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The Gulf Journal of Oncology

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Extensive Review In The Detection Of The Malignant Transformation Of Pleomorphic Adenoma

B. Tarakji¹, K. Baroudi², S. Hanouneh³, M.Y. Kharma⁴, M.Z. Nassani⁵

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Abstract

Background and Objectives

There is an increasing likelihood of malignant change in pleomorphic adenoma (PA) with time. This extensive review aims to highlight the current areas of difficulty or controversy in the diagnosis of malignant transformation of pleomorphic adenoma – a subject of most interest and challenge to a pathologist. It is also the objective of this review to compare the clinical and pathological points-of-view on the diagnosis of malignant transformation of pleomorphic adenoma.

Methods

A literature search using MEDLINE, accessed through the National Library of Medicine PubMed interface, for articles relating to malignant transformation of pleomorphic salivary adenoma written in the English language.

Introduction

The application of molecular biological tools to the study of pleomorphic salivary adenoma and its transformation to malignant has significantly advanced the field of salivary gland research. Such study has demonstrated the involvement of two classes of highly conserved cellular genes in the malignant transformation process: oncogenes and tumor suppressor genes. The development in the management of carcinoma arising from pleomorphic adenoma (CXPA) has aided in the differentiation between benign pleomorphic adenoma and carcinoma arising in pleomorphic adenoma from clinical point view.

Results

The updated literature indicates that carcinomas in pleomorphic adenoma may arise in an older age group than benign lesions and are usually larger and longer standing lesions. The use of molecular changes to study malignant transformation of pleomorphic adenoma, unfortunately, have no specific expression on the tumor suppressor genes to detect the malignant transformation of pleomorphic adenoma from pathological point view.

Conclusion

The use of combined clinical evidence and pathological evidence are very important in the detection of the malignant transformation of pleomorphic adenoma.

Keywords

pleomorphic adenoma, malignant transformation of pleomorphic adenoma

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Carcinoma originating from within a pre-existing in pleomorphic adenoma was questioned by some authors⁴. In addition, it was also recognized that carcinoma in pleomorphic adenoma were misdiagnoses of other tumor types. Some pathologists described a spectrum of pleo-morphic adenomas including: ‘benign’, ‘semi-malignant’, and ‘malignant’. The picture was more confused when terms such as ‘primary malignant mixed tumor’ were used to describe what was considered to be a carcinoma in pleomorphic adenoma arising de novo⁵.
In addition, there were scattered reports of histo-logically benign pleomorphic adenomas that had undergone distant metastasis.

**Materials and methods**


We also used the “Related Articles” feature of PubMed to identify further references of interest within the primary search. These references were obtained and from their bibliographies, pertinent secondary references were also identified and acquired. The process was repeated until no further new articles could be identified. The abstracted literature was reviewed.

**Results**

Table 1 summarizes all the clinical data on carcinomas arising from pleomorphic adenoma (1977-2009).

<table>
<thead>
<tr>
<th>Results</th>
<th>Description of carcinoma ex pleomorphic adenoma cases</th>
<th>Type of study</th>
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<tr>
<td>Prolonged follow-up is required because recurrences and death from tumor may be seen many years following the diagnosis of MMT.</td>
<td>Forty-seven cases of malignant mixed tumor (MMT) arising in major and minor salivary glands are presented.</td>
<td>Case series</td>
<td>LiVolsi and Perzin (1977)</td>
</tr>
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<td>Pleomorphic adenomas formed the largest group of tumours in most sites, but were particularly common in the parotid. Malignant tumours were more common in the submandibular and the minor glands than in the parotid.</td>
<td>To date the British Salivary Gland Tumour Panel has accumulated 2569 salivary gland tumours.</td>
<td>Case series</td>
<td>Eveson, and Cawson (1985)</td>
</tr>
<tr>
<td>After total resection, histological examination revealed that the tumour was composed partly of benign pleomorphic adenoma and partly of an adenocarcinomatous component</td>
<td>A case of carcinoma ex pleomorphic adenoma arising in the soft palate is reported.</td>
<td>Case report</td>
<td>Yoshihara et al, (1995)</td>
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<tr>
<td>Important prognostic factors include tumor size, grade, and clinical and pathologic stage. Patients with minimally invasive tumors (&lt;5 mm) should do well with appropriate surgical medical records of 73 carcinoma ex pleomorphic adenoma patients with major salivary gland treated</td>
<td></td>
<td>Retrospective study</td>
<td>Olsen and Lewis (2001)</td>
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<tr>
<td>The immunohistochemical profile of CXPA included positive staining reactions in the malignant component for AE1/AE3 in 97% of cases, CK7 in 94%, epithelial membrane antigen in 86%, carcinoembryonic antigen in 75%, vimentin in 52%, and S-100 protein in 29%. Expression of p53 and c-erbB-2 oncoproteins was detected in 41% and 30% of the carcinomas, respectively, but neither was associated with decreased survival.</td>
<td>73 cases of CXPA of the major salivary glands treated at Mayo Clinic. Paraffin section immunostaining for keratins (AE1/AE3, CK7, CK20), epithelial membrane antigen, carcinoembryonic antigen, vimentin, actin, S-100 protein, glial fibrillary acidic protein, and p53 and c-erbB-2 oncoproteins was performed in 69 cases.</td>
<td>Retrospective study</td>
<td>Lewis et al, (2001)</td>
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<td>Results</td>
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<td>For parotid tumors, acinic cell carcinomas had the best prognosis with a 10-year relative survival of 88%. The corresponding figures for mucoepidermoid carcinomas, adenoidcystic carcinomas and carcinoma ex pleomorphic adenoma were 80, 74 and 73%. Age and gender had an impact on relative survival for patients with mucoepidermoid carcinoma, adenocarcinoma and undifferentiated cancer of the parotid.</td>
<td>For parotid tumors, acinic cell carcinomas had the best prognosis with a 10-year relative survival of 88%. The corresponding figures for mucoepidermoid carcinomas, adenoidcystic carcinomas and carcinoma ex pleomorphic adenoma were 80, 74 and 73%. Age and gender had an impact on relative survival for patients with mucoepidermoid carcinoma, adenocarcinoma and undifferentiated cancer of the parotid.</td>
<td>Retrospective study</td>
<td>Wahlberg et al.(2002)</td>
</tr>
<tr>
<td>Histologic subclassification points out that there is no prototypical carcinoma ex pleomorphic adenoma and that high- and low-grade carcinomas can be found. Only one of the patients with low-grade (terminal duct) carcinomas died of his disease during follow-up periods extending to over 20 years.</td>
<td>This study of 40 malignant mixed tumors indicates that two previously unreported variables, measured invasion in millimeters and histologic subclassifications of the malignant neoplasm, are valuable guides to prognosis and biologic behavior..</td>
<td>case series</td>
<td>Tortoledo et al. (1984)</td>
</tr>
<tr>
<td>New entities are: polymorphous low-grade adenocarcinoma, basal cell adenocarcinoma, salivary duct carcinoma and malignant myoepithelioma. Carcinoma in pleomorphic adenoma can be distinguished as non-invasive and invasive carcinoma, and carcinosarcoma.</td>
<td>The group of malignant salivary gland tumours contains carcinomas, malignant non-epithelial tumours, malignant lymphomas and secondary tumours.</td>
<td>Report study</td>
<td>Seifert (1992)</td>
</tr>
<tr>
<td>. Carcinosarcoma is a very rare malignant neoplasm, accounting for 0.16% of malignant salivary gland tumors</td>
<td>Carcinosarcoma in a 77-year-old man with peculiar morphological findings. Fine-needle aspiration cytology allowed a preoperative diagnosis of poorly differentiated carcinoma.</td>
<td>Case study</td>
<td>Sironi et al.(2000)</td>
</tr>
<tr>
<td>The most common type of the former is squamous cell carcinoma or adenocarcinoma and the most common type of the latter is chondrosarcoma, followed in frequency by fibrosarcoma, leiomyosarcoma, osteosarcoma, and in rare instances liposarcoma.</td>
<td>True malignant mixed tumor (carcinosarcoma) of the salivary gland is an extremely rare tumor. By definition, it is composed of both malignant epithelial and malignant mesenchymal elements.</td>
<td>Case report</td>
<td>Kwon and Gu (2001)</td>
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<td>RESULTS: Eight of 24 (33%) CXPAs versus 41 of 300 (14%) PAs were localized in the deep lobe (P &lt; 0.05). Forty-two percent of CXPAs versus 6 percent of PAs, respectively, were greater than 4 cm (P &lt; 0.05). CONCLUSION: CXPAs are difficult to identify preoperatively. FNAC has a low accuracy and sensitivity. CXPAs versus PAs are significantly more frequently localized in the deep lobe and are significantly greater in size.</td>
<td>To analyze a series of carcinoma ex pleomorphic adenoma (CXA) and to assess the diagnostic difficulties. STUDY DESIGN: The clinical presentation of 24 CXPAs was compared with 300 pleomorphic adenomas (PAs). Furthermore, pathohistological findings and follow-up results of CXPAs were evaluated</td>
<td>Case report</td>
<td>Zbären et al.(2008)</td>
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<td>Results</td>
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<td>Clinical rather than pathologic evidence seems to justify inclusion of metastasizing salivary pleomorphic adenoma in the group of low-grade malignant salivary tumors.</td>
<td>METHODS: We simultaneously examined apoptosis-related protein expression and markers of cell-proliferation activity in our case of benign pleomorphic adenoma metastasis and compared outcome with a control group of primary parotid pleomorphic adenomas.</td>
<td>Case series</td>
<td>Marioni et al.(2003)</td>
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<tr>
<td>the following histological findings were thought to be important criteria for the diagnosis of carcinomas: (1) capsular invasion, (2) infiltration into adjacent organs, (3) proliferation of atypical cells within fibrous tissues and chondroid matrix in the area of pleomorphic adenoma, (4) vascular involvement, and (5) mitotic figures.</td>
<td>Five-hundred-eighteen cases of primary epithelial tumors of the parotid gland were examined.</td>
<td>Case series</td>
<td>Naqgo et al.(1981)</td>
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<td>The mitotic rate was also analyzed. The age of the patient, and the site, size, and prediagnostic duration of the tumor were recorded and, together with the histologic findings, were correlated with follow-up information. Nine (13.8%) of the 65 tumors underwent malignant transformation. Clinical findings at the initial diagnosis that indicated a greater likelihood of malignant transformation were occurrence in the submandibular gland, older patient age, and large tumor size.</td>
<td>65 mixed tumors of the major and minor salivary glands that exhibited atypical histologic features were examined in an attempt to analyze which, if any, of these features might indicate a greater likelihood of malignant transformation. The atypical features evaluated were hypercellularity, capsule violation, hyalinization, necrosis, and cellular anaplasia. The mitotic rate was also analyzed.</td>
<td>Case series</td>
<td>Auclair and Ellis (1996)</td>
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<td>Neither recurrences nor metastases were seen in 11 of 12 patients after surgical resection with a follow-up of 1.2 to 13 yrs (mean, 4.2 years). Ploidy studies were performed on the paraffin-embedded tissue in 11 cases and yielded results for 7 cases. Aneuploid cell populations were found in five tumors; two had normal diploid populations; and the ploidy results are not predictive of tumor behavior. This type of salivary gland tumor fits diagnostically within the category of noninvasive and minimally invasive carcinoma ex pleomorphic adenoma (also referred to as in situ and low-grade malignant mixed tumors), a class that requires additional awareness and precise recognition as it signifies a good prognosis after surgical resection.</td>
<td>We studied 12 histologically malignant salivary tumors that showed complete encapsulation or only limited microscopic invasion. Most cases were histologically characterized by atypical and mitotically active luminal cells forming dilated, angular, variably sized glands in the subcapsular region, varying proportions of nonluminal tumor cells, and a background of central fibroded hyalinized stroma.</td>
<td>Case series</td>
<td>Brandwein et al., (1996)</td>
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<td>This study confirms that superficial parotidectomy with identification and dissection of the facial nerve greatly decreases the incidence of recurrent benign pleomorphic adenoma, and, in the small number that recur, are easier to cure.</td>
<td>Twenty-seven patients with recurrent pleomorphic adenomas of the parotid gland were seen.</td>
<td>Case series</td>
<td>Myssiorek et al.(1990)</td>
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<td>This study emphasizes the distinction between multinodular and uninodular recurrences; the former is at high risk of relapse and benefits from adjuvant radiotherapy whereas solitary tumors may be adequately treated by surgery alone</td>
<td>A series of 114 patients with first recurrences treated between 1952 and 1992 is reviewed</td>
<td>Retrospective study</td>
<td>Renehan et al,(1996)</td>
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<td>In view of the fact that an alternative and apparently superior treatment is available in the form of formal parotidectomy, we urge that this should be universally adopted for the management of both primary and recurrent pleomorphic adenomas</td>
<td>We have analysed the interval between first treatment and tumour recurrence in 65 patients with parotid pleomorphic adenomas which had recurred following local excision.</td>
<td>Case series</td>
<td>Watkin and Hobsley (1986)</td>
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<td>The highest S-phase fractions were observed in recurrent and malignant pleomorphic adenomas. Immunostaining with p105, a nuclear proliferation antigen, revealed increased proliferative activity in a majority of pleomorphic adenomas. Increased proliferative activity and aneuploidy occurred in benign pleomorphic adenomas.</td>
<td>We used flow cytometry in a retrospective study of pleomorphic adenoma and carcinoma arising in pleomorphic adenoma, using paraffin-embedded tissue, to assess the relationship among proliferative activity, ploidy, and recurrence or malignant transformation.</td>
<td>Retrospective study</td>
<td>Martin et al, (1994)</td>
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<td>The tumour showed areas of dysplasia and the difficulties in distinguishing this from benign pleomorphic adenoma or carcinoma in pleomorphic adenoma are considered, and the literature is reviewed.</td>
<td>A case of pleomorphic adenoma in the sublingual gland is described.</td>
<td>Case report</td>
<td>Clark,(1993)</td>
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<td>Our results indicate that PLAG1 activation due to promoter swapping is a crucial event in salivary gland tumourigenesis</td>
<td>Microscopically, pleomorphic adenomas show a marked histological diversity with epithelial, myoepithelial and mesenchymal components in a variety of patterns. In addition to a cytogenetic subgroup with normal karyotypes, pleomorphic adenomas are characterized by recurrent chromosome rearrangements, particularly reciprocal translocations, with breakpoints at 8q12, 3p21, and 12q13-15, in that order of frequency. The most common abnormality is a reciprocal t(3;8)(p21;q12).</td>
<td>Case series</td>
<td>Kas et al, (1997)</td>
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<td>The results suggest that in addition to chromosomal translocations and cryptic rearrangements, PLAG1 may also be activated by mutations or indirect mechanisms. Our findings establish a conserved mechanism of PLAG1 activation in salivary gland tumors with and without 8q12 aberrations, which indicates that such activation is a frequent event in these tumors</td>
<td>We have studied the expression of PLAG1 by Northern blot analysis in 47 primary benign and malignant human tumors with or without cytogenetic abnormalities of 8q12</td>
<td></td>
<td>Astrom et al,(1999)</td>
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<td>no translocation partner genes of HMGIC are known for pleomorphic adenomas. Here, we report that in a primary pleomorphic adenoma of the parotid gland, the FHIT gene, which spans the chromosome 3p14.2 fragile site FRA3B, and is frequently disrupted in tumors, acts as a fusion partner of HMGIC. In addition to normal HMGIC and FHIT transcripts, an HMGIC/FHIT hybrid transcript as well as its reciprocal counterpart, FHIT/HMGIC, were found to be expressed by reverse transcription-PCR.</td>
<td>The developmentally regulated HMGIC gene, which encodes an architectural transcription factor, has recently been linked to the pathogenesis of benign solid tumors with chromosome aberrations involving 12q13-15. Among these tumors are pleomorphic adenoma of the salivary glands, lipoma, uterine leiomyoma, hamartomas of the breast and lung, fibroadenoma of the breast, angiomyxoma, and endometrial polyps.</td>
<td>Case report</td>
<td>Geurts et al,(1997)</td>
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<td>The finding of a preferential association between c-erbB-2 overexpression and high-grade malignant mixed tumour may indicate prognostic implications for the oncogene protein and may also be indicative of its specific relationship with the putative pathway of malignant transformation in pleomorphic adenomas.</td>
<td>A series of 19 cases of carcinoma ex-pleomorphic adenoma was studied for the immuno-expression of c-erbB-2 oncoprotein</td>
<td>Case series</td>
<td>Rosa et al,(1996)</td>
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<td>overexpression of p53 oncoprotein was noted immunohistochemically in 13% of adenomas, 50% of transitional areas and 75% of carcinomas. All of the tumors with immunoreactivity for p53 oncoprotein demonstrated LOH. Moreover, when LOH was present in adenomatous or transitional areas, the identical LOH was always detected in the corresponding carcinomatous areas in the same CPA tumors. These findings indicate that p53 gene mutation is an early event and occurs frequently at an early stage of precancerous lesions and may be responsible for most cases of malignant transformation of PA.</td>
<td>Where and how frequently p53 abnormalities are involved in the development of pleomorphic adenoma (PA) and its malignant progression to carcinoma was investigated</td>
<td>Case series</td>
<td>Yamamoto et al,(1998)</td>
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<td>Results of this study suggest that two different genetic alterations, the inactivation of the p16 gene and genetic instability, play roles in the malignant transformation of carcinoma in pleomorphic adenoma. The MSI observed in the adenoma suggests that genetic alterations occur in pleomorphic adenoma.</td>
<td>Recent studies have revealed that malignant transformation of various human cancers may involve two different genetic alterations: inactivation of the p16 gene, which is a putative tumor suppressor gene, and genetic instability represented by microsatellite instability (MSI).</td>
<td>Case series</td>
<td>Suzuki and Fujioka (1998)</td>
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<td>Our study indicates that (1) benign salivary gland neoplasms lack gross DNA content and numerical chromosomal abnormalities, (2) clonal chromosomal alterations are manifested in most DNA diploid and all DNA aneuploid malignant tumors, (3) chromosomal gain is the most common alteration; chromosomal loss is less frequent and restricted to certain chromosomes, and (4) DNA aneuploidy and chromosomal aneusomy characterize tumors with aggressive features.</td>
<td>Concurrent DNA ploidy by flow cytometry and interphase FISH analysis of chromosomes 6 through 12, 17, 18, X, and Y were prospectively performed on 22 salivary gland neoplasms (four benign and 18 malignant) to investigate the diagnostic and biological implications of their alterations in these neoplasms</td>
<td>Case series</td>
<td>Naggar et al,(1997)</td>
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<td>Loss of heterozygosity at microsatellite loci on 8q, a breakpoint at which translocations have been previously documented in pleomorphic adenoma, is a frequent event in this tumor. The incidence is not increased in patients with focal carcinoma ex pleomorphic adenoma, suggesting that loss of heterozygosity at 8q is an early event in tumorigenesis</td>
<td>DNA extracted from paired normal and tumor tissue specimens from 1 patient with carcinoma ex pleomorphic adenoma and 17 patients with pleomorphic adenoma (3 contained foci of carcinoma ex pleomorphic adenoma) was evaluated for loss of heterozygosity at microsatellite loci with a multiplex polymerase chain reaction-based analysis. Correlation with clinical and pathologic features was performed.</td>
<td>Case series</td>
<td>Gillenwater et al,(1997)</td>
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<td>It was observed that loss of chromosome 17 may occur in PA before its transformation to carcinoma. p53 expression was frequently associated with deletion of the p53 gene as detected by FISH. Polysomy 17 was more frequent in CIPA than PA and was associated with mutation of p53</td>
<td>The authors analyzed the numeric aberrations of chromosome 17 and p53 gene deletions in 11 paraffin embedded pleomorphic adenomas (PA) and 9 carcinomas in pleomorphic adenoma (CIPA), using FISH techniques. The centromere specific DNA probe for chromosome 17 and p53 cosmid DNA probe was used. The aberrations of chromosome 17 and p53 deletion were correlated with immunohistochemical detection of p53 protein.</td>
<td>Case series</td>
<td>Li etal,(1997)</td>
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<td>Increased expression of XIAP from PA to cellular PA to CXPA and in atypical cells within cellular areas of PA adds to our growing understanding of defective apoptotic pathways in malignant transformation in this group of salivary gland tumors and suggests an adenoma to adenocarcinoma model of progression. Further correlation with other oncogene expression may provide insight into the multiple molecular pathways that are affected in these tumors. Targeted therapy of XIAP may play a future role in the management of CXPA.</td>
<td>Formalin-fixed, paraffin-embedded representative sections of 14 cases of PA and seven cases of CXPA (four invasive and three intracapsular) were stained with anti-XIAP (# 610763; BD Biosciences, San Jose, CA, USA) following citrate-based antigen retrieval. Granular cytoplasmic staining was considered positive and intensity was assessed from weak (1+) to strong (3+). PAs were morphologically evaluated for cellularity, cytological atypia and mitotic activity.</td>
<td>Case series</td>
<td>Hoch et al,(2008)</td>
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<td>Statistically significant reduction in reactivity was evident in mucoepidermoid carcinoma and adenocarcinoma, when compared to pleomorphic adenoma.</td>
<td>10 cases of pleomorphic adenoma (PA), 2 cases of canalicular adenoma (CA), 2 cases of myoepithelioma (MY), 24 cases of adenoid cystic carcinoma (ACC), 12 cases of mucoepidermoid carcinoma (MEC), 9 cases of adenocarcinoma (AC) and 1 case of carcinoma ex pleomorphic adenoma (Ca Ex PA).</td>
<td>Case series</td>
<td>Prabhu et al,(2009)</td>
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### Results

<table>
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<th>Description of carcinoma ex pleomorphic adenoma cases</th>
<th>Type of study</th>
<th>Author name</th>
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<td>The proliferative activity of the tumor cells and the expression of tumor-associated genes and sex steroid hormone receptors were investigated immunohistochemically in ten cases of carcinoma ex pleomorphic adenoma (Ca-ex-PA) of the salivary glands.</td>
<td>Case series</td>
<td>Matsubayashi and (2007)Yoshihara</td>
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<td>These results support the hypothesis that the carcinomatous and sarcomatous components of carcinosarcomas are clonally related. Furthermore, these data support prior studies that suggest a common clonal origin for the benign and malignant components of carcinomas ex pleomorphic adenoma.</td>
<td>Case series</td>
<td>Fowler et al,(2006)</td>
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<td>Maspin expression was studied by means of immunohistochemistry in 16 cases of CXPA, using the labelled polymer method.</td>
<td>Case series</td>
<td>Martins et al,(2005)</td>
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<td>We studied the immunolocalization of beta-catenin in a series of pleomorphic adenomas (PA) and carcinomas ex-pleomorphic adenomas (Ca-ex-PA).</td>
<td>Case series</td>
<td>Genelhu et al,(2007)</td>
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<td>We analyzed the tumor vascularization in carcinomas ex-pleomorphic adenoma (CXPA) to investigate the angiogenic switch during the malignant transformation of pleomorphic adenoma (PA) to carcinoma and during tumor progression</td>
<td>Case series</td>
<td>Soares et al,(2007)</td>
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<td>Although intraductal carcinoma has been demonstrated in intracapsular carcinoma ex pleomorphic adenoma (CEPA), the morphological and genetic stages of transformation of pleomorphic adenoma (PA) to CEPA are not fully understood.</td>
<td>Case series</td>
<td>- Ihrler et al,(2007)</td>
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- Ihrler et al., 2007
- Fowler et al., 2006
- Martins et al., 2005
- Genelhu et al., 2007
- Soares et al., 2007
- Matsubayashi and Yoshihara, 2007
Results | Description of carcinoma ex pleomorphic adenoma cases | Type of study | Author name
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The data support the hypothesis that increased COX-2 expression is associated with early events in malignant transformation of pleomorphic adenoma. | In the present study, we attempted to identify cyclooxygenase-2 (COX-2) expression and Ki-67 index in carcinoma ex-pleomorphic adenoma (Ca ex-PA) using quantitative immunohistochemical analysis and to compare the benign component of the neoplasia. We also aimed to relate the overexpression of COX-2 with the pathways of malignant transformation of Ca ex-PA as evidenced by distinct morphological features. | Case series | Katori et al., (2007)

Table 1: Summary of clinical data on carcinomas arising from pleomorphic adenoma (1977-2009).

Diagnosis of malignant mixed tumor in salivary gland

Pleomorphic adenoma (PA), the most frequent tumor in salivary glands, can undergo malignant transformation. Carcinoma arising in pleomorphic adenoma represents 4.5–15% of salivary gland malignancies(3-5). Carcinoma arising in pleomorphic adenoma has no distinctive sex predilection(5-8), and is more frequent in the 5–6th decades of life. These tumors are highly aggressive, with high rates of metastasis, and carry a poor overall prognosis. It has been suggested that a carcinoma may develop within a recurrent PA or when it remains untreated over an extended period of time(6-9). Despite the recognized clinical importance of carcinoma arising in pleomorphic adenoma, little is known about its biology. The detection of early transformation in PA is a diagnostic challenge in pathology. Using the interpretation of cellular atypia, increased mitotic index, and lack of encapsulation as signs of malignant transformation is controversial, because these signs can also be seen in ordinary PA.

Malignant mixed tumors of the salivary gland are diverse and include three different subcategories of lesions: carcinosarcomas, carcinoma ex pleomorphic adenoma, and metastasizing pleomorphic adenomas. Both types of malignant tumors behave aggressively, with poor 5-year survival(10-11). Carcinosarcomas (true malignant mixed tumors) of the salivary glands are rare biphasic tumors that exhibit both carcinomatous and sarcomatous elements(12-13). These tumors are thought to develop de novo in the salivary gland, and contain malignant stromal and epithelial elements(14). The carcinomatous component varies, but can be composed of adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma. They may also show specific salivary carcinoma phenotypes, including salivary duct carcinoma or adenoid cystic carcinoma. Sarcomatous elements can also be variable, including chondrosarcoma, osteosarcoma, fibrosarcoma, and malignant fibrous histiocytoma. Most frequently, the sarcomatous component dominates, though the two elements can be found in an intermixed pattern(13-14). Carcinoma ex-pleomorphic adenoma arises from a pre-existing benign mixed tumor. Usually, the patient will have a long-standing history of a salivary gland lesion, and may have undergone multiple operations for recurrent pleomorphic adenoma(15).

Metastasizing pleomorphic adenomas without histologic evidence of malignancy have rarely been reported(16). Metastatic lesions have been discovered in bone, lymph nodes, the lung, oral cavity, pharynx, skin, liver, retroperitoneum,
kidney, calvarium, and central nervous system\textsuperscript{(16)}.

Carcinoma arising from pleomorphic adenoma is now a well-established phenomenon. It is defined as a ‘tumor showing definitive evidence of malignancy’, such as cytological and histological characteristics of anaplasia, abnormal mitoses, progressive course, and infiltrative growth, and in which evidence of pleomorphic adenoma can still be found\textsuperscript{(17)}. Within this category, there is a spectrum of tumors that includes: carcinoma in pleomorphic adenoma, non-invasive (in situ or intra-capsular carcinoma), carcinosarcoma, and metastasizing benign pleomorphic adenoma.

A diagnosis of carcinoma arising in pleomorphic adenoma can only be made with certainty if a focus of benign pleomorphic adenoma can be identified or if there is a history of a benign pleomorphic adenoma having been removed from the site of a malignant recurrence. However, this strict definition probably underestimates the true frequency of carcinoma arising in pleomorphic adenoma as many appear to arise in an old, scarred pleomorphic adenoma with little if any of the original tumor remaining, and in other cases the original tumor is probably replaced by the malignant elements.

Discussion

The evidence for the development of malignancy in pleomorphic adenoma is clinical, pathological, and molecular.

1. Clinical evidence

There is an increasing likelihood of malignant change in pleomorphic adenoma with time. Eneroth and Zetterberg\textsuperscript{(18)} reported a rate of malignant change in pleo-morphic adenoma of 1.6\% in 0-4 years, 5.9\% in 10-14 years, and 9.4\% in tumors present for more than 15 years. LiVolsi and Perzin\textsuperscript{(18)} state that in 45\% of cases of carcinoma in pleomorphic adenoma, a mass had been present for less than 3 years. In the series reported by Spiro and colleagues\textsuperscript{(19)}, a swelling had been present for less than 2 years in about half of their cases. However, some of the cases in Spiro’s series had arisen in the deep lobe of the parotid and this may have masked their presence for some time.

There is an increased frequency of carcinoma in pleomorphic adenoma in patients who have had one or more operations for pleomorphic adenoma before the diagnosis of malignancy. LiVolsi and Perzin\textsuperscript{(18)} reported that nine out of their 47 cases (20\%) of carcinoma in pleomorphic adenoma followed previous surgery for pleomorphic adenoma. However, post-operative radiation had been given in two cases. In the AFIP series\textsuperscript{(20)}, 86\% of cases arose in the major glands, even though they only accounted for 71\% of all cases of pleomorphic adenoma. It was thought that this related to the much higher rate of recurrence of pleomorphic adenoma in the major as opposed to the minor glands.

There is a strong correlation between carcinoma in pleomorphic adenoma and the age of the patient. The average age at presentation for patients with carcinoma in pleomorphic adenoma is 10-20 years later than patients with pleo-morphic adenoma. In the AFIP series\textsuperscript{(20)}, the average age was 46.9 years for pleomorphic adenoma and 60.1 years for carcinoma in pleomorphic adenoma. In the British Salivary Gland Tumor Panel series\textsuperscript{5}, the equivalent ages were 46 and 63.3 years. In addition, carcinoma in pleo-morphic adenoma is very uncommon in younger patients and there were no cases in two major series of salivary gland tumors in children\textsuperscript{(21-22)}.

There was an association between the size of the tumor and the likelihood of malignancy in pleomorphic adenoma, particularly in tumors over 5 cm in diameter\textsuperscript{(23)}. Zbären et al\textsuperscript{(15)} reported that a series of carcinoma ex pleomorphic adenoma were significantly greater in size than pleomorphic adenoma cases (Forty-two percent of carcinoma ex pleomorphic adenoma versus 6 percent of pleomorphic adenomas, respectively, were greater than 4 cm (P < 0.05).

Pleomorphic adenoma and its transformation to malignant tumor is a particular challenge to the diagnostic pathologist. This is mainly because lack of strong evidence to interpret the malignant transformation of this tumor and the rarity of this tumor compared with others. Carcinoma in pleomorphic adenoma (malignant mixed tumor)
represented 2.2% of all salivary tumors and 6.5% of malignant tumors in the AFIP series. Gnepp and Wenig\(^{(20)}\) calculated the average incidence from 58 reported series to be 3.6% of all tumors and 11.7% of malignancies, with a range from 2.8 to 42.4%. Although debated in the older literature, carcinoma in pleomorphic adenoma is now an accepted entity and it is recognized that there is a progression of benign to malignant change in pleomorphic adenoma\(^{(24)}\). This is supported by both clinical and histological evidence. Carcinomas in pleomorphic adenoma arise in an older age group than benign lesions and are usually larger and longer standing lesions.

2. Pathological evidence:

Auclair and Ellis\(^{(25\text{-}26)}\) reported that malignant tumors were twice the size (4.5 cm) of their benign counterparts and had been present for an average of 76.5 months, which was almost twice the duration of benign lesions. Histologically, the primary criterion for diagnosis is the presence of carcinoma in an otherwise benign and typical pleomorphic adenoma. However, in practice, the residual benign lesion may be focal and difficult to find, or may have been completely overtaken by the malignant component. The diagnosis may not therefore always be apparent. Clues to the diagnosis of carcinoma in pleomorphic adenoma may come primarily from the clinical history of a large longstanding lesion, with evidence of recurrence or a previous lesion. Histological evidence that a carcinoma may have arisen in a pleomorphic adenoma includes areas of hyalinization of the stroma with focal calcifications, and of morphological diversity in the type of carcinoma\(^{(27)}\). The overall malignant change rate in pleomorphic adenoma has been estimated at about 6% \(^{(4)}\) but there are at present no histological features that are predictive of which benign lesions may transform. Features suggested as predictive include cytological atypia, increased mitoses, invasion of the capsule, hypercellularity, hyalinization or scarring and focal calcifications. However some of these features, including atypia, mitoses and capsular invasion, are commonly seen in typical benign pleomorphic adenomas\(^{(27\text{-}28)}\) and some pleomorphic adenomas, especially on the palate, may be hypercellular. In an analysis by Auclair and Ellis\(^{(25)}\) none of these features were predictive of malignant change. Indeed cytological atypia was more often seen in lesions that did not progress. The only feature which showed any evidence of being predictive was the presence of a hyalinized stroma and of focal calcifications. However, the authors point out that any pleomorphic adenoma may progress and that all lesions should be managed accordingly. In some lesions, foci of carcinoma or dysplasia may be seen which are confined within the capsule. Such lesions are termed non-invasive carcinoma, or intracapsular or in situ carcinoma. Provided that the capsule has not been breached these lesions have the same prognosis as benign pleomorphic adenoma. The presence of dysplasia, however, supports the concept of progression and of a spectrum of change from benign to malignant.

3. Molecular evidence

Brandwein et al\(^{(29)}\) have shown that 70% of dysplastic lesions have an aneuploid DNA content suggesting that they are histologically distinct from benign lesions. Eveson and Yeudal\(^{(24)}\) reviewed the molecular evidence and suggested a progression model for benign to malignant change involving loss of heterozygosity (LOH) at multiple chromosomal locations, activation of the PLAG1 gene and mutations in c-myc, p21 and p53. A further area of controversy is the role that recurrence may play in the etiology of carcinoma in pleomorphic adenoma. Clearly if a malignant lesion arises at a site of a previous benign pleomorphic adenoma, then it is associated with recurrence. However, some reports have suggested that repeated recurrence and the associated surgical interference might be a factor in progression. Overall however, malignant transformation in recurrent disease is rare, and there is no evidence that recurrent pleomorphic adenomas should be regarded as inherently more malignant or potentially malignant\(^{(30)}\). In a large series of recurrent pleomorphic adenomas\(^{(31)}\) there were no cases of malignant transformation in patients with one recurrence only. In three patients with three or more recurrences, malignant change was seen, but all three had received postoperative radiotherapy. This suggests that
Radiotherapy may be a risk factor for malignant change. Radiotherapy is only used to manage gross tumor spillage, or multifocal recurrent disease, but in large series the incidence of malignant change in such lesions has been less than 2%. A further argument against the role of recurrence and repeated surgical intervention as a factor in malignant transformation is that while recurrence rates have dropped dramatically from 40 to 50% 70 years ago, to less than 2% today, there is no evidence of a reduction in the incidence of carcinoma in pleomorphic adenoma. This supports the view that some pleomorphic adenomas may be inherently potentially malignant from the outset. Eifert and Sobin defined CPA as a ‘tumor showing definitive evidence of malignancy, such as cytological and histological characteristics of anaplasia, abnormal mitosis, progressive course and infiltrative growth, and in which evidence of pleomorphic adenoma can still be found.’ A histopathological diagnosis of CPA can only be made definitively if a focus of benign pleomorphic adenoma, sometimes referred to as a ‘ghost’ can be identified. It is reasonable to accept old, scarred pleomorphic adenoma matrix as a diagnostic feature. A clinical history of removal of a previous pleomorphic adenoma or of a long-standing swelling at the site is also a strong indicator but is less reliable than the histopathological finding of a ‘ghost’. The use of strict pathological criteria may underestimate the true frequency of carcinoma ex pleomorphic adenoma (CPA) because the malignant cells in some cases may obliterate the original pleomorphic adenoma. On the other hand the recognition by pathologists that thorough sampling is required for diagnosis of salivary malignancy often leads to the identification of residual adenoma and or multiple patterns of differentiation and the diagnosis of CPA is made more often than was previously the case.

The most frequent pattern of carcinoma to arise in CPA is poorly differentiated adenocarcinoma, although all recognized patterns may arise including myoepithelial carcinoma, polymorphous low-grade adenocarcinoma, adenoid cystic carcinoma and acinic cell carcinoma. Multiple patterns and types may be seen and prognosis is based on staging and histological grading in these rare types.

There is a grouping of non-invasive (intracapsular or in situ) carcinoma and, in addition, some recognize minimally invasive mixed tumor. These tumors show dysplastic features without invasion of the surrounding structures. The presence of aneuploid cell populations in 70% of tumors examined, suggested that these tumors are of histological category distinct from benign pleomorphic adenoma. However, a further study of 16 benign pleomorphic adenomas showed that only 25% were aneuploid. Dysplastic pleomorphic adenomas appear to have a similar prognosis to benign pleomorphic adenoma but probably represent part of a spectrum that ultimately would lead to frankly invasive carcinoma.

The progression from dysplastic epithelium and/or adenoma to carcinoma is well recognized in colorectal and esophageal carcinogenesis, and is related to the accumulation of genetic mutations. It is tempting to postulate a similar situation for salivary glands and in particular, from pleomorphic adenoma to carcinoma.

During the development of pleomorphic adenomas, chromosomal rearrangements occur at 8q 12-15 and 12q. The former results in promoter swapping between the pleomorphic adenoma gene (PLAG 1) which encodes a zinc finger protein, and the gene encoding f3-catenin (CTNNB1). The latter leads to abnormalities of the gene encoding a high mobility group protein (HMGIC).

Activation of c-myc, p21, and p53 mutations may also be important. Loss of heterozygosity (LOH) of the p53 gene was detected in 57% of pleomorphic adenomas and 86% of carcinomas in pleomorphic adenomas. These findings strongly suggest that mutation of the p53 gene is an early event in the progression of benign to malignant pleomorphic adenoma.

It has also been suggested that inactivation of the p16 gene (a putative tumor suppressor gene) and genetic instability are a feature of malignant transformation in carcinoma in pleomorphic adenoma.
During conversion of pleomorphic adenoma to carcinoma, LOH occurs at multiple chromosomal loci. LOH at loci on 8q has been widely reported in pleomorphic adenoma\(^{43}\). The incidence is not increased in areas of focal car-cinoma, which suggests that LOH at 8q is an early event in tumorigenesis\(^{44}\). It has been shown that there may be loss of chromosome 17 in pleo-morphic adenoma before the development of carcinoma and, in addition, polysomy 17 was found to be more frequent in carcinoma in pleomorphic adenoma than pleomorphic adenoma and was associated with mutation of p53\(^{45}\). In addition, loss of the short arm of chromosome 17 may also be related to tumor progression\(^{43}\).

Hoch et al\(^{46}\) reported that increased expression of XIAP from pleomorphic adenoma to carcinoma ex pleomorphic adenoma. Prabhu et al\(^{47}\) reported that the significant reduction in reactivity of E-cadherin expression in mucoepidermoid carcinoma and adenocarcinoma, when compared to pleomorphic adenoma. Matsubayashi and Yoshihara\(^{48}\) have suggested that carcinoma ex pleomorphic acquired the particular biological behavior in contrast to the other salivary neoplasms in the long-standing process while pleomorphic undergoes malignant transformation.

Fowler et al\(^{49}\) have founded that in carcinomas ex pleomorphic adenoma, loss of heterozygosity of 17q21 and 9p21 was uncommon in the benign component, but the mutations were conserved in the corresponding malignant areas. Martins et al\(^{50}\) founded that only epithelial cells undergo malignant transformation, maspin expression is gradually lost. In cases with a myoepithelial component, maspin expression is high, and this might be related to the tumor suppressor activity attributed to this cell. Genelhu et al\(^{51}\) have indicated that their data showed decreased cell membrane beta-catenin expression in higher-grade tumors suggesting that beta-catenin may play an important role in histologic differentiation and transition to malignant phenotype of carcinoma ex pleomorphic adenoma. Soares et al\(^{52}\) have reported that the antibody CD105 reveals an angiogenic switch during the progression from adenoma to carcinoma in salivary glands. The degree of angiogenesis and the total vascular area (TVA) have distinctive patterns in carcinoma ex pleomorphic adenoma with and without myoepithelial differentiation. Low angiogenesis associated with high TVA value is more characteristic of carcinoma ex pleomorphic adenoma with myoepithelial differentiation. Ihrler et al\(^{53}\) have mentioned that the frequent demonstration of intraductal carcinoma indicates that this pre-invasive lesion is likely to be a constant feature in the malignant transformation of pleomorphic adenoma to carcinoma ex pleomorphic adenoma. It appears to be a feature of carcinoma ex pleomorphic adenoma developing from both primary and recurrent pleomorphic adenoma. The combined immunohistochemical and genetic data show that 14/19 cases of carcinoma ex pleomorphic adenoma and 11/15 cases with intraductal carcinoma showed genetic or morphological evidence of dysfunctional p53, indicating that this is an early event in malignant transformation.

Katori et al\(^{54}\) have indicated that in the immunohistochemical analysis of COX-2 and Ki-67 index, significant increase was observed in carcinoma ex pleomorphic adenoma, especially with adenocarcinoma, compared to pleomorphic adenoma and sialadenitis. Their data support the hypothesis that increased COX-2 expression is associated with early events in malignant transformation of pleomorphic adenoma.

**Conclusion**

The use of combined clinical evidence and pathological evidence are very important in the diagnosis of the malignant transformation of pleomorphic adenoma. The review does not show that clinical evidence is more accepted than pathological and molecular evidence; therefore, it highlights the current inadequacies of molecular for pathological science for diagnosing malignant transformation of a pleomorphic adenoma. It also highlights useful clinical indicators that raise suspicion of malignant transformation.

This study shows that there is the strong association between the size of the tumor and the likelihood of malignancy in pleomorphic adenoma (clinical evidence). The presented
Malignant transformation of pleomorphic adenoma, B. Tarakji, et al.

pathological studies mentioned above comprise a limited number of cases for carcinoma ex pleomorphic adenoma because of the rarity of these tumors. There are pathologic findings allowing for the identification of this process. The interpretation of the malignant transformation of pleomorphic adenoma is so difficult for the following reasons:

1. The use of different antibodies
2. Different classifications e.g. (0=negative staining, 1=low, 2= moderate, 3= strong or 0-3= negative and 4= positive or 0-2= negative and 3-4=positive or negative and positive staining) to evaluate the intensity of immunostaining.
3. Fixation times and concentrations of antibodies
4. The sensitivity of the technique used
5. The limited sample size because of the rarity of this tumor
6. The use of immunostaining technique alone without other technique such as PCR so that it might gives a bias

References


