Virchows Arch (1999) 434:537–546

ORIGINAL ARTICLE

Alena Skálová · Michal Michal · Aleš Ryška
Roderick H.W. Simpson · Zdenčk Kinkor
Jiří Walter · Ilmo Leivo

Oncocytic myoepithelioma and pleomorphic adenoma of the salivary glands

Received: 24 September 1998 / Accepted: 31 January 1999

Abstract Twenty oncocytic myoepitheliomas (MEs) and pleomorphic adenomas (PAs) were composed of interlacing fascicles of swollen spindle-shaped or/and epithelioid oncocytic myoepithelial cells showing intense finely granular immunoreactivity with anti-mitochondrial antibody. Focal vacuolation of the cytoplasm of oncocytic myoepithelial cells and their gradual transition into sebaceous metaplasia were observed in 3 cases. Another unusual feature found in 5 cases was the presence of slit-like adenomatoid spaces lined with double-layered oncocytic myoepithelium closely resembling Warthin's tumour. The nuclei of oncocytic cells were characterized by enlargement, hyperchromasia and polymorphism, which should not be confused with malignancy. Oncocytic change in myoepithelial cells in MEs and PAs can cause pitfalls in the differential diagnosis of salivary gland tumours. We describe some unusual histological features associated with onococytic metaplasia in benign myoepithelial cell-derived salivary gland tumours, hoping to help to avoid the overdiagnosis of malignancy.

A. Skálová (✉)[1] · M. Michal
Department of Pathology, Medical Faculty, Charles University, Pilsen, Czech Republic

A. Ryška
Department of Pathology, Medical Faculty, Charles University, Hradec Králové, Czech Republic

R.H.W. Simpson
Postgraduate Medical School, University of Exeter, England

Z. Kinkor
Department of Pathology, Faculty Hospital Bulovka, Prague, Czech Republic

J. Walter
Division of Maxillofacial Surgery, Department of Stomatology, Medical Faculty, Charles University, Pilsen, Czech Republic

I. Leivo
Department of Pathology, The Haartman Institute, University of Helsinki, Helsinki, Finland

Mailing address:
[1] Šikl's Department of Pathology, Medical Faculty Hospital, dr. E. Beneše 13, 305 99 Pilsen, Czech Republic
e-mail: skalova@fnplzen.cz
Tel.: +420-19-7402545, Fax: +420-19-273040

Key words Salivary gland · Oncocytic myoepithelioma · Pleomorphic adenoma

Introduction

Benign myoepithelial cell-derived neoplasms, such as myoepitheliomas (MEs) and pleomorphic adenomas (PAs), are the most common salivary gland tumours, and their diagnosis is not usually difficult [5, 8, 13, 32]. However, both spindle-cell MEs and myoepithelial cell-rich PAs may be highly cellular and can then be mistaken for malignant neoplasms [9, 10]. In one series, 7 of 22 benign MEs were originally diagnosed as carcinomas by the referring pathologists [30].

A further area of difficulty with benign myoepithelial neoplasms, which has attracted relatively little attention, is oncocytic metaplasia. In our experience, oncocytic neoplastic myoepithelial cells can display substantial cytological atypia, and thus the tumour is not infrequently thought to be malignant by those unaware of this phenomenon. We have therefore reviewed our archives, and here describe the clinical, histological and immunohistochemical findings in 20 cases of pure oncocytic MEs and myoepithelial-rich PAs with widespread oncocytic metaplasia of modified neoplastic myoepithelial cells. We are not aware of any papers specifically addressing the topic of oncocytic changes in myoepithelial tumours, with the exception of sporadic case reports [16–18, 28]. We also include some previously unreported features.

Materials and methods

The Salivary Gland Tumour Registry of the Department of Pathology in Plzeň, and the surgical pathology files of the Departments of Pathology in Prague-Bulovka and Hradec Králové (Czech Republic), Exeter (England) and Helsinki (Finland) yielded 84 neoplasms of the major and minor salivary glands with prominent oncocytic differentiation, from which 11 cases of pure oncocytic ME and 9 cases of myoepithelial-rich oncocytic PA were selected. The diagnosis of each tumour was based on light microscopic examination of conventionally prepared sections stained with HE, and

the tumours were categorized according to the revised WHO international classification [32]; Dardick's criteria were applied to distinguish ME from PA [9, 10]. The presence of only a few ducts (less than 5%) in an otherwise typical is still consistent with a diagnosis of ME. If ducts were more extensive and if there were chondromyxoid areas, the tumour was diagnosed as a PA. The tumours with prevailing oncocytic change representing more than 50% of the tumour mass were included in the study as an oncocytic variant of ME and PA.

For comparison, 5 cases of ordinary spindle-cell ME, 5 cases of plasmacytoid ME, and 10 cases of myoepithelial cell-rich non-oncocytic PA were also studies immunohistochemically.

All tumour tissues were fixed in 10% formaldehyde, embedded in paraffin and routinely stained. Neither fresh tissue nor formaldehyde-fixed wet tissue was available for electron microscopy in any of these cases. In 2 cases, however, the tissue samples previously fixed in 10% buffered formaldehyde were washed in phosphate buffer, fixed in 4% paraformaldehyde, postfixed in 1% osmium tetraoxide and embedded in epoxy resin (Durcupan-Epon). Sections 1 µm thick were stained with uranyl acetate and lead citrate and studied in the electron microscope.

For immunohistochemistry, the following primary antibodies were used: cytokeratins AE1–AE3 (dilution 1:500, Boehringer Mannheim, Germany), cytokeratins CAM 5.2 (1:50, Becton-Dickinson, Mountain View, Calif.) epithelial membrane antigen (EMA; 1:200, Dakopatts, Glostrup, Denmark), S-100 protein (polyclonal, 1:1000, Dakopatts), antibodies to mitochondrial antigen (clone 113-1, 1:100, Biogenex, San Ramon, Calif.), to muscle actin (HHF35 1:400, Dakopatts), to smooth muscle actin (1A4 1:1000, Dakopatts) and to CD68 (clone KP1, 1:40, Dakopatts), and MIB1 antibody (dilution 1:100, Immunotech, Marseille, France). For immunohistochemistry with the MIB1 antibody, sections 4 µm thick were cut from the specimens and placed on slides coated with 3-aminopropyltriethoxy-silane (Sigma, St. Louis, Mo.) and incubated in a microwave oven for 2×5 min at 700 W in citrate buffer (pH 6.0) prior to incubation with primary antibody. The bound antibodies were visualized using the supersensitive streptavidin–biotin–peroxidase complex (Biogenex) and 3,3-diaminobenzidine (Sigma) as chromogen.

Clinical information was extracted from the patients records. Follow-up data were obtained from the referring pathologists.

Results

The clinical features are summarized in Table 1. The mean age at diagnosis was 48 years (range 20–73), and there were 13 women and 6 men (for 1 patient the data on sex and age were not available). Two tumours arose in the submandibular gland and 2 in the minor salivary glands of the palate, and 1 each presented as parapharyngeal mass and as a tumour of the lower lip. The remaining 14 tumours were found in the parotid gland. The most common presenting symptom was a palpable painless mass.

Grossly, the tumours were all well circumscribed, and in most cases the tumour was enclosed by a fibrous thin capsule. In three cases the tumours were multilobular, whilst the others comprised a single nodule.

Microscopically, each tumour had a fibrous capsule of variable thickness. The microscopic composition of the tumours was heterogeneous in both cellular composition and architectural growth patterns. Eleven tumours were classified as ME, while, for the remaining 9 tumours the diagnosis of myoepithelial-rich PA was more appropriate. The tumours diagnosed as MEs were composed principally of spindle-shaped eosinophilic myoepithelial cells compactly arranged in interlacing fascicles (Fig. 1A). A very prominent feature was oncocytic change of these spindle tumour cells, seen in their possession of abundant eosinophilic granular cytoplasm.

Table 1 Clinical Data and Proliferative Activity in Cases of Oncocytic Myoepitheliomas and Oncocytic Pleomorphic Adenomas of the Salivary Glands

No	Age/sex	Size(cm)	MIB1 index(%)	Location	Operation and treatment	Diagnosis	Follow-up period and outcome
1	58/F	1.6	4	Parotis	excision	ME	20 years
2	67/F	3×3.2×3	2.6	Submandibular	excision	ME	2 years
3	42/M	3.5×3x3	2.5	Parotis	Superficial PE	PA	2 years
4	31/F	1.5	2.1	Parotis	Superficial PE	PA	5 years
5	20/M	5.5×4x3.5	2	Parotis	Superficial PE	PA	5 years
6	56/F		2.5	Parotis		PA	3 years
7	49/M	2×2.5×3	3	Parotis	PE	PA	2 years
8	73/M		1.8	Parotis		ME	2 years
9	38/F	2	3	Parotis	PE	PA	14 years
10	32/F	2.5×3x2.5	2.8	Parotis	PE	ME	lost
11	57/F	3.5	2.5	Parotis	Superficial PE	ME	6 years
12	52/M	2.5	0.7	Palate	Excision	ME	9 years
13[a]	58/F	4.5×5x3.5	1.3	Parapharyng. mass	Excision, RT	PA	12 years
14	61/F	1.5	1.5	Palate	Excision	ME	6 years (D)
15	47/F	1.2	0.8	Parotis	Superficial PE	ME	1 years
16	20/F		1.5	Submandib	Excision	PA	5 years
17	39/M	4.7×3.7×2.5	0.6	Parotis	PE	PA	4 years
18	Unknown	1.5×1	0.7	Lip	Excision	ME	lost
19	64/F		1.8	Parotis	PE	ME	13years
20	41/F	4.5×4x3.5	2.5	Parotis	PE	ME	5 months

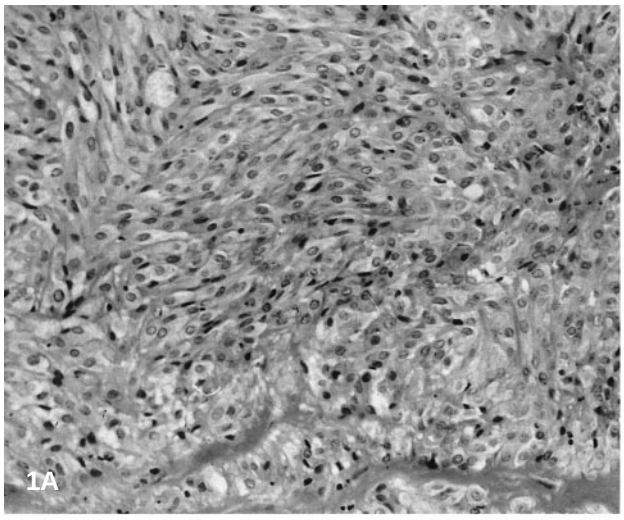
[a] this tumour was first diagnosed as PA 6 years before an incomplete excision

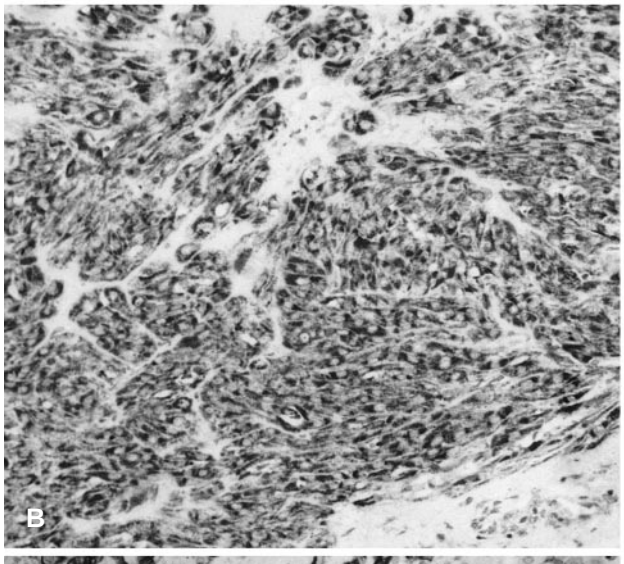
ME – myoepithelioma RT – postoperative radiotherapy

PA – pleomorphic adenoma PE – parotidectomy

Y – year(s) D – died, no evidence of disease

M – month(s)





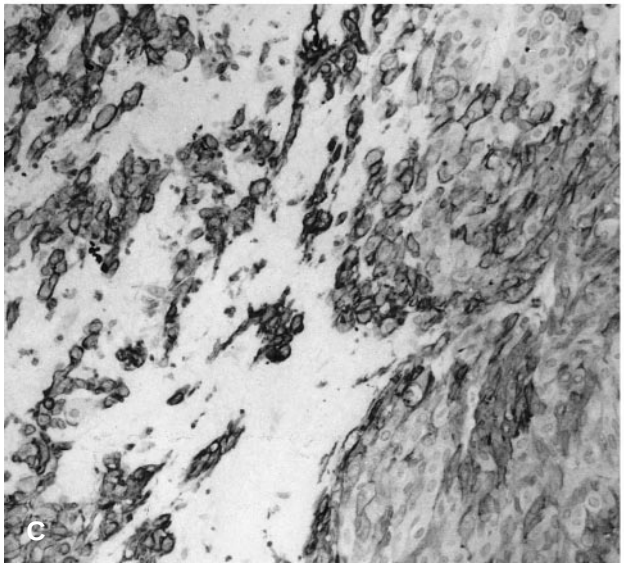
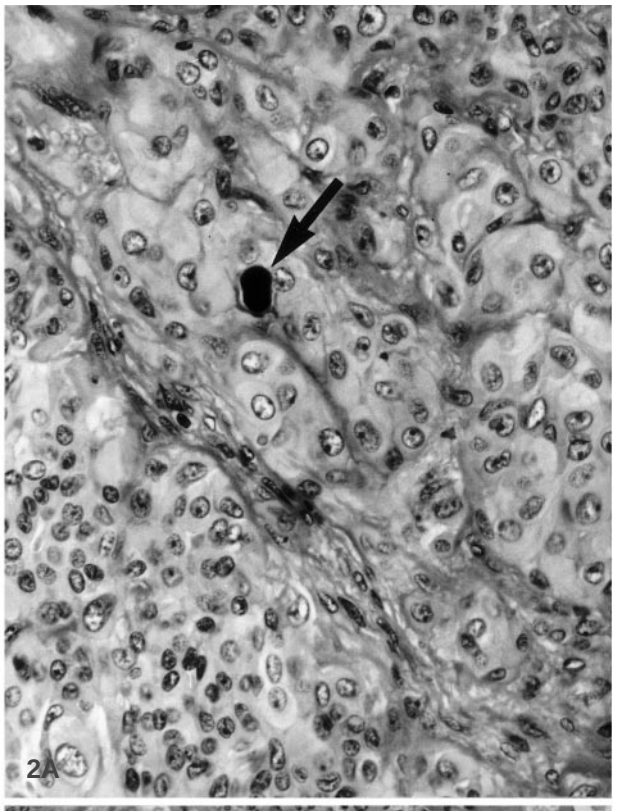


Fig. 1A–C Spindle cell oncocytic myoepithelioma (ME). **A** The tumour is composed of spindle-shaped eosinophilic cells with abundant granular cytoplasm arranged in interlacing fascicles. ×180. Immunohistochemically, tumour cells reveal both positive staining **B** with anti-mitochondrial antibody or **C** with actin antibodies. **B** ×180, **C** ×90



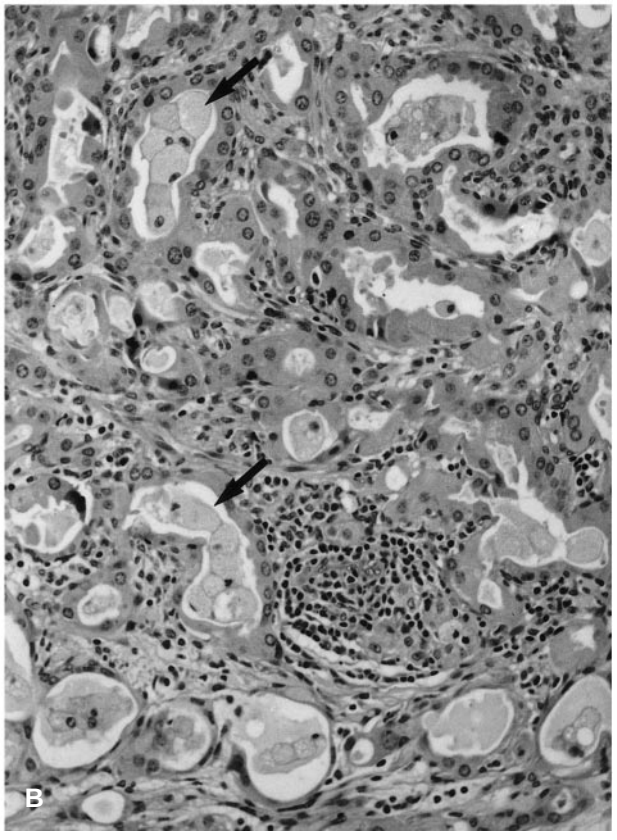


Fig. 2A, B Oncocytic pleomorphic adenoma (PA). **A** Psammoma bodies (*arrow*) are scattered between large oncocytic epithelioid myoepithelial cells. ×360 **B** Tubules are lined with oncocytic cells with slight nuclear atypia, and the stroma contains numerous reactive lymphocytes. Clusters of foamy macrophages (*arrows*) can be seen within lumina. ×180

The spindle cells had centrally located vesicular nuclei, mostly with inconspicuous nucleoli. There was slight nuclear polymorphism within the oncocytic cells, but mitotic figures were few. All tumours were hypercellular and had a limited amount of myxoid stroma. A few mucin-filled tubules were lined with oncocytic cells identical to those seen in the solid portions of the tumour. This was always a minor tumour component. In other cases of ME large polygonal epithelioid myoepithelial cells were predominant. In some tumours, hyaline plasmacytoid cells were observed and abundant clear cells with ”empty-looking” cytoplasm were prominent focally. There was often a gradual transformation from one cell type to the other, and all these types of modified myoepithelial cells showed striking oncocytic metaplasia in places.

Immunohistochemically, the neoplastic cells showed intense, granular cytoplasmic reactivity for anti-mitochondrial antibody (Fig. 1B). Especially strong staining for antimitochondrial antigen was observed in spindle-shaped myoepithelial cells that also stained strongly for actin, S-100 protein, and cytokeratins (Fig. 1C). Intense cytoplasmic staining for the mitochondrial antigen was observed in majority of epithelioid cells, which also co-expressed cytokeratin, vimentin, and S-100 protein. Clear cells were stained for cytokeratins, S-100 protein and in some cases also actin. The MIB1 index (percentage of tumour cell nuclei positively stained for the Ki-67 antigen with the MIB1 antibody) for each case is given in Table 1. The figures in MEs ranged from 0.7% to 4.0%, with a mean of 2.1%.

The tumours diagnosed as myoepithelial-rich pleomorphic adenomas were encapsulated and multilobulated, and typically consisted of two different portions. One was that of typical PA composed of epithelial cords, glands and tubular structures surrounded by myxoid and chondromyxoid stroma. Most of the tumour, however, consisted of sheets and clusters of large polygonal cells with abundant eosinophilic cytoplasm with prominent granularity and well-defined cell borders (Fig. 2A). In other places, neoplastic tubules lined with oncocytic cells were surrounded by lymphocyte-rich stroma (Fig. 2B). The neoplastic cells had large vesicular nuclei with prominent nucleoli or basophilic nuclei with irregular contours and possessed a variable degree of cellular atypia and nuclear hyperchromatism. However, proliferative activity measured in the areas with obvious oncocytic metaplasia was rather low, with a mean MIB1 index of 2.0% (range 0.6–3.0%). The cells exhibited strong granular cytoplasmic immunoreactivity with anti-mitochondrial antibody (Fig. 3A), and they were also positive for cytokeratins, vimentin, and S-100 protein. Most tumour oncocytic cells also expressed actin (Fig. 3B). Broad sheets of large oncocytic cells with little intervening stroma constituted the bulk of neoplasms. Psammoma bodies were scattered throughout the tumour stroma in 4 cases (Fig. 2A). Focally, the stroma was more prominent and consisted of hyalinized collagen that separated the cords of neoplastic oncocytic cells. In other places, there were PAS-positive hyaline deposits of basement membrane-rich extracellular matrix material. These structures varied in size from small hyaline droplets to larger collagenous spherules [34] and were often surrounded by neoplastic plasmacytoid myoepithelial cells. Interspersed clear cells were seen in 5 cases.

In 3 cases of oncocytic ME there was a further very unusual feature: part of each tumour was composed of solid sheets of large neoplastic oncocytic cells with numerous intracytoplasmic vacuoles (Fig. 4A). The vacuolated cells stained strongly with the antibody to mitochondrial antigen 113-1 (Fig. 4B). In places, the oncocytic cells had vacuolated cytoplasm, producing a strong resemblance to sebaceous differentiation (Fig. 4B). There was a gradual transition between these vacuolated cells, clear cells with myoepithelial features, spindle-shaped cells with typical oncocytic morphology and myoepithelial immunophenotype. The clear and vacuolated cells were PAS (periodic acid–Schiff), mucicarmine and alcian blue (pH 2.5) negative. The vacuolated cells showed a myoepithelial immunophenotype in addition to oncocytic features, with a positive reaction to cytokeratins, actin and S-100 protein, and positive staining with EMA. Another unusual feature was the occurrence of pinched-off snouts typical of decapitation secretion seen in apocrine metaplasia in some of glandular structures in 2 cases of oncocytic pleomorphic adenoma (Fig. 4C). The secretion of this glandular component stained positively with PAS with and without diastase digestion and alcian blue at pH 2.5, and it was mucicarmine negative.

Clusters of foamy macrophages were observed within the lumina of ducts in 2 cases of PA (Fig. 5). In 2 other cases of ME we observed a small portion of the tumour to be composed of clear and epithelioid cells with numerous microcystic spaces, and in 4 other cases (2 PAs and 2 MEs) there were prominent foci of adipose metaplasia. Another unusual feature observed in 5 cases (1 ME and 4 PAs) was the presence of slit-like and narrow cystic adenomatoid spaces lined by bilayered oncocytic epithelium resembling oncocytic cystadenoma (Fig. 6A). These slit-like spaces often acquired a complicated labyrinthine configuration hardly ever seen in common pleomorphic adenomas and myoepitheliomas. The epithelium lining these spaces showed a strong staining with the anti-mitochondrial antibodies (Fig. 6B), and most but not all cells expressed actins (Fig. 6C). In 1 case of PA these labyrinthine spaces were highly reminiscent of Warthin tumour. The tall oncocytic epithelias were arranged into bilayered cystopapillary structures with basally situated nuclei in the inner layer, and they were associated with lymphoid-rich stroma in these areas (Fig. 7A–B). Gradual transitions between these components and solid oncocytic myoepithelial areas of the tumour were seen.

For comparison, we stained 10 nononcocytic PAs and 5 spindle-cell-type and 5 plasmacytoid-type MEs. With the anti-mitochondrial antibodies, the spindle-shaped myoepithelial cells in chondromyxoid areas, and most neoplastic cells in solid and tubular structures, were nonreactive. Hyaline cells were also negative with anti-mito-

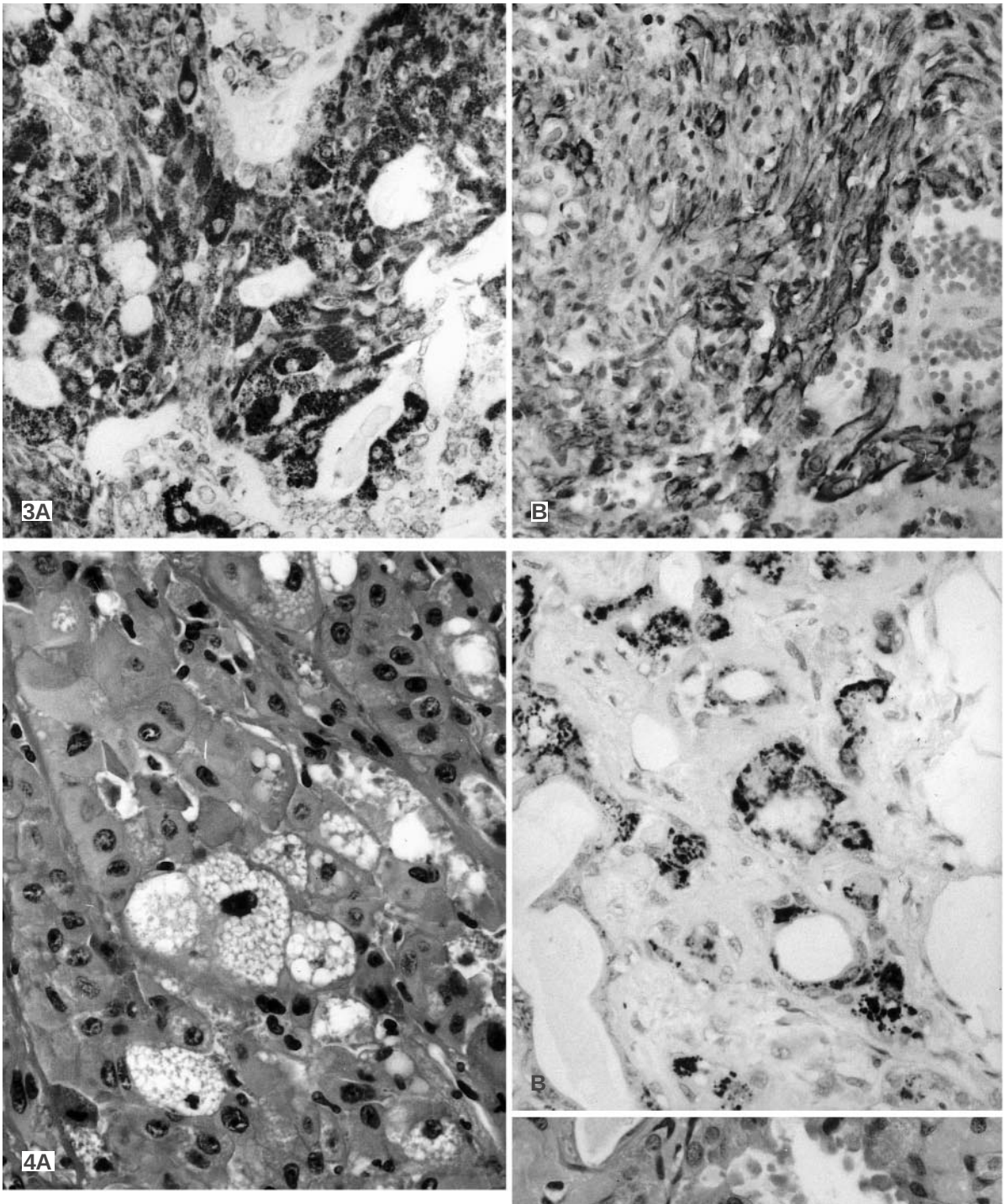


Fig. 3A, B Oncocytic PA (same case as in Fig. 2). **A** Strong granular cytoplasmic staining with anti-mitochondrial antibody can be observed in most tumour cells. ×360 **B** Most spindle-shaped and epithelioid myoepithelial cells express actin. ×360

Fig. 4A–C Oncocytic ME. **A** Oncocytic myoepithelial cells have polymorphic and hyperchromatic nuclei. Numerous intracytoplasmic vacuoles can be seen in some tumour cells. ×360 **B** Positive immunostaining of vacuolated cells with anti-mitochondrial antibody. ×180 **C** Pinched-off snouts (*arrows*) typical of decapitation secretion are present in foci of apocrine metaplasia of the glandular epithelium. ×180

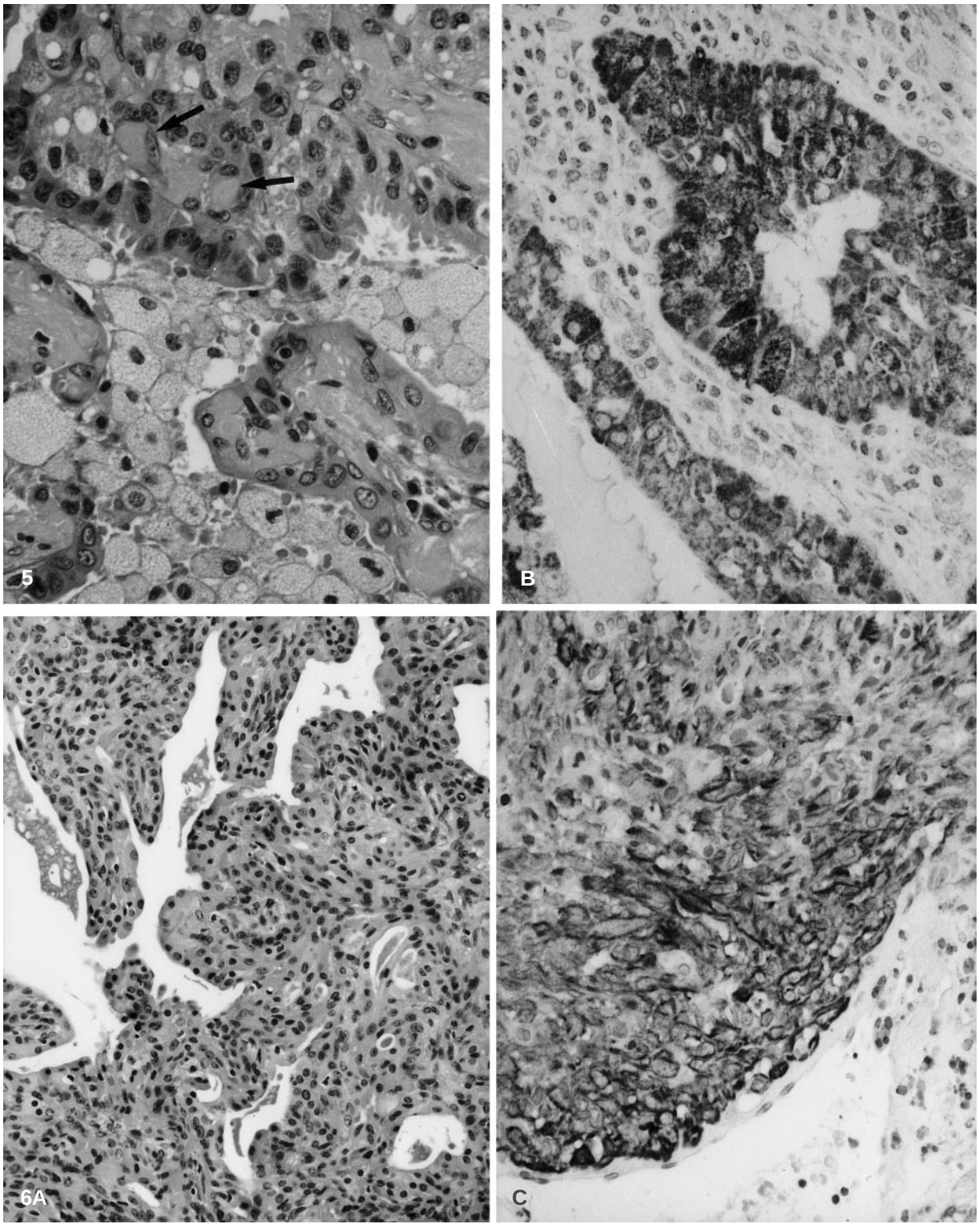
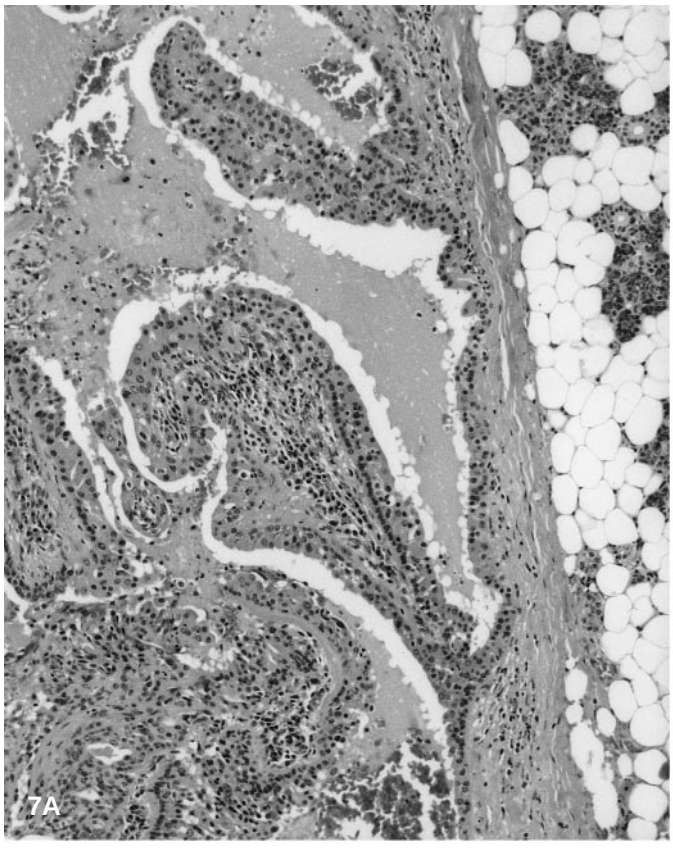


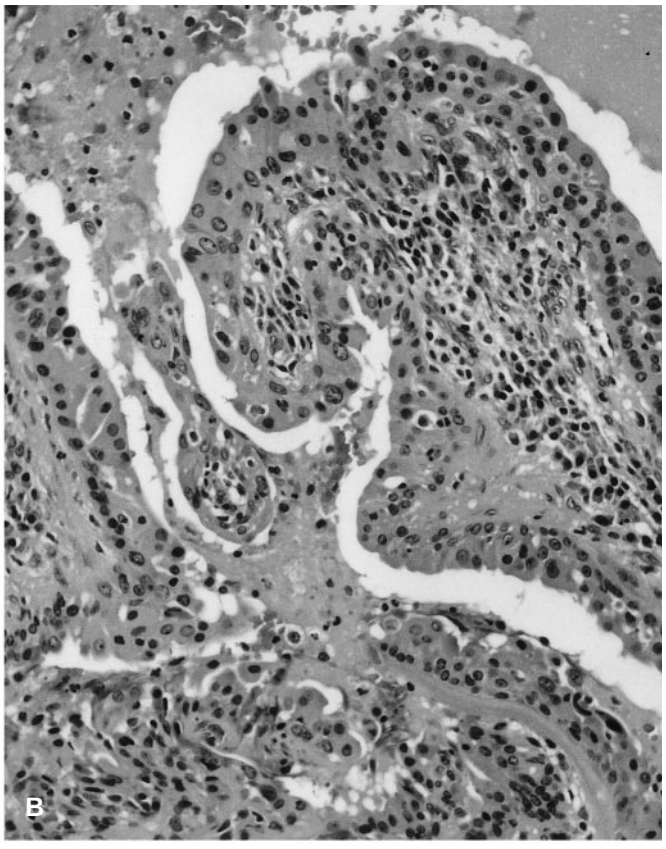
Fig. 5 Oncocytic PA. Hyaline plasmacytoid cells (*arrows*) merge with oncocytic myoepithelium to form glandular cystic spaces. There are clusters of foamy macrophages within neoplastic lumina. ×360

Fig. 6 **A–C** Oncocytic PA. **A** Labyrinthine spaces are surrounded by oncocytic cells. ×180 **B** Neoplastic cells show granular cytoplasmic positivity with anti-mitochondrial antibody. ×180 **C** Some neoplastic cells are also positive with actin antibodies. ×180

chondrial antibodies. Isolated large epithelial cells both in solid areas of PAs and in MEs showed moderate immunoreactivity. Foci of squamous metaplasia showed weak granular cytoplasmic staining. In normal salivary glands the epithelium of striated ducts showed finely granular positivity of the cytoplasm.

In case 1 (oncocytic spindle cell myoepithelioma) and in case 3 (oncocytic variant of pleomorphic adenoma)





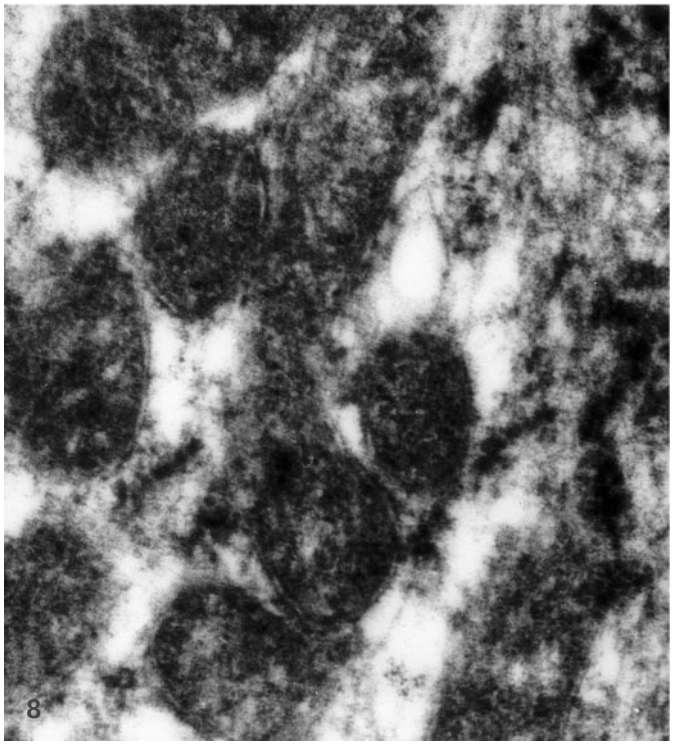


Fig. 7 A, B Oncocytic PA. **A** Focal cystopapillary structures lined with bilayered oncocytic epithelium associated with lymphoid stroma closely resembling Warthin's tumour are present in otherwise typical oncocytic pleomorphic adenoma. ×90 **B** At higher magnification, nuclear polymorphism of neoplastic oncocytes can be demonstrated. ×180

Fig. 8 Oncocytic PA (case 3). Electron micrograph shows tumour cell with closely with packed mitochondria. ×43,000

electron microscopic examination was performed. Though the tissue preservation was not optimal, groups of polyhedral and spindle-shaped oncocytic cells were seen, with numerous mitochondria in the cytoplasm (Fig. 8). Nuclei were large, with dispersed chromatin and one or more prominent nucleoli. Some cells had less abundant mitochondria and contained haphazardly arranged intermediate cytoplasmic filaments. Oncocytic myoepithelial cells were also present. In these, numerous mitochondria and fascicles of microfilaments could be

observed in the cytoplasm. Neither Golgi complex nor granular endoplasmic reticulum were prominent in the cells. We were unable to find vacuolated or clear cells in the examined tissue specimens.

In the time of study, 17 patients were still alive and well with no evidence of disease 5 months to 20 years after surgical treatment (mean follow-up period 6 years). One patient had died of unrelated causes 6 years after the initial diagnosis, with no clinical evidence of recurrence or metastatic disease. Two patients were lost to follow-up.

Discussion

In 1931 Hamperl coined the term oncocyte (Onkocyten) to describe cells each having abundant eosinophilic granular cytoplasm and a centrally located hyperchromatic nucleus [20]. Oncocytic metaplasia of ductal and acinar cells is commonly encountered in normal salivary glands in persons over 50 years of age [13], but primary oncocytic neoplasms and tumour-like lesions are comparatively rare, accounting for less than 1% of salivary tumours [13]; these have been reviewed elsewhere [6, 13].

Less attention has been paid to oncocytic metaplasia in other salivary neoplasms, but it has been reported in mucoepidermoid carcinomas [17, 19], and in PAs [18], canalicular adenoma, acinic cell carcinoma, cystadenoma [13] and epithelial–myoepithelial carcinoma [21]. As a minor component there are several tumours in which it is not uncommon, but to our knowledge, only one PA composed predominantly of oncocytic cells has been reported in the literature [28], and we have been unable to find any description of a pure oncocytic variant of ME similar to those presented in this paper.

In our study, oncocytic differentiation was demonstrated in all cases by conventional histology and immunohistochemistry, and in 2 cases electron microscopic examination was performed. Oncocytes are plump, ”swollen” cells with abundant cytoplasm filled with numerous mitochondria [20]. Usually, oncocytes are easily recognized in routine haematoxylin and eosin (HE)-stained sections. However, oxyphilic properties are nonspecific, because cytoplasmic eosinophilia can be related to intracytoplasmic accumulation of organelles other than mitochondria. A commercially available monoclonal antibody (clone 113-1) that recognizes a mitochondrial antigen in formalin-fixed, paraffin-embedded tissues was shown to distinguish mitochondrion-rich oncocytes and oncocytic tumours from the cells with oxyphilic properties unrelated to mitochondria. Specific labelling of the mitochondria by monoclonal antibody 113-1 in the absence of staining of other cytoplasmic structures was documented by immunoelectron microscopy [26]. A crucial point in the application of the anti-mitochondrial antibody 113-1 seems to be the working dilution, because nononcocytic cells rich in mitochondria, such as hepatocytes, cardiac and skeletal muscle cells, and apocrine cells, can be immunoreactive in certain conditions [26]. However, a working dilution of 1:100 had already been demonstrated to allow selective labelling of the oncocytes with no immunoreactivity in eosinophilic cells other than oncocytes [26].

Oncocytic metaplasia has long been regarded as affecting both secretory and ductal epithelial cells in salivary glands [5], although Askew et al. provided ultrastructural and light microscopic evidence of both epithelial and myoepithelial oncocytes [3]. In agreement with this, a recently described case of an oncocytic adenoma of the parotid gland revealed immunohistochemical co-expression of S-100 protein and cytokeratins, which was interpreted as indicating myoepithelial differentiation of oncocytes [16]. This is the only published case of a tumour that bears any resemblance to the pure oncocytic MEs in our study. In our cases the MEs were composed predominantly of spindle-shaped oncocytic myoepithelial cells admixed with variable proportions of epithelioid and clear cells set in relatively small amounts of intervening stroma, and they thus appeared highly cellular. Nuclear polymorphism was often prominent. Therefore, the differential diagnosis includes spindle-cell mesenchymal tumours, such as leiomyoma/sarcoma, benign and malignant nerve sheath tumours, and synovial sarcoma. In our experience, a useful morphological pointer is the presence of myoepithelial cell-derived deposits of extracellular matrix, such as collagenous spherules [34]. Immunohistochemistry can be helpful, with certain caveats: strong cytoplasmic reactivity for anti-mitochndrial antibody in tumour cells displaying a myoepithelial phenotype is effectively diagnostic [33]. However, it should be noted that ASMA is positive in smooth muscle neoplasms and S-100 protein, in nerve sheath tumours. Staining for both, as well as for cytokeratin indicates myoepithelial differentiation, but difficulties may still arise as myoepithelial cells do not always express the markers they should [11].

Arguably, the most confusing and important feature associated with oncocytic foci in ME and PA is the presence of nuclear polymorphism, which we have observed in all cases. In two consultation cases this resulted in original diagnosis as malignant made by the referring pathologists. The whole issue of malignant change in PA (and ME) is a major practical clinical and histopathological problem. The finding of metastases, destructive invasion or abnormal mitotic figures leaves no room for doubt, but there ist still no agreement on the significance of focal atypical features [4, 13]. While hypercellularity with a mild degree of nuclear polymorphism and hyperchromatism are acceptable for the diagnosis of a benign tumour, more severe abnormal features, such as prominent nucleoli and high mitotic rate have been said to be indicative of carcinomatous transformation [13]. Other workers have shown that cellular anaplasia alone in a PA did not indicate an increased risk of developing a subsequent malignancy [4]. In the present series of MEs and PAs with oncocytic change, we observed substantial cytological atypia, including enlarged and hyperchromatic nuclei, prominent nucleoli, and mildly increased mitotic figures. None of our patients developed malignant transformation of the tumour within follow-up periods vary-

ing between 1 and 20 years. Although arguably these times are still too short, at this stage we believe that nuclear atypia associated with oncocytic metaplasia of myoepithelial cells should not be regarded as a predictor of malignant behaviour. Similar nuclear atypia is seen in oncocytic neoplasms in other sites, such as thyroid (Hürthle cell adenoma) [29], and kidney [2, 27], and in our experince in oncocytic eccrine poromas of the skin (unpublished observations), and in none of these does this finding indicate aggressive behaviour.

Clear cell change is a well-known phenomenon seen in many salivary gland tumour types [22, 31], including both benign and malignant myoepithelioma [23]. It often occurs in pure oncocytomas [12, 14], but these tumours do not express myoepithelial markers.

A further interesting feature was the occurrence of cells with sebaceous-like and apocrine differentiation. In addition to clear cells with empty cytoplasm, we observed tumour cells with vacuolated cytoplasm resembling sebaceous cells in 3 cases [7]. At the light microscope level the vacuolated cells fulfilled the minimum criteria for sebaceous differentiation of vacuolated cytoplasm with scalloped nuclei, as defined for skin tumours by Abenosa and Ackerman [1]. Simultaneous occurrence of sebaceous and apocrine differentiation in tumours other than skin tumours is not unique to salivary glands [7]. Similar sebaceous and glandular differentiation was recently described by one of us (M.M.) in a verrucous carcinoma of the urinary bladder [24]. It was shown recently that apocrine cells can also be distinctly foamy [8, 15]. Damiani et al. [8] studied foam cells (cells with abundant finely vacuolated cytoplasm) in benign breast lesions and demonstrated a spectrum of phenotypes from epithelial apocrine cells to macrophage-derived phagocytic cells. Both apocrine cells and oncocytes have abundant eosinophilic granular cytoplasm, and the distinction between the two may be difficult by light microscopy alone [15]. The true nature of the vacuolated cells is uncertain in our cases, as the ultrastructural examination revealed nothing of this. Similar cells were noted previously, however, and thought to represent autophagic vacuoles or degenerate mitochondria within oncocytic neoplastic cells [16, 18]. The vacuolated cells in the present study stained strongly with the anti-mitochondrial and anti-cytokeratin antibodies, and there were gradual transitions to true oncocytic myoepithelial cells. Thus, we believe the vacuolated cells seen in our cases were most probably modified oncocytes. Recently we have described similar vacuolated cell change in a case of oncocytic cystadenoma of the parotid gland (not included in the present series), which was prominent enough to make the cell look similar to a signet ring [25].

This study also revealed two histological features not previously reported in MEs: psammoma bodies and Warthin's tumour-like foci. True psammoma bodies were identified in 4 cases in our study. They were sparse, and distributed at random with no apparent relationship to papillae or blood vessels. To our knowledge they have not been reported before in MEs, although they are occasionally seen in acinic cell carcinoma, oncocytic adenoma, and canalicular adenoma [13]. Brandwein and Huvos [6] found psammoma bodies in one case among 68 primary oncocytic tumours, and 1 other case of oncocytic adenoma with scattered psammoma bodies has been reported [16]. The significance and origin of the psammoma bodies in salivary gland tumours is not known, as they do not particularly seem to be related to neoplasms with papilla formation. Interestingly, oncocytic tumours of other organs occasionally contain psammoma bodies (Hürthle cell adenoma of the thyroid gland [29] and renal oncocytomas [2, 27].

The second possibly unique finding in this study was that of labyrinthine adenomatoid and Warthin's tumour-like structures in otherwise typical PAs and MEs. This feature has not been reported before. In 4 cases there were cystopapillary bilayered structures lined with oncocytic epithelium, producing a resemblance to oncocytic cystadenoma. In another case of oncocytic PA of the parotid gland, these spaces were associated with rich lymphoid stroma, leading to a pattern closely resembling that seen in Warthin's tumour. In all 5 cases, these adenomatoid and Warthin-like structures were situated adjacent to foci of apparent oncocytic metaplasia of myoepithelial cells. Though not so far observed in primary myoepithelial lesions, a relationship between oncocytoma and Warthin's tumour is not surprising. The two tumours contain identical cells – oncocytes. In addition, Warthin's tumour may contain foci of solid nodular oncocytic hyperplasia, and cysts associated with sparse lymphoid stroma have been described in occasional oncocytomas [13].

In summary, oncocytic metaplasia is relatively uncommon in salivary MEs and PAs, but it can cause significant diagnostic problems in practice.

References

1. Abenoza P, Ackerman AB (1990) Neoplasms with eccrine differentiation. Lea & Febiger, Philadelphia
2. Amin MB, Crotty TB, Tickoo SK, Farrow GM (1997) Renal oncocytoma: a reappraisal of morphologic features with clinicopathologic findings in 80 cases. Am J Surg Pathol 21:1–12
3. Askew JB, Fechner RE, Bentinck DC, Jenson AB (1971) Epithelial and myoepithelial oncocytes. Ultrastructural study of a salivary gland oncocytoma. Arch Otolaryngol 93:46–54
4. Auclair PL, Ellis GL (1996) Atypical features in salivary gland mixed tumors: their relationship to malignant transformation. Mod Pathol 9:652–657
5. Auclair PL, Ellis GL, Gnepp DR (eds) (1991) Surgical pathology of the salivary glands. Saunders, Philadelphia
6. Brandwein MS, Huvos AG (1991) Oncocytic tumors of major salivary glands. Am J Surg Pathol 15:514–528
7. Cameron WR, Stenram U (1979) Adenoma of parotid gland with sebaceous and oncocytic features. Cancer 43:1429–1433
8. Damiani S, Cattani MG, Buonamici L, Eusebi V (1998) Mammary foam cells. Characterization by immunohistochemistry and in situ hybridization. Virchows Arch 432:433–440
9. Dardick I (1995) Myoepitheliomas: definitions and diagnostic criteria. Ultrastruct Pathol 19:359–369
10. Dardick I (1996) Color atlas/text of salivary gland tumor pathology. Igaku-Shoin Medical, New York, Tokyo

11. Dardick I, Ostrynski V, Ekem K, Burford-Mason A (1992) Muscle actin expression in pleomorphic adenomas and myoepitheliomas: immunohistochemical and ultrastructural correlates based on comparison of formalin and methanol fixation. Virchows Arch [A] 421:95–104
12. Davy CL, Dardick I, Hammond E, Thomas MJ (1994) Relationship of clear cell oncocytoma to mitochondrial-rich (typical) oncocytoma of parotid salivary gland. An ultrastructural study. Oral Surg Oral Med Oral Pathol 77:469–478
13. Ellis GL, Auclair PL (eds) (1996) Atlas of tumor pathology. Tumors of the salivary gland. Armed Forces Institute of Pathology, Bethesda
14. Ellis GL (1988) "Clear cell" oncocytoma of salivary gland. Hum Pathol 19:862–867
15. Eusebi V, Damiani S, Losi L, Millis RR (1997) Apocrine differentiation in breast epithelium. Adv Anat Pathol 4:139–155
16. Feiner HD, Goldstein S, Ittman M, Pelton K, Jacobs J (1986) Oncocytic adenoma of the parotid gland with psammona bodies. Arch Pathol Lab Med 110:640–644
17. Ferreiro JA, Stylopoulos N (1995) Oncocytic differentiation in salivary gland tumours. J Laryngol Otol 109:569–571
18. Gray SR, Cornog JL, Seo IS (1976) Oncocytic neoplasms of salivary glands: a report of fifteen cases including two malignant oncocytomas. Cancer 38:1306–1317
19. Hamed G, Shmookler BM, Ellis GL, Punja U, Feldman D (1994) Oncocytic mucoepidermoid carcinoma of the parotid gland. Arch Pathol Lab Med 118:313–314
20. Hamperl H (1931) Beiträge zur normalen und pathologischen Histologie menschlicher Speicheldrüse. Z Mikroscopisch-anatomischer Forschung 27:1–22
21. Kusama K, Saito M, Kozu M, Shimizu K, Hori M, Tanaka H, Moro I (1996) Epithelial-myoepithelial carcinoma of the palate. J Oral Pathol Med 25:463–466
22. Maiorano E, Altini M, Favia G (1997) Clear cell tumors of the salivary glands, jaws, and oral mucosa. Semin Diagn Pathol 14:203–212
23. Michal M, Skálová A, Simpson RHW, Rychterová V, Leivo I (1996) Clear cell malignant myoepithelioma of the salivary glands. Histopathology 28:309–315
24. Michal M, Šulc M, Mukenšnábl P (1997) Verrucous carcinoma of the urinary bladder associated with sebaceous and glandular differentiation. J Urol Pathol 6:153–158
25. Michal M, Hrabal P, Skálová A (1998) Oncocytic cystadenoma of the parotid gland with prominent signet-ring cell features. Case report. Pathol Int 48:629–633
26. Papotti M, Gugliotta P, Forte G, Bussolati G (1994) Immunocytochemical identification of oxyphilic mitochondrion-rich cells. Appl Immunohistochem 2:261–267
27. Perez-Ordonez B, Hamed G, Campbell S, Erlandson RA, Russo P, Gaudin PB, Reuter VE (1997) Renal oncocytoma: a clinicopathologic study of 70 cases. Am J Surg Pathol 21:871–883
28. Pulitzer DR, Reitmeyer WJ (1987) Oncocytic pleomorphic adenoma of the parotid gland. J Surg Oncol 34:198–201
29. Rosai J, Carcangiu ML, DeLellie RA (1992) Atlas of tumor pathology. Tumors of the thyroid gland. Armed Forces Institute of Pathology, Bethesda
30. Sciubba JJ, Brannon RB (1982) Myoepithelioma of salivary glands: report of 23 cases. Cancer 49:562–572
31. Seifert G (1996) Classification and differential diagnosis of clear and basal cell tumors of the salivary glands. Semin Diagn Pathol 13:95–103
32. Seifert G, Sobin LH, Seifert G, Sobin LH (eds) (1991) World Health Organization international histological classification of tumours: histological typing of salivary gland tumours, 2nd edn. Springer, Berlin Heidelberg New York
33. Shintaku M, Honda T (1997) Identification of oncocytic lesions of salivary glands by anti-mitochondrial immunohistochemistry. Histopathology 31:408–411
34. Skálová A, Leivo I (1992) Extracellular collagenous spherules in salivary gland tumors. Immunohistochemical analysis of laminin and various types of collagen. Arch Pathol Lab Med 116: 649–653