepithelial differentiation and led to the designation of these lesions as "mixed tumors". But few newer researches show that there is lack of true myoepithelial differentiation based on immunohistochemical and ultrastructural evidences. Hence a better term "spindle cell epithelioma" was introduced.²⁴ The lesion is benign, but it may recur locally.

Pleomorphic adenoma of the External Auditory Canal: Pleomorphic adenomas of the External Auditory Canal are generally assumed to be ceruminous gland origin. Pleomorphic adenoma of EAC is a rare entity.²⁵ The first report of PA in the ear canal by Mark and Rothberg in 1951.²⁶ There have been 37 similar cases reported in the English literature. There were 16 males and 16 females (the gender of the other five cases was not mentioned) and their ages ranged from 15 to 79 years (average 46.0 years).²⁷

These tumors usually have benign course. The normal EAC lined by a very thin squamous lining covering scant fibrous stroma containing both sebaceous & modified apocrine sweat glands – ceruminous glands. PA of EAC is very rare. Kuo *et al.* reported 37 cases of PA arising from sites other than the major salivary glands, and only one of the 37 cases was observed in the ear canal.²⁸

Pleomorphic adenoma is a biphasic tumor & characterized by admixture of polygonal epithelial & spindle shaped myoepithelial cells in a variable stromal background that may be mucoid, myxoid,

chondroid, or hyaline.(FIG. 4) A 40 year old male presented with the complaints of pain in the left ear with hearing loss exacerbating since last six months. The history of pain goes well beyond almost 2 years. There is no history of any sero-sanguinous discharge or tinnitus & he has received only medical treatment. There was no history of any previous surgery or trauma. On investigations otoscopy revealed a smooth, non-tender lesion covered by normal skin that almost obstructs the EAC. Pure tone audiometry showed residual hearing at low frequency. CT findings confirmed the presence of a 2 x 1.7cm T2 high-signal intensity lesion in the wall of EAC. The diagnosis was confirmed by histopathology. Histopathological findings revealed a well-circumscribed tumor composed of biphasic pattern comprising of tubular and ductal structures lined by polygonal epithelial and spindle shaped myoepithelial cells in the background of mucoid, myxoid, chondroid & fibrous stroma. Few glands were showing secretions and ceroid deposition. Thus final diagnosis of Pleomorphic adenoma of the EAC was made. In this case after his last follow up visit which was 12 weeks after operation there was no evidence of recurrence.

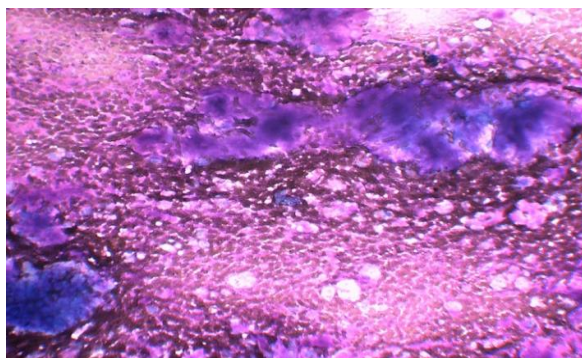


Fig. 1: Photomicrograph of cytology showing area of epithelial elements arranged in ducts, tubules, strands, clumps lined by polygonal cells & myoepithelial cells in parotid gland. Fibrochondromyxoid stroma is remarkable. (Giemsa, x 100).

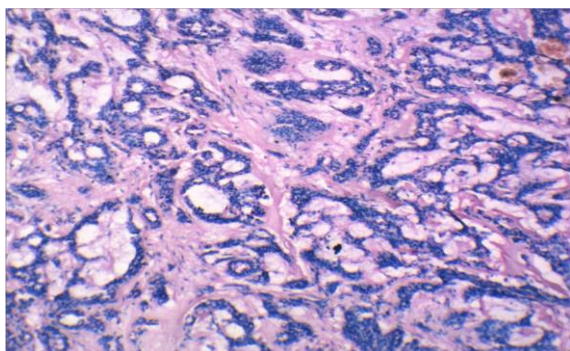


Fig. 2: Photomicrograph showing area of epithelial elements arranged in ducts, tubules, strands, clumps lined by polygonal cells & myoepithelial cells in parotid gland (H&E, x 400)

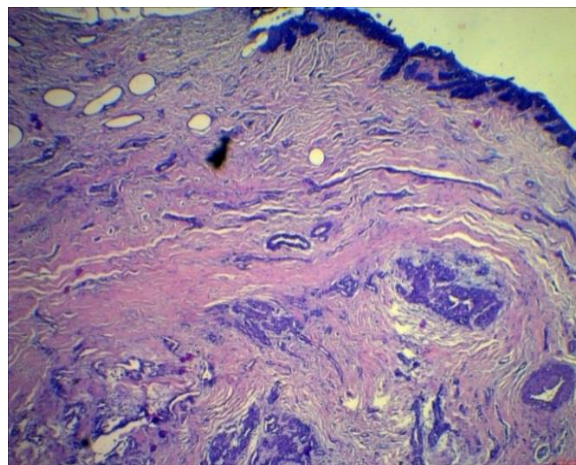


Fig. 3: Photomicrograph showing benign epithelial cells forming tubular structures along with area of myxoid, fibrous stroma & myoepithelial cells in vagina. Stratified squamous epithelium is overlying the tumor. (H & E, x400)

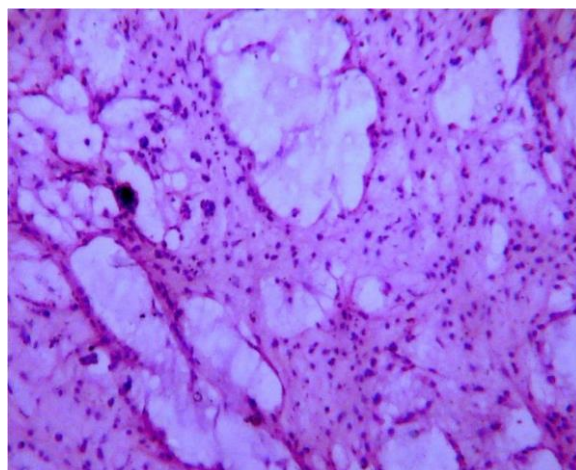


Fig. 4: Photomicrograph showing benign epithelial cells forming tubular structures along with area of chondroid material, fibrous stroma & myoepithelial cells in external auditory canal. Ceroid material is also seen. (H & E, x400)

CONCLUSION

Pleomorphic adenoma is the most common neoplasm of the major salivary glands, in particular of the parotid gland. Occasionally it can be found in various unusual sites. Excision is treatment of choice. Wide excision is necessary to avoid recurrences. Histological architecture is highly variable but the epithelial and mesenchymal elements are recognizable in most lesions. In case of difficulty in diagnosis immunohistochemistry is the real guide. The results from the present study displayed the various presentations, locations and variability on histopathological architecture, thus highlighting the various clinicopathological aspects of pleomorphic adenoma and anatomically analogous tumors.

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