ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 7 | July - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PLEOMORPHIC ADENOMA OF PAROTID GLAND –A REVIEW

ENT

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ABSTRACT

Pleomorphic adenomas are benign salivary gland tumors, which predominantly affect the superficial lobe of the parotid gland. The "pleomorphic" nature of the tumor can be explained on the basis of its epithelial and connective tissue origin. The tumor has a female predilection between 30-50 years of age. Slowly progressing asymptomatic swelling is the usual presentation of the tumor. Pleomorphic adenoma (PA), originally called mixed tumour, is the most common neoplasm of the salivary glands and is generally accepted as benign biologically. Surgical excision of the tumor mass forms the mainstay of treatment, with utmost care taken to preserve the facial nerve. Occasionally Parotid adenoma may give rise to metastasis. The metastasis may develop in a PA in which a malignant transformation occurs, either arising a carcinoma in the PA (carcinoma ex-mixed tumour) or as a carcinosarcoma (so-called true malignant mixed tumour). However, very rare benign PA eventually metastasise, usually after having a previous recurrence, displaying benign histological features as well in the primary tumour as in the metastasis. These tumours have been termed metastatic PA or metastatic mixed tumours. The aim of the review of literatures is to know about the nature of pleomorphic adenoma of parotid , and to consider the clinical, pathological and therapeutic consequences of these tumours as well as its possible causes and mechanisms for its behaviour.

KEYWORDS

Pleomorphic adenoma, Parotid gland neoplasms, Tumor recurrence

INTRODUCTION

The term pleomorphic adenoma was suggested by Willis (Rajendran & Sivapathasundaram, 2009). It was referred by different names like mixed tumor, enclavoma, branchioma, endothelioma, enchondroma,etc. in earlier years (Regezi & Batsakis, 1977). It is the most common benign salivary gland in children and adults. The morphological complexity, exists among the tumor between individuals and glands, and even within the same tumor, which actually explains the term pleomorphic adenoma. The histopathologic features of pleomorphic adenoma is pathognomonic (Stennert *et al.,* 2001). It has been postulated that rather than simultaneous proliferation of neoplastic epithelial and myoepithelial cells, a single cell with the potential to differentiate toward either epithelial or myoepithelial cells may be responsible for these tumors.

Approximately 80% of parotid tumors are benign; of these, 80% are pleomorphic adenomas . Pleomorphic adenoma (PA), also known as benign mixed tumor, is the most common salivary tumor, constituting up to two-thirds of all salivary gland neoplasms (1). Mostly, PA is located in the parotid glands (85%), minor salivary glands (10%), and the submandibular glands (5%).

In the majority of cases, tumors originate in the superficial lobe. However, occasional cases may involve the deep lobe of the parotid gland and the parapharyngeal space. Minor salivary gland tumors are frequently encountered on the palate, followed by the lip, cheek, tongue and floor of the mouth .

PA usually manifest as a slow progressing asymptomatic, parotid gland swelling without facial nerve involvement . These tumors are almost uniformly characterized by a slow-growing, painless mass in the preauricular or retromandibular area with no associated facial weakness. They are best treated by a wide local excision with good safety margins , typically via superficial parotidectomy and follow-up for at least 3-4 years .The associated risk of facial nerve injury, Frey' s syndrome and other complications, is generally justified by the risk of malignant degeneration , which is quoted to be in the range of 1.4 6.3%.However, this statistic also suggests that more than 95% of pleomorphic tumors will continue to behave in an indolent fashion , and that the only real "morbidity" they will produce is cosmetic.

Given the relative ease of diagnosing pleomorphic adenomas with clinical and cytological evidence, and the low risk of malignant degeneration, a recent paper has supported expectant management for those patients who do not desire surgery. This is in contrast to the traditional view , which emphasizes that "aggressive treatment of primary and recurrent mixed tumors is necessary' due to their malignant potential.

Etiology

The etiology of pleomorphic adenoma is unknown, but the incidence of this tumor has been increasing in the last 15-20 years in relation to the exposure of radiation. One study suggests that oncogenic simian virus (SV40) may play a role in the onset or progression of pleomorphic adenoma. Prior head and neck irradiation is also a risk factor for the development of these tumors.

Epidemiology

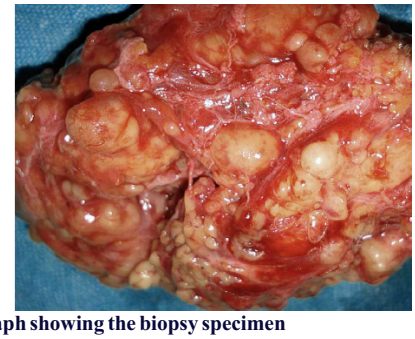
Pleomorphic adenoma is the most common benign salivary gland neoplasm. In most studies, it represents 45-75% of all salivary gland tumors; the annual incidence is approximately two to three and a half cases per 100,000 population. Pleomorphic adenoma occurs in individuals of all ages; however, it is most common in the third to sixth decades. Pleomorphic adenoma incidence is slightly more in females than in males (2:1 ratio). Pleomorphic adenomas account for 70-80% of benign salivary gland tumors and are especially common in the parotid gland. [5]Pleomorphic adenoma predominantly affects superficial lobe of the parotid gland. Distribution among the various salivary glands is as follows:

- Parotid gland: 84%
- Submandibular gland: 8%
- Minor salivary glands: 6.5%

Pathophysiology

Microscopically pleomorphic adenoma has a highly variable appearance, hence the name pleomorphic. It is characterized by mixed proliferation of polygonal epithelial and spindle-shaped myoepithelial cells in a variable stroma matrix of mucoid, myxoid, cartilaginous or hyaline origin. Epithelial elements are usually of polygonal, spindle or stellate-shaped cells which may be arranged to form duct-like structures, sheets, clumps, or interlacing strands. The ducts and tubules are seen usually exhibiting an outer lining in addition to an inner cuboidal epithelial cell layer. This is outer myoepithelial cell layer (or layers) which merges into the surrounding stroma which also contains dispersed or clumped myoepithelial element cells. Areas of squamous metaplasia and epithelial pearls can be found. The tumor lacks the true capsule and is surrounded by a fibrous pseudo capsule of variable thickness. The tumor extends through normal glandular

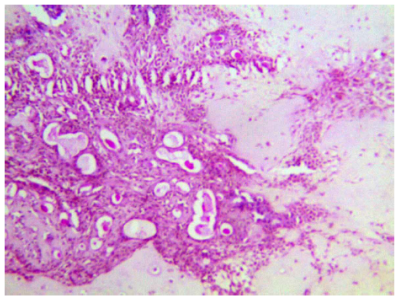
parenchyma in the form of finger-like pseudopodia. These microscopic extensions account for the high risk of recurrence in cases treated with simple enucleation or surgical resections performed with inadequate surgical margin.



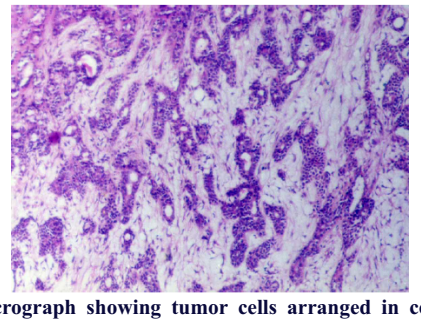
Photograph showing the biopsy specimen

Histopathology

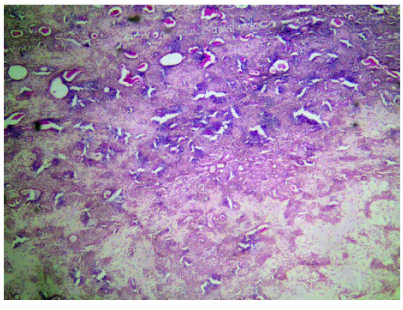
Histology will reveal proliferation of myoepithelial and epithelial cells of the ducts. There is also a marked increase in stromal components. The tumor is usually not well encapsulated.



Photomicrograph showing ductal pattern and myxoid pattern



Photomicrograph showing tumor cells arranged in cords and sheets



Photomicrograph showing ductal pattern, eosinophilic material and myxoid pattern.

History and Physical

Pleomorphic adenoma mostly presents as a solitary mobile slow-growing, painless mass, which may be present for many years. Symptoms and signs mainly depend on size, location, and potential to undergo malignant transformation. In the parotid gland, signs of facial nerve weakness occur when the tumor is large or if it undergoes malignant change. Pleomorphic adenoma in the deep lobe of the parotid gland may present as an oral retro tonsillar or para-pharyngeal mass which is visible or usually palpable. Rapid enlargement of a tumor nodule should raise a concern of malignant change. Minor salivary gland tumors may present with a variety of symptoms, including dysphagia, hoarseness, dyspnea, difficulty in chewing, and epistaxis dependent on the site of the tumor.

Evaluation

The diagnosis is made both on tissue sampling and radiographic studies. Tissue sampling procedures including fine needle aspiration (FNA) and core needle biopsy which can be done in an outpatient setting. These procedures are associated with very low tumor seeding rates.

FNA can determine whether the tumor is malignant in nature with an approximate sensitivity of 90%. Core needle biopsy is more invasive but provides more accurate histological typing of the tumor with a diagnostic accuracy of around 97%. Immunohistochemistry may prove to be supportive in delineating the different cell components.

CT examination a pleomorphic adenoma usually appears as smoothly marginated or lobulated homogeneous soft tissue density globular mass. Necrosis can be seen in larger masses. Few foci of calcification are common. Smaller tumors show early homogenous prominent enhancement while in the case of larger tumors enhancement is less marked and delayed.

MRI is similar to CT; smaller masses appear well-circumscribed and homogeneous whereas larger tumors appear heterogeneous.

- T1: usually of low intensity.
- T2: usually of very high intensity (especially myxoid type) 6 often have a rim of decreased signal intensity on T2-weighted images representing the surrounding fibrous capsule.
- T1 C+ (Gd): usually demonstrates homogeneous enhancement.
- The presence of either T2 hypointensity or ill-defined margins after contrast administration can be a simple MR imaging malignancy test for parotid tumors, with a sensitivity and specificity of 0.70 and 0.73, respectively.
- Post contrast STIR images help the delineate the perineural spread of tumor in case of malignant change.
- Ultrasound pleomorphic adenomas characteristically appear hypoechoic in texture. They usually show a lobulated distinct border with or without posterior acoustic enhancement. Ultrasound guided biopsy or FNA are minimally invasive and cost effective procedures.
- Angiography (DSA) can also be considered.

Treatment / Management

- Previously carried out enucleation procedure has been abandoned because of high associated rates of recurrence. Presently pleomorphic adenoma of the parotid gland is treated either with superficial (Patey's operation) or total parotidectomy with the latter being the more frequently performed procedure due to lower incidence of recurrence. Meticulous technique is required to preserve the facial nerve. The tumors of the submandibular glands are treated with simple excision procedure with preservation of adjacent nerve including the mandibular branch of the trigeminal nerve, the hypoglossal nerve, and the lingual nerve.
- When in the minor salivary glands, a five mm margin should be obtained. These tumors do not invade into periosteum. Thus, the bone need not be resected. When tumor bed recurrences occur, they show significant resistance to treatment, with management options including monitoring only, surgery, and radiotherapy.
- Pleomorphic adenomas harbor a small risk of malignant transformation. The malignant potential is proportional to the time the lesion is in situ (1.5% in the first five years, 9.5% after 15 years). Therefore, excision is warranted in almost all cases. Other risk factors for malignancy include advanced age, radiation therapy, large size, and recurrent tumors.

Differential Diagnosis

Differentials for pleomorphic adenoma include Warthin tumor, parotid nodal metastasis, facial nerve schwannomas, myoepitheliomas, mucoepidermoid and adenoid cystic carcinoma, and a large variety of other neoplasms nonspecific to salivary glands. Histopathology remains the gold standard in differentiating them all.

DISCUSSION

Pleomorphic adenoma or benign mixed tumor is the most common salivary gland neoplasm. It accounts for 53-77% of parotid tumors, 44-68% of submandibular tumors and 33-43% of minor salivary gland

tumors (Rajendran & Sivapathasundaram). It is a benign tumor consisting of cells capable of differentiating to epithelial (ductal and nonductal) cells and mesenchymal (chondroid, myxoid and osseous) cells (Neville *et al*., 2009). Its morphologic complexity results from the ability of tumor cells to differentiate into fibrous, hyalinized, myxoid, chondroid and osseous areas, as a result of metaplasia or actual products of tumor cells per se (Rajendran & Sivapathasundaram; Friedrich *et al*., 2005; Frazell, 1954).

Numerous theories have been proposed regarding the histogenesis of pleomorhic adenoma. It is related to the myoepithelial cells and to reserve cells in the intercalated duct. Neoplastically altered epithelial cells with the potential for multidirectional differentiation may be responsible for the tumor (Ellis & Auclair, 1996). Cytogenetic abnormalities of chromosome 12q 13-15 has been identified (Rajendran & Sivapathasundaram; Mendenhall *et al.*, 2008). The putative pleomorphic adenoma gene (PLAG1) has been mapped to chromosome 8q12 (Neville *et al.*).

Pleomorphic adenomas can occur at any age, but most common in young and middle aged adults, between 30 to 60 years. A slight female predilection is noticed. Most reported PA of parotid gland occur in thesuperficial lobe and present as a swelling on the ramus in front of the ear. The tumor is usually an irregular nodular lesion, firm in consistency, although areas of cystic degeneration may be palpated if superficial, and does not show fixation.

Facial nerve involvement and pain are rare (Rajendran & Sivapathasundaram; Frazell). If neglected, pleomorphic adenomaÊ can grow to grotesque proportion. About 10% of the reported pleomorphic adenoma develop within the deep lobe of the gland beneath the facial nerve. A few lesions grow in a medial direction between the ascending ramus and stylomandibular ligament resulting in dumbbel shaped tumor that appears as a mass of the lateral pharyngeal wall or soft palate. Pleomorphic adenoma of minorsalivary gland commonly occur in the palate (50%), upper lips (27%) and buccal mucosa (17%).

In cut gross sections, the tumor appears as an irregular - ovoid mass with well-defined borders. It may have an incomplete fibrous capsule or are unencapsulated. Cut surface may be rubbery, fleshy, mucoid, or glistening with a homogenous tan or whitecolour. Areas of hemorrhage and infarction may be noted.Pleomorphic adenoma, microscopically is characterized by variable diverse structural patterns. It consists of glandular epithelium and mesenchymal like tissue. Foote & Frazell (1954) categorized the tumor into a) principally myxoid, b) myxoid and cellular in equal proportion, c) predominantly cellular and d) extremely cellular.

The epithelial component form ducts and small cysts that contain an eosinophilic coagulum. The epithelium may also occur as small cellular rests, sheets of cells, anastamosing cords and foci of keratinizing squamous, mucous or spindle shaped cells (Rajendran & Sivapathasundaram; Neville *et al.*). The myoepithelial cells have variable morphologies like angular or spindle shape, rounded with eccentric nuclei and hyalinized eosinophilic cytoplasm resembling plasma cells (hyaline cells). Accumulation of mucoid material around the myoepithelial cells give a myxoid pattern (Neville et al.). Vacuolar degeneration results in cartilaginous appearance. Foci of hyalinization, bone and even fat can be noted. When highly cellular, it is referred to as Ôcellular adenomaÕ. When myoepithelial cells predominate, it is referred to as ÔmyoepitheliomaÕ (Dardick, 1995).

The treatment of pleomorphic adenoma is surgical excision (Rajendran & Sivapathasundaram; Ellis & Auclair, Bradley, 2001). For pleomorphic adenomaÕ of superficial lobe of parotid gland, superficial parotidectomy with preservation of facial nerve is done. For tumors of deep lobe total parotidectomy is necessary. Intraoral lesions can be treated more conservatively by extracapsular excision.

Submandibular tumors are treated by total removal of gland with tumor (Bradley). Prognosis is excellent with a cure rate of 95%. The tumor is radio resistant. So radiotherapy is not indicated. Frey syndrome is one of the rare complications after parotidectomy. Malignant transformation, though rare, has been reported in about 5% of cases. Carcinomas ex pleomorphic adenoma and metastasizing benign mixed tumor are two varients of this tumor undergoing malignant transformation.

CONCLUSION

Pleomorphic adenoma of the parotid gland is not a common lesion. Pleomorphic adenoma, though a benign tumor of salivary gland, should be diagnosed at an early stage and surgically excised. When involving parotid gland, precaution should be taken to preserve facial nerve, if possible. Care must be taken to remove the lesion entirely to avoid recurrence and malignant transformation. The ideal treatment for pleomorphic adenomas is surgical excision. Even though the lesion is benign, there is a reported recurrence rate of 7-15%. All patients who undergo excision of this lesion need to be informed about the potential for facial nerve injury, which can occur if the tumor is in close proximity of the nerve. If the facial nerve is injured, the patient must be taught an eye care program and how to use lubricating drops to prevent keratopathy. A referral to an ophthalmologist is highly recommended. Depending on the severity of nerve injury, it may take months or years to fully recover eyelid function.

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