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Atypical features in pleomorphic adenoma—a clinicopathologic study and implications for management

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Abstract. Pleomorphic adenoma is the most common salivary gland neoplasm and infrequently undergoes malignant transformation. Carcinoma ex pleomorphic adenoma is typically an infiltrative neoplasm with features of cellular pleomorphism, high mitotic activity, peri-neural and vascular invasion. More recently, sub-groups of pleomorphic adenoma have been described exhibiting vascular invasion and features of malignancy without evidence of extra-capsular extension. There is little information in the literature regarding how these different histological variants influence clinical presentation and outcome following primary treatment.

Following a review of 100 consecutive pleomorphic adenomas removed from the major salivary glands, 4 cases with atypical histological features were found. Three tumours exhibited features of dysplasia/carcinoma without evidence of extra-capsular invasion and a further case demonstrated benign vascular invasion. There were no clinical features suggestive of the atypical nature of these neoplasms, though fine needle aspiration cytology (FNAC) was suspicious of a malignancy in 2 cases and CT scan in 1 case. Patients underwent a superficial parotidectomy or submandibular gland excision based on the location of the lesion. All lesions were completely excised and there were no recurrences in this series.

Key words: salivary gland; pleomorphic adenoma; intra-capsular carcinoma; non-invasive carcinoma; carcinoma ex pleomorphic adenoma.

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Pleomorphic adenoma is the most common benign salivary gland tumour. It is epithelially derived and typically presents as a cytologically benign circumscribed mass with variable encapsulation[8,9,19,21]. Histomorphically it is characterized by a variegated architecture comprising epithelial elements admixed with a mucoid, myxoid, fibrohyaline or chondroid stoma.

Historically, the main clinical problems with pleomorphic adenoma have been the risk of recurrence and progression to a clinically- or histologically-based malignancy[19].

Over recent years there has emerged a rare but nonetheless well-documented subgroup of pleomorphic adenoma entities that require additional awareness and precise recognition in terms of their propensity for future aggressiveness. These include features of vascular invasion[1,6,23],

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Table 1. Synopsis of patients with atypical pleomorphic adenoma

Case	Age/sex	Clinical features	FNAC*	Imaging	Histology	Treatment	Follow-up
1	48/F	3 cm × 2 cm mass, tail of parotid, present 6 months, occasional discomfort, normal facial nerve function.	Inconclusive	CT—well defined mass, no sinister features	Cellular PA†, no atypia, completely excised, benign vascular invasion	Superficial parotidectomy	32 months ANED‡
2	64/F	3 cm × 4 cm mass, pre-auricular, present many years, normal facial nerve function	PA	MRI—lobulated cystic mass, no sinister features	PA, focal dysplasia, completely excised	Superficial parotidectomy	28 months ANED
3	59/F	2.5 cm firm submandibular mass, present many years, normal nerve function	Pleomorphic epithelial cells with myxoid stroma, ? PA, ? sinister neoplasm	CT—well defined mass, no sinister features	PA with features of non-invasive (intra-capsular) carcinoma, completely excised	Sub-mandibular gland excision	15 months ANED
4	77/M	2 cm × 2 cm mass, tail of parotid, present 5 months, normal facial nerve function	? malignant	CT—well defined rim enhancing mass with low density cystic centre	PA with features of non-invasive (intra-capsular) carcinoma, completely excised.	Superficial parotidectomy	36 months, ANED

* FNAC, fine needle aspiration cytology.
† PA, pleomorphic adenoma.
‡ ANED, alive with no evidence of disease.

focal dysplasia[2,5] and non-invasive (intra-capsular) carcinoma ex pleomorphic adenoma[3,10,13,14]. There is little information in the literature regarding how these different histological variants influence clinical presentation and outcome following primary treatment.

This paper presents 4 cases outlining these variants and examines the literature regarding this sub-group of pleomorphic adenoma, offering implications for management.

Patients and methods

The case records and histology reports of 100 consecutive cases of pleomorphic adenoma of the major salivary glands treated at the Queen Alexandra Hospital, Portsmouth were reviewed and patients with atypical features identified. Four cases were noted to have atypical features and form the basis of this study. The age range was 47–77 years and included 3 female and 1 male patient. The lesion affected the parotid gland in 3 cases and the submandibular gland in 1 case. Two cases of non-invasive (intra-capsular) carcinoma, 1 case of focal dysplasia and a further case of benign vascular invasion were identified. The demographic characteristics, clinical presentation, results of investigations undertaken and outcome of these patients were analysed and are summarized in Table 1.

The histological features of these cases are described in the following sections.

Case 1

Cellular pleomorphic adenoma was surrounded by a fibrous capsule, with no signs of atypia or malignancy. In addition, the presence of benign-looking tumour cells within vessels outside the main tumour was also noted. These features were interpreted as benign vascular invasion (Figs 1 and 2).

Case 2

Chondro-myxoid pleomporphic adenoma, with no evidence of malignancy. Very close to the periphery, however, there was a small focus of atypical change within the epithelial cells, in which the cells were arranged in more solid cords and showed enlarged, pale, pleomorphic nuclei. The atypical cells had abundant

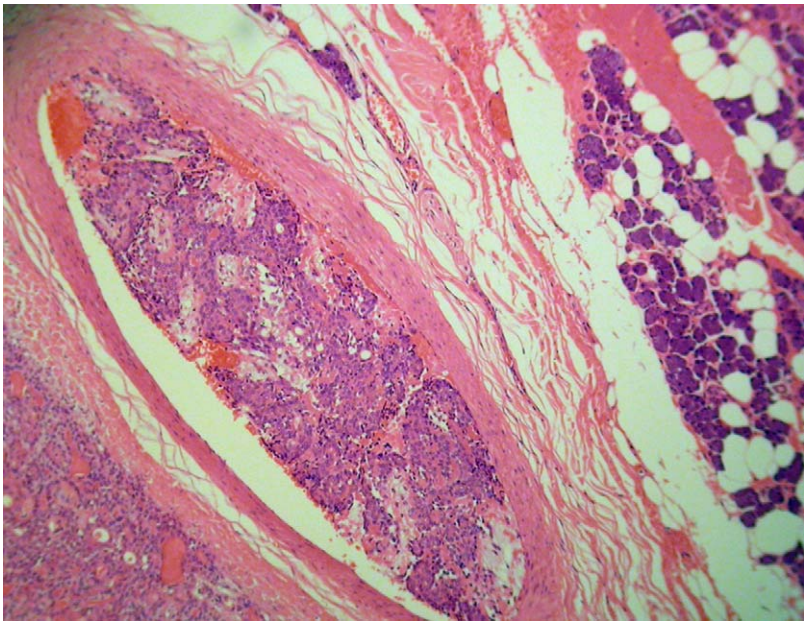

Fig. 1. Island of tumour cells within a vessel outside of the tumour specimen. Normal parotid tissue can be seen in the top right (original magnification ×60, H&E).

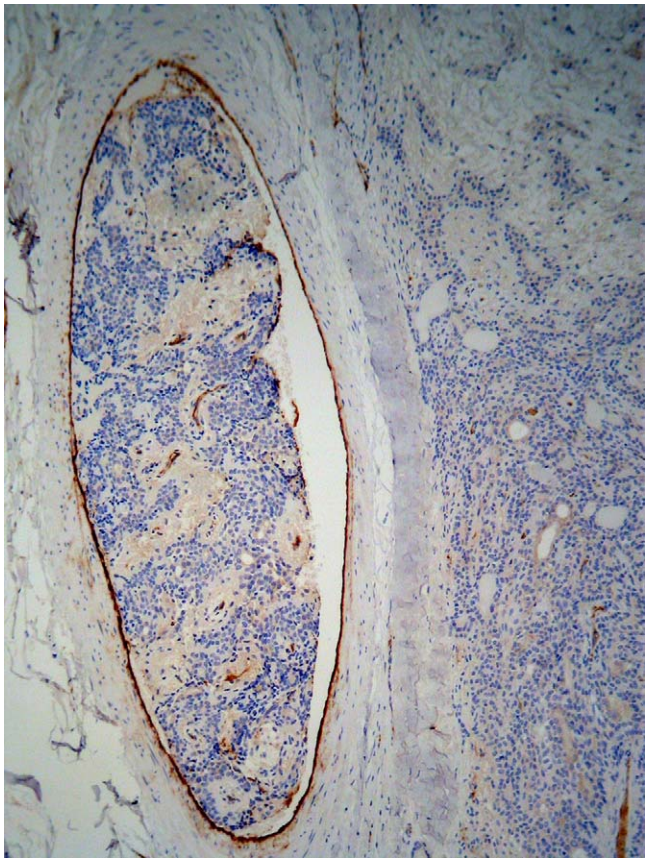

Fig. 2. Tumour island within a vessel. The endothelial lining of the vessel highlighted with CD34 (original magnification ×60, immunohistochemistry CD34).

eosinophilic cytoplasm and mitoses were not seen (Fig. 3). These changes were best regarded as 'dysplasia within a pleomorphic adenoma'.

Case 3

Well circumscribed pleomorphic adenoma surrounded by a fibrous capsule, which was not infiltrated by tumour. In addition to the presence of definite benign areas, there was marked cellular atypia and malignant changes occupying most of the tumour mass. These changes were seen in the clear cells, solid and papillary areas of the tumour (Fig. 4). This tumour was reported as a non-invasive (intra-capsular) carcinoma in a pleomorphic adenoma.

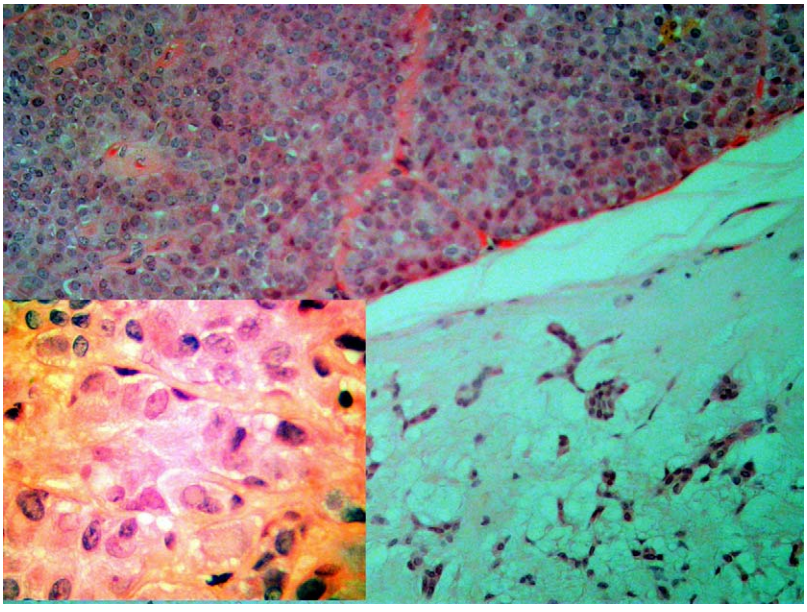

Fig. 3. Chondromyxoid pleomorphic adenoma with an area displaying (inset, ×100) pleomorphic cells with abundant eosinophilic cytoplasm, hyperchromatic and pleomorphic nuclei consistent with dysplasia (original magnification ×60, H&E).

Case 4

Well circumscribed pleomorphic adenoma was surrounded by a fibrous capsule. In addition there was a focal area of carcinomatous change with cells exhibiting eosinophilic cytoplasm, atypical nuclei, prominent nucleoli and mitosis. The appearances were considered to be similar to that of a salivary duct carcinoma. There was no evidence of vascular or peri-neural invasion and the tumour was confined by capsular tissues (Fig. 5). This tumour was reported as a non-invasive (intra-capsular) carcinoma in pleomorphic adenoma.

Discussion

Pleomorphic adenoma is the most common neoplasm of the salivary glands and infrequently undergoes malignant transformation[8,9,19,21]. The propensity for malignant transformation (either clinical or histological) has been documented in the literature at 1.9–23.3% and carcinoma ex pleomorphic adenoma represents approximately 12% of malignant neoplasms[8,9,12–15,17,20,24]. The clinical diagnosis is based on local features of malignancy in addition to regional or distant metastasis while the tissue diagnosis is based on the identification of features of invasion and cellular atypia. The 3 common sub-types of malignant change described are carcinoma ex pleomorphic adenoma, true malignant mixed tumour (carcino-sarcoma) and metastasising mixed tumour[4,12–15,17–20,24,25].

The tendency to progress to malignancy has traditionally been based on the diagnostic criteria for carcinoma ex pleomorphic adenoma (a mixed tumour in which a second epithelial tumour develops). It typically is an infiltrative neoplasm showing invasion of salivary parenchyma with extension into adjacent structures, high mitotic rate, nuclear pleomorphism, peri-neural involvement, vascular invasion and necrosis[13,14]. The prognosis of carcinoma ex pleomorphic adenoma is dependant on the size, grade, extent of invasion and the presence of regional and distant metastasis[13,14,15,21,24].

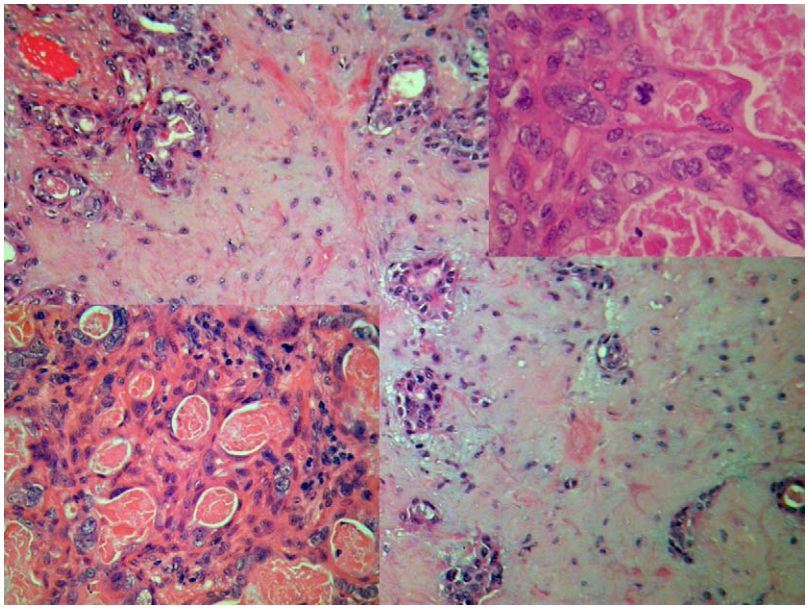

Fig. 4. Typical appearances of pleomorphic adenoma found in a small area of the tumour specimen. Inset (lower left, ×60) demonstrating large pleomorphic cells with hyperchromatic, pleomorphic nuclei and prominent nucleoli. Inset (upper right, ×100) demonstrating abnormal mitosis in addition to the cellular and nuclear atypia (original magnification ×40, H&E).

The implications of benign vascular invasion, focal dysplasia and non-invasive (intra-capsular) carcinoma occurring in a benign pleomorphic adenoma however, still remain poorly understood.

The presence of vascular invasion in a benign pleomorphic adenoma is uncommon[1,6,23]. This has mostly been reported in minor salivary gland tumours, and these authors know of only one documented report involving the parotid gland[1]. In this series, the vascular invasion was present in a tumour originating from the parotid gland, and was considered to represent true vascular invasion rather than tumour embolus or artefactual spillage based on criteria similar to that described by Coleman & Altini[6]. Though the presence of vascular invasion has been associated with a higher grade of malignancy and metastatic potential in a wide variety of malignant tumours, the implications of vascular invasion in a benign pleomorphic adenoma remains unknown. The relationship between benign vascular invasion and metastasising pleomorphic adenoma has not been established and the presence of vascular invasion has not been documented in any of the reported cases of metastasising pleomorphic adenoma[4,18,25]. It was, however, interesting to note that most instances of metastasising pleomorphic adenoma have been reported from the parotid gland, whereas benign vascular invasion has been more frequent in minor salivary glands. There is currently little evidence to suggest more aggressive treatment of these patients, though it is likely that a more critical follow-up regimen may be warranted to define its significance.

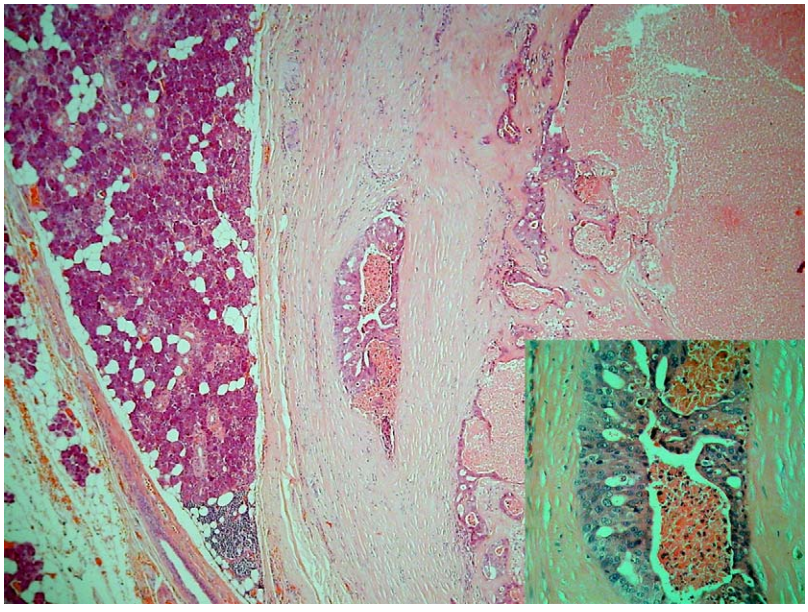

Fig. 5. A small focus of high grade carcinoma within the tumour capsule in a pleomorphic adenoma (inset, ×60), demonstrating comedo-necrosis, cytological atypia and apoptotic cells (original magnification ×40, H&E).

Malignant change in a pleomorphic adenoma has been associated with long duration of the tumour, recurrent tumour, radiotherapy, increasing age of patient and tumour size[12,14,20]. It is interesting to note that none of our patients had any previous surgery or radiotherapy and the largest tumour was 4 cm × 3 cm. The lesions were present for many years in 2 of the 3 patients who developed non-invasive (intra-capsular) carcinoma ex pleomorphic adenoma. The progression from dysplastic epithelium and/or adenoma through to carcinoma is well recognized in colorectal carcinogenesis and is related to accumulation of genetic mutations.[11] In our series, there were cases of focal dysplasia, small focus of obvious malignant change and malignant change involving a significant portion of the gland, all without evidence of capsular invasion. It is tempting to postulate a similar progression in benign salivary gland pleomorphic adenoma to invasive carcinoma ex pleomorphic adenoma.

Auclair & Ellis[2] found atypical cells in 2% of benign pleomorphic adenoma in the Armed Forces Institute of Pathology files, and their presence was associated with an increased incidence of malignant change, especially those with hyalinization, necrosis and high mitotic rate. More recently, molecular and histogenetic studies have suggested that a greater proportion of benign pleomorphic adenoma exhibit abnormal foci, though their precise significance in relation to malignant change remains uncertain[7,16,22].

Though carcinoma ex pleomorphic adenoma accounts for approximately 12% of malignant salivary gland tumours, we are aware of only 15 previous cases of non-invasive (intra-capsular) carcinoma ex pleomorphic adenoma reported in the English literature[3,10,13,14]. In 9 of these cases the tumour arose in a major salivary

gland and in the remaining 6 cases reported, the site of the tumour was not documented.

There is very little information in the literature pertaining to the clinical presentation and results of preoperative investigations undertaken in this group of patients. In this series all patients had a noticeable mass in the salivary gland of long duration (6 months–many years), though none exhibited any salient clinical features of malignancy. The imaging investigation was suggestive of a malignant lesion in 1 case and the fine needle aspiration was inconclusive in 1 case, suggestive of a pleomorphic adenoma in 1 case and in 2 patients there was a suspicion of malignancy (Table 1).

Previous reports of non-invasive (intracapsular) carcinoma ex pleomorphic adenoma, seem to suggest an excellent prognosis for these lesions, with no evidence of recurrence or metastasis if these lesions are completely excised[3,13,14]. They found the absence of capsular invasion correlated with a 'benign' clinical course of these neoplasms. Tortoledo et al.[24] had previously demonstrated the prognostic significance of neoplastic extension beyond the capsular confines and suggested that carcinoma ex pleomorphic adenoma which extended less than 8 mm beyond the residual capsule was associated with a good prognosis, regardless of the grade of the tumour.

Felix et al.[10], however, reported a case of high grade intra-capsular carcinoma ex pleomorphic adenoma, which initially presented as metastatic cervical lymphadenopathy of unknown origin and was subsequently found to originate from a deep lobe of the parotid. The patient underwent a total parotidectomy and cervical lymphadenectomy and received adjuvant radiotherapy and remained free of disease.

The natural history of these non-invasive (intra-capsular) carcinoma ex pleomorphic adenoma, if left untreated, is unknown. It would be reasonable to speculate that the excellent prognosis of these lesions is associated with fact that they were removed at an early stage in their tumour progression, prior to the development of capsular invasion and metastatic potential. The authors of the present study concur with previous reports that pleomorphic adenoma with focal areas of malignant change should be carefully assessed by serial sectioning to document evidence of capsular invasion[3,14]. The prognosis and future therapy will depend on careful study of these lesions.

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