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Pleomorphic adenoma: Review literature(พลีโอมอร์ฟิก อะดีโนม่า)

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Abstract

Pleomorphic adenoma is the most common benign salivary gland neoplasm of both the major and minor salivary glands. This review article describes the clinical features, the histopathology, the immunohistochemical markers of both the epithelial and myoepithelial components, the differential diagnosis and the treatment. The histopathology of this tumor can display diverse morphological patterns, but it traditionally presents with ducts or tubules lined by inner ductal cells and outer myoepithelial cells arranged in a variety of matrix.

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Keywords : pleomorphic adenoma, clinical features, histopathology, treatment

Introduction

Approximately 75-85% of salivary gland neoplasms occur in the parotid gland of which 70-80% are benign. The most common of these is pleomorphic adenoma.[1] Most pleomorphic adenomas arise in the major salivary glands.[2] However, their developments in the minor salivary glands of the oral cavity[,3,4], parapharyngeal space[5], external auditory canal[6,7], external nose[8], bronchus[9], ciliary body[10], and lacrimal gland[11] have been reported.

Clinical features

The favorite site of pleomorphic adenoma is the tail of the parotid gland (60%), with the majority of the tumors lying superficial to the facial nerve.[13,14,15] The commonly affected age groups are the fifth and sixth decades.[15,16] It affects more women than men.[1,13,16] Pleomorphic adenoma is a slow growing, usually well-demarcated benign lesion of salivary gland.[2,16]An asymptomatic lump is the normal mode of presentation, but occasionally there may be pain and rarely a facial palsy.[12] On palpation, 78% of the tumors are mobile. Pleomorphic adenomas in the parotid gland are found to be located in the superficial lobe in 77% of cases, in deep lobe in 14% of cases and in both the superficial and deep lobes in 8% of cases. The average tumor size is 3.3 cm.[17] Benign salivary gland tumors in children are unusual. Pleomorphic adenoma is by far the most common of benign childhood salivary gland tumors accounting for more than 80% of the cases presenting in the parotid or the submandibular gland.(reviewed by Noghreyan et al)[18] In the longstanding pleomorphic adenoma, there is a propensity for malignant transformation, but this is fortunately rare.[12] Cases of rapid growth after a long period of quiescence have been reported and malignant transformation such as carcinoma expleomorphic adenoma occasionally occurs.[16] Malignant mixed tumor of the salivary gland is a broad term that encompasses carcinoma expleomorphic adenoma, true malignant mixed tumor (carcinosarcoma), and metastasizing mixed tumor. In carcinoma expleomorphic adenoma, only the epithelial component displays malignant histologic features. A true malignant mixed tumor shows carcinomatous and sarcomatous elements. A metastasizing mixed tumor is histologically identical to a benign mixed tumor, but for unknown reason, it metastasizes.[19] Factors associated with a higher chance of malignant disease are age greater than 40 years at initial treatment, male sex, nodules greater than 2 cm. in diameter, deep lobe tumor and more than one previous operation.[20]

Histopathology

Pleomorphic adenoma, unlike most other salivary gland tumors, does not have a true fibrous capsule. It consists of a capsule of varying thickness and completeness. This allows fingerlike branchings or pseudopodia to extend outside the main tumor lump.[21] It presents with morpological diversity and complexity. The ducts of pleomorphic adenoma are composed of an inner layer of ductal epithelium and an outer layer of myoepithelium[22] (figure 1). In occasional areas, the duct cells may be the prominent feature, but usually they are found only as a single layer lining the tubules, varying from flattened and inconspicuous to columnar and prominent. The lumen of the ducts may contain clear fluid, or inspissated eosinophilic and strongly PAS-positive material.[23] The epithelial component can show diverse patterns, namely, cylindromatous structures, tubular structures, and adenomyoepitheliomatous pattern in which the duct elements are seperated from each other by closely packed round, polyhedral or spindle myoepithelial cells. In some areas, the epithellial cells are more loosely arranged and individual cells and strands of cells appear to stream away from the compact sheets of cells.[24] Outside the duct-lining cells, there are smaller, darker myoepithelial cells. These myoepithelial cells are arranged either as a single layer or, more often, they have proliferated to form thick, ill-defined sheaths around the ducts. Frequently, material of very characteristic basophilic appearance accumulates between myoepithelial cells, increasingly seperating them from one another. Some of the myoepithelial cells undergo a type of vacuolar degeneration and assume characteristics of cartilage cells(figure 2A). As an alternative to chondroid change, mucoid accumulation may leave the cells in small groups or strands, giving a myxoid appearance to the tissue (figure 2B). The myoepithelial cells may give rise to a hyaline material(figure 2C). The hyaline material may surround tumor ducts and cell groups as sheaths producing areas of so-called cylindromatous appearance.[25]

The constituents of pleomorphic adenoma are present in varying proportion and show such a great variety of characteristics. In addition to the common epithelial and myoepithelial components, oncocytic cells, plasmacytoid cells, mucous goblet cells, sebaceous cells, and focal collection of adipose tissue are occasionally present in pleomorphic adenoma.[26] The pleomorphic adenomas showing oncocytic change are predominantly epithelial tumor of solid type. The distinction between oncocytic change in pleomorphic adenoma and oncocytoma is easily made by considering the capsule and the presence or absence of significant internal fibrous stroma. The capsule of pleomorphic adenoma is overall thicker but with an irregular internal margin, which is penetrated by the tumor in some areas. The presence of satellite

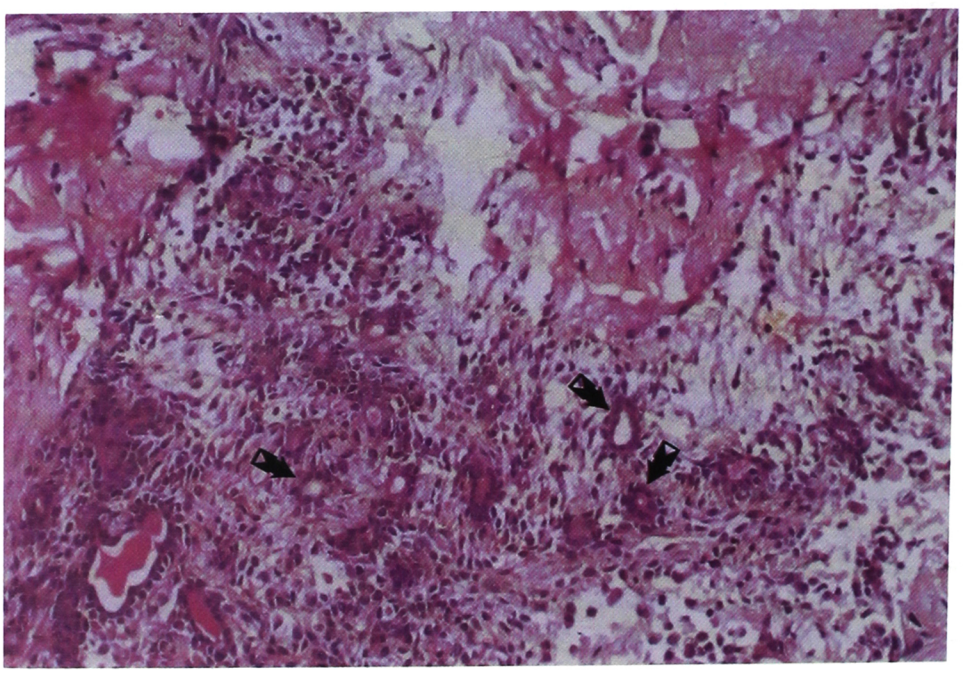

Figure 1 Photomicrograph showing ducts of pleomorphic adenoma(arrows) which consist of an inner layer of ductal epithelium and an outer layer of myoepithelium. Hematoxylin and eosin stain. X 180.

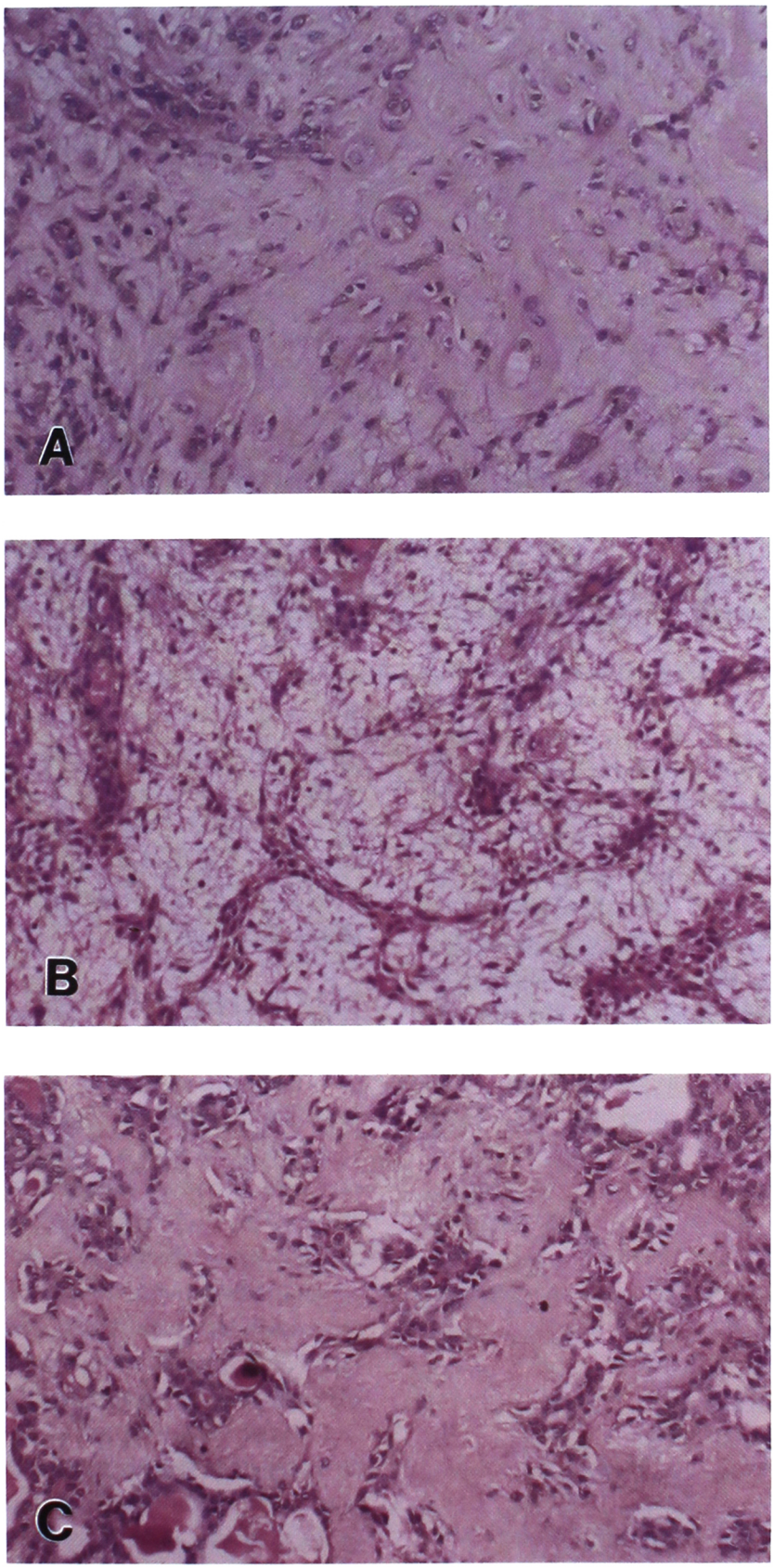

Figure 2A,B,C Photomicrographs showing several types of matrix. A) chondroid B) myxoid and C) hyaline. Hematoxylin and eosin stain. X 180.

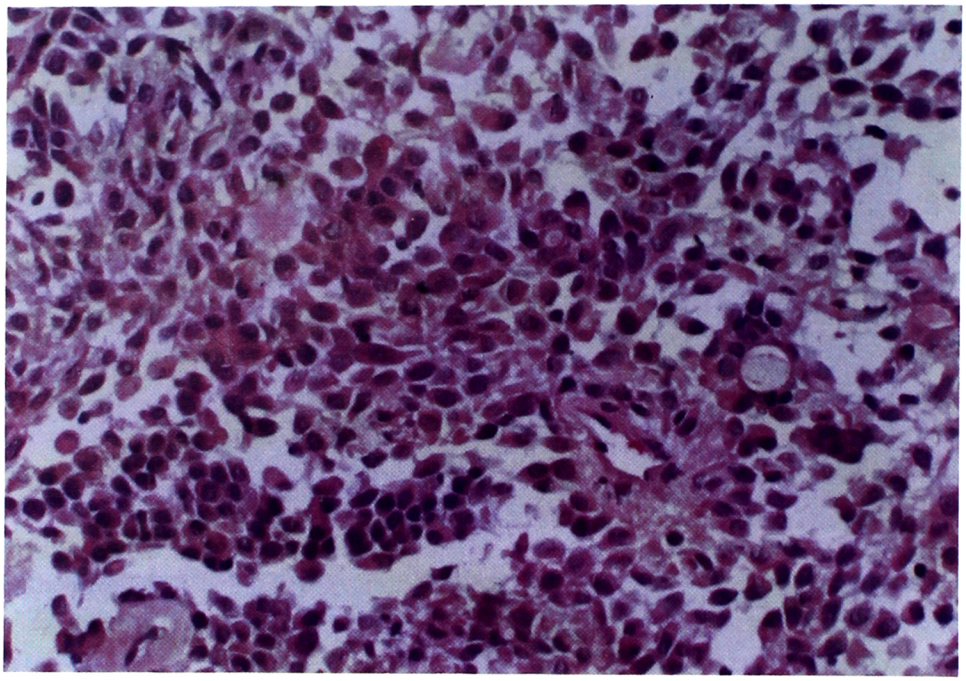

Figure 3 Photomicrograph showing an aggregate of plasmacytoid cells. Hematoxylin and eosin stain. X 360.

nodules adjacent to the main tumor mass supports the diagnosis of pleomorphic adenoma.[27] Plasmacytoid cells may form limited to extensive foci in pleomorphic adenoma or present as single to a few cells interspersed with other nonluminal tumor cells. The presence of plasmacytoid cells in pleomorphic adenomas is a unique variety of this neoplasm. They usually appears as oval cells with hyaline eosinophilic cytoplasm and eccentric nuclei which exhibit peripheral clumped chromatin described as "clock-face" pattern(figure 3). Plasmacytoid cells are found in 38% of minor salivary gland and 21% of major salivary gland pleomorphic adenomas.[28] Formation of a cyst that originates from a pleomorphic adenoma is relatively rare and most such cysts are degenerative pseudocysts without lining cells. By contrast, a true cyst with ciliated lining cells along with scattered mucous cells, resulting from a cystic dilatation of the glandular element of a pleomorphic adenoma has been reported.[29] Jin et al[26] presented a case of pleomorphic adenoma containing adipose tissue in over 90% of the tumor. Takeda and Yamamoto[30] reported a case of pleomorphic adenoma showing several islands of fibrous bone because they contained entrapped cells and Sharpey's fibers as opposed to the endochondral ossification previously reported. They also indicated the modified myoepithelial cells played an important role in the expression of morphologic diversity, especially in myxochondroid and chondral tissue formation[30] Areas of squamous epithlium, some of which show squamous metaplasia, are commonly encountered.[24] There have been reports of pleomorphic adenomas that contain deposits of crystalline material such as tyrosine crystals from both fine needle aspiration specimens[31] and from biopsy specimens.[32]

Cytology

Pleomorphic adenoma shows tumor cells containing abundant cytoplasm in clusters and isolated cells. Plasmacytoid appearance is a reliable finding in pleomorphic adenoma. Fibrillary chondromyxoid ground substance and a mixture of epithelial cells with stroma are found in two-thirds of pleomorphic adenomas. The amount of cytoplasm and the pattern of cell clusters are helpful to differentiate pleomorphic adenoma from adenoid cystic carcinoma. Most adenoid cystic carcinomas show little cytoplasm. Large, loose clusters with a spindle cell core or cell clusters with a sunburst appearance caused by peripheral spindle cells streaming into a fibrillar myxoid stroma suggest pleomorphic adenoma while tightly cohesive, basaloid cells surrounded mucoid or hyaline globules or clear spaces in a honeycomb pattern are more suggestive of adenoid cystic carcinoma.[33,34] The sensitivity and specificity of the cytologic diagnosis of pleomorphic adenoma are 92.6% and 98.4% respectively.[35]

Immunohistochemistry

In salivary gland tumors as in neoplasms of many other organs, lineage specific polypeptides in the normal salivary gland are used as markers indicating histogenetic origin.[36] Proteins such as actin as well as S-100 identify myoepithelium in normal gland, whereas the markers epithelial membrane antigen, carcinoembryonic antigen, and cytokeratin preferentially label duct luminal cells.[36,37] In pleomorphic adenoma, regardless of their cellular morphology, the tumor cells most likely to be positively stained for muscles pecific actin are those immediately adjacent to the ductal cells. Staining for muscle-specific actin never involves all tumor cells, but spindle cells are most likely to be positive. All pleomorphic adenomas are extensively stained for vimentin. Vimentin immunoreactivity is present in almost all tumor cells of epithelial and mesenchymal differentiation, except for inner tubular cells and squamous epithelial cells. No less than 90% to 95% of nonductal tumor cells are positive for vimentin regardless of their shapes. Overall, 94% of pleomorphic adenomas have a significant number of population with glial fibrillary acidic protein-positive nonluminal cells. Stellate to spindle shaped tumor cells isolated in myxoid material are invariably positive. Glial fibrillary acidic protein immunoreactivity is significantly reduced in the mature chondroid cells showing lacunar formation in the chondromatous tissue.[36,38] S-100 protein is localized in basal layer cells of the ducts, spindle-shaped, stellate myxoid and chondroid cells. These are believed to be myoepithelial cells.[13,39,40] For cytokeratin, inner tubular cells and squamous epithelial cells are intensely positive.[38,39]

Treatment

There is general agreement concerning the treatment of pleomorphic adenoma that surgical removal is the proper therapy.[17] The treatment of pleomorphic adenoma in children as in adult should be designed to remove the complete tumor with a satisfactory margin.[41,42] For parotid tumors, a parotidectomy designed to provide adequate tumor margins is the procedure of choice. Superficial parotidectomy can adequately control benign and malignant neoplasms confined to the superficial lobe. Deep lobe tumors require total parotidectomy. Facial nerve sacrifice is not necessary unless the nerve is directly invaded or the intact nerve limits the resection.[43] The standard therapy for benign submandibular tumors involves extirpation of the diseased gland.[44] In the palate, the excision should include the periosteum or bone if they are involved.[18] Following superficial parotidectomy, permanent nerve injury occurs in about 1% and transient paresis in about 30% of patients.[45] Apart from injury to the facial nerve which may result in paralysis of the facial muscles, the complictions of parotid surgery are minor. They comprise neuroma, fistula and Frey's syndrome which is characterized by dermal flushing and sweating of the skin preliminary to or during saliva production.[1,12] Postoperative radiotherapy should only be considered after uncontrollable tumor spillage and non-radical excision.[1]

Recurrence

The rate of tumor recurrence after surgery for benign salivary gland pleomorphic adenoma varies considerably in different clinical settings and seem to depend to a greater extent on surgical technique used. Overall tumor recurrence after surgery is 32.5% after one operation, 7.1% after two operations and 1.6% after three operations. The mean time between initial treatment and the detection of subsequent recurrence is 9.9 years.[21] Tumor recurrence must be regarded as being closely associated with incomplete surgical excision.[18,46] or with accidental rupture of the tumor pseudocapsule during surgery, which allows spillage of tumor cells into the wound.[20,21] Tumor size and location also appear to influence recurrence. As size increases, the incidence of first recurrence after initial treatment doubles. Deep lobe tumors have a greater chance of recurrence after initial operation. Parapharyngeal pleomorphic adenoma has the highest chance of persistent tumor when diagnosis is done by tumor location.[20] The risk of recurrence is significantly increased if microscopic fingerlike formations of tumor tissue extend beyond the main lump.[21] It is accepted that the control of the disease becomes more difficult with each recurrence. Operating on recurrent disease increases the morbidity with respect to preservation of the facial nerve.[47] Permanent injury occurs in 15% of patients after a second operation and in 30% of patients after a third operation.[48] The incidence of recurrent local disease has diminished considerably since the abandoning of the enucleation procedures and the introduction of parotidectomy with facial nerve dissection as the standard treatment of these lesions.[20]

Discussion

Pleomorphic adenoma should be put high on the list of clinical differential diagnosis of the lump in the parotid gland since most parotid lumps are salivary gland neoplasms and the most common of these is

pleomorphic adenoma.[12] Other differential diagnoses should include the neoplasms that result from the indigenous tissue to that region such as monomorphic adenoma, lipoma, schwannoma, fibroma or even the malignant neoplasms such as mucoepidermoid carcinoma, adenoid cystic carcinoma, lymphoma and other malignant salivary gland neoplasms. The only way to know exactly, which benign salivary gland is, is through histopathologic examination. The exact kind of malignant neoplasm can only be known by histopathologic examination, but certain characteristics can differentiate malignant neoplasms from the benign ones such as pain, ulceration facial nerve involvement and fixation to underlying or overlying structures. The presence of the fingerlike branching of the tumor is significantly associated with an increased recurrence risk. This provides solid ground for adopting a more radical surgical approach such as superficial lobectomy with a margin of normal parotid tissue to control pleomorphic adenomas and may explain why the use of a more radical technique can reduce the risk of recurrence.[21]

Conclusion

Pleomorphic adenoma is the most common benign tumor of both the major and minor salivary glands. It has the peak incidence in the fifth and the sixth decades of life with the predilection for women. Its favorite locations are the tail of parotid gland and the palate for the intraoral site. It usually presents with slowly growing, asymptomatic lump. Histologically, it demonstrates morphological diversity and complexity. Clasically, it has an inner layer of epithelial cells and an outer layer of myoepithelial cells. These may be arranged in a variety of pattern associated with scant or abundant stroma which may be mucoid, chondroid, hyaline or myxochondroid. The myoepithelium in pleomorphic adenoma have positive staining reactions for muscle-specific actin, cytokeratin, vimentin and glial fibrillary acidic protein while the epithelium are positive for cytokeratin. Surgery with adequate tumor margins is the treatment of choice. Facial nerve sacrifice is not necessary unless the nerve is directly involved.

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พลีโอมอร์ฟิก อะดีโนม่า

บทคัดย่อ

พลีโอมอร์ฟิก อะดีโนม่าเป็นเนื้องอกแบบไม่ร้ายแรงของต่อมน้ำลายหลักและต่อมน้ำย่อยที่พบบ่อยมากที่สุด บทความปริทัน์นี้จะบรรยายถึงลักษณะทางคลินิก ลักษณะทางจุลพยาธิวิทยา ตัวบ่งชี้ทางอิมมูโนฮิสโตเคมีของทั้งเซลล์บุผิวและเซลล์ไมโอเอ็พพิธิเลียม การวินิจฉัยแยกโรคและการรักษา ลักษณะทางจุลพยาธิวิทยาของเนื้องอกชนิดนี้มีได้หลากหลายแบบมากแต่โดยทั่วไปแล้วเนื้องอกชนิดนี้จะมีลักษณะเป็นท่อซึ่งถูกล้อมรอบโดยเซลล์บุท่อด้านในและเซลล์ไมโอเอ็พพิธิเลียมด้านนอกเรียงตัวกันอยู่ในเมทริกซ์หลายแบบ

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