

Epithelial-myoepithelial carcinoma of salivary glands

R H W Simpson, T J Clarke, P T L Sarsfield, P G C Gluckman

Abstract

Four cases of epithelial-myoepithelial carcinoma of the salivary glands arose as painless masses in patients over 60 years old, three in the parotid and one in the submandibular gland. Histologically, all the tumours were composed of small ducts with a double cell lining surrounded by a basement membrane. The inner cells were epithelial and the outer cells myoepithelial, the latter usually possessing clear cytoplasm. There was a variable degree of intervening hyalinised stroma. All the tumours were partly encapsulated, but also displayed local invasiveness. One of the tumours also showed areas of dedifferentiation when it later recurred and metastasised. The other three were apparently cured by initial excision, with adjuvant radiotherapy in one instance. In the past this tumour has been described as clear cell adenoma, and it was only recently that its true malignant nature, albeit low grade, was recognised.

Reports of epithelial-myoepithelial carcinoma are still relatively few, with only one case described from Britain. It is recommended that this histologically distinct neoplasm deserves wider recognition.

The 1972 WHO classification of salivary gland tumours¹ lists adenocarcinoma, but does not attempt further subdivision. It has since become increasingly clear, however, that there is considerable variation within this group, both in histological appearance and in clinical behaviour. One distinctive subtype was first described as epithelial-myoepithelial carcinoma (Epithelial-myoepitheliales Schaltstückcarcinom) by Donath in 1972,² although several similar tumours had previously been documented under other names.³⁻⁶ This neoplasm was illustrated in the WHO classification¹ and the AFIP Tumor Fascicle⁷ as clear cell monomorphic adenoma, but this was before its truly malignant nature had been realised. By 1987, a review of published findings had identified 35 cases,⁸ and a 1989 study from Germany and Sweden added a further 21.⁹ The entity was not specifically referred to either in a 1976 Scottish survey of 643 salivary tumours,¹⁰ or among the 2410 cases of the British Salivary Gland Tumour Panel reported in 1985.¹¹ We have found only one case from the United Kingdom described

as epithelial-myoepithelial carcinoma,¹² although the parotid clear cell adenoma reported by Corridan in 1956³ was almost certainly another.

The purpose of this study was to present four new cases of epithelial-myoepithelial carcinoma and to document the clinical, histopathological, and immunohistochemical findings, and thus permit wider recognition of this distinctive tumour.

Methods

The Area Department of Pathology in Exeter serves a population of about 300 000 in East Devon. The surgical pathology archives contained 212 parotid tumours between 1978 and June 1990, of which three were classified on review as epithelial-myoepithelial carcinoma. One was found among 25 submandibular neoplasms, but none among 43 minor salivary gland tumours. Paraffin wax embedded blocks were available from all four cases. Sections were prepared in the conventional manner and stained with haematoxylin and eosin, periodic acid Schiff (PAS) (before and after diastase digestion) alcian blue at pH 2.5, Masson's trichrome, Weigert's stain for elastin with a van Gieson counterstain, and Gordon and Sweet's reticulin. A panel of commercially available antibodies (table 1) was applied to sections using the streptavidin-biotin technique. Appropriate positive and negative controls were used. Immunoperoxidase staining was assessed semiquantitatively, with 0 as negative, ± as equivocal, and +, ++, and +++ indicating different intensities of positive reaction. "F" indicated that the pattern was focal. Where mitotic counts are given, the area of a high power field is 0.16 mm².

Results

CLINICAL FINDINGS

These are summarised in table 2. All the patients were British and white, and there were no common factors in their medical or occupational histories. All presented with a painless salivary gland mass. None had enlarged lymph nodes at presentation, and there was no evidence of nerve symptoms. The overlying skin appeared normal in each case. General clinical and radiological examination excluded the possibility that any was a metastasis. Surgical excision was considered complete in each patient, and case 1 received a course of postoperative radiotherapy. One of the patients (case 3) developed a local

Postgraduate
Medical School,
University of Exeter,
Barrack Road, Exeter,
Devon EX2 5DW
R H W Simpson

Area Department of
Pathology, Exeter
T J Clarke
P T L Sarsfield

Department of Ear,
Nose and Throat
Surgery, Royal Devon
and Exeter Hospital
P G C Gluckman

Correspondence to:
Dr R H W Simpson

Accepted for publication
31 October 1990

recurrence 18 months later, which was completely excised. At the same time she was noted to have an enlarged supraclavicular lymph node, which was not biopsied. Two patients (cases 1 and 2) died of presumed cerebrovascular disease, and case 4 was lost at sea in a boating accident. None had any clinical evidence of persistent tumour. Post mortem examinations were not performed.

PATHOLOGICAL FINDINGS

Macroscopically, all the tumours were well circumscribed masses with a grey cut surface. Haemorrhagic areas were noted in case 3.

Microscopically, each tumour was composed of small ducts, some of which contained small quantities of intraluminal inspissated mucin. The lining consisted of two layers: the inner comprised small cuboidal or low columnar cells with generally eosinophilic cytoplasm, and was surrounded by an outer mantle of cells, almost all of which had clear cytoplasm. The nuclei in both cell types were single with evenly dispersed chromatin, and rare almost inconspicuous nucleoli. Glycogen could be shown in both layers, especially the outer, but no intracellular mucin was seen. The outer layer was surrounded by prominent, PAS positive basement membrane material, and the intervening stroma were composed of almost acellular collagen, with neither elastin nor alcian blue positive mucin.

The relative prominence of the stroma and both cell types varied not only from case to case, but also within each individual tumour. Three basic morphological patterns could be recognised, as well as transitional areas. In the first, or classic pattern (fig 1) the two layers lining the ducts were easily discernable, as were the surrounding basement membranes. In the second, or clear cell predominant pattern (fig 2)

sheets of cells resembling the outer layer of the classic pattern were divided into alveolar structures by thin strands of stroma. An inner layer of cells was present, but was often difficult to identify. Zones with this pattern were observed in all four tumours, and were particularly prominent in case 1. The third, or sclerotic pattern (figs 3 and 4) consisted of abundant hyalinised stroma separating relatively sparse double-layered ducts. There was no myxoid or chondroid change, as seen in a pleomorphic adenoma: Small cyst formation (cases 3 and 4), scanty microcalcification (cases 2 and 4), and focal necrosis (case 4) were uncommon findings.

Although the tumours were well circumscribed and partly encapsulated, each showed invasion into surrounding tissue including blood vessels and nerves (fig 5). There was no pleomorphism, and mitotic figures were rare (fewer than 3 per 20 high power fields). An exception was the recurrent tumour in case 3 which showed areas of dedifferentiation with pleomorphic spindle and polygonal clear cells (fig 6), prominent haemorrhage, and necrosis and numerous mitotic figures (36 per 20 high power fields).

IMMUNOHISTOCHEMISTRY

The findings are summarised in table 1. In all cases there was a noticeable difference in the reactions of the two ductal cell layers: the inner cells showed luminal staining with HMFG 1 and 2 antibody, and cytoplasmic positivity with low molecular weight cytokeratins (AE1 and CAM 5.2); the outer layer stained almost exclusively with S100 protein (fig 7) indicating myoepithelial differentiation. Myosin (ICN, dilution 1 in 10) was applied to cases 3 and 4 and was completely negative in each case. This biphasic staining reaction was best seen in the classic pattern, but was preserved even in the

Table 1 Immunohistochemical findings

Marker	Source	Dilution	Case 1		Case 2		Case 3		Case 4	
			Inner layer	Outer layer	Inner layer	Outer layer	Inner layer	Outer layer	Inner layer	Outer layer
AE1	ICN	1:200	+++	F+	+++	○	+++	○	+++	○
AE3	ICN	1:800	+	○	○	○	○	○	F+	○
CAM 5.2	Becton-Dickinson	1:8	+++	+	F+	○	+++	○	+	○
Keratin	Dako	1:1500	+++	+	++	○	++	○	++	○
HMFG 1 & 2	Oxoid	1:600	+++	○	F+	○	+++	○	++	○
CEA	Dako	1:400	++	F+	○	○	+	±	+	+
S100	Dako	1:1500	F±	+++	++	++	F+	+++	○	++
Vimentin	Dako	1:15	F+	++	○	F+	±	+	○	F+
Desmin	Dako	1:50	○	○	○	○	○	○	○	○

Table 2 Clinical findings

Case No	Sex	Age at diagnosis	Clinical presentation	Size (cm)	Initial treatment	Outcome
1	M	62	Left parotid swelling many years; recent growth over 2 months; at operation firm, lobulated tumour superficial lobe	5 × 4 × 3.5	Superficial parotidectomy	DOC 8 yr 7 m NED
2	F	69	Left parotid nodule 6 weeks	3.5 × 3 × 2	Total parotidectomy	DOC 4 m NED
3	F	103	Left submandibular mass 1 year; rapid growth 2 months	6 × 5 × 3	Excision	Recurrence 1 yr 6 m; supra-clavicular lymph node; alive 2 yr 6 m
4	M	71	Left parotid mass 10 years; recent growth 3 months	3.5 × 2.5	Superficial parotidectomy	DOC 2 yr NED

DOC: died of other causes NED: no evidence of disease

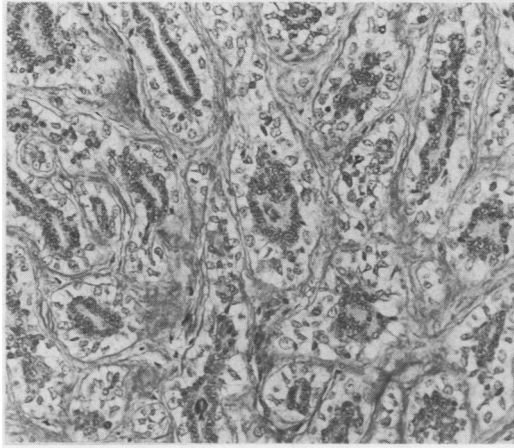


Figure 1 Case 4: classic pattern illustrating ducts lined by inner low columnar cells and an outer mantle of clear cells surrounded by a basement membrane (PAS diastase).

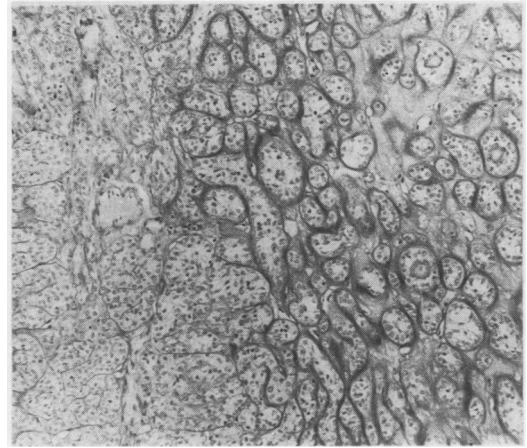


Figure 4 Case 2: transition between clear cell predominant pattern on the left and sclerotic pattern on the right, with thickened basement membranes (PAS diastase).

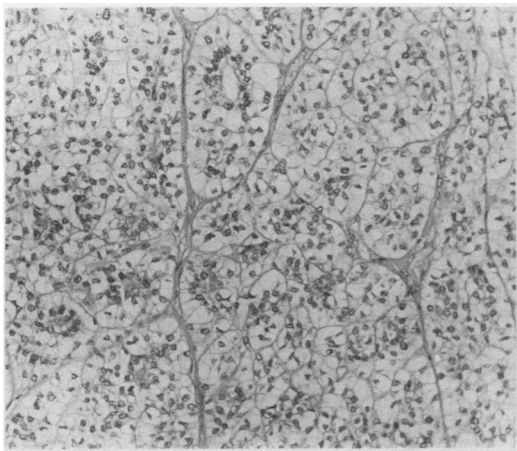


Figure 2 Case 1: clear cell predominant pattern with clear cell-filled alveolar structures, some of which contain small lumina (haematoxylin and eosin).

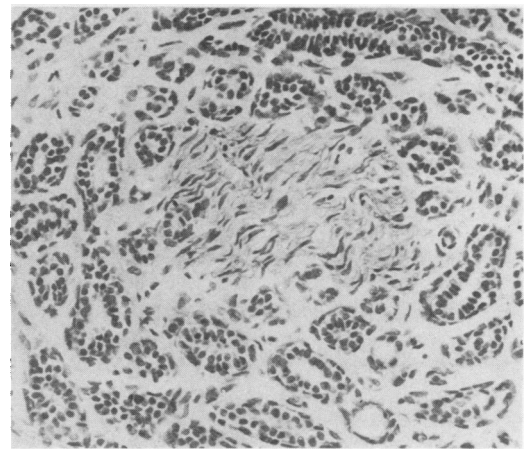


Figure 5 Case 4: invasion of a nerve by tumour. The outer cell layer also shows positive staining (S100 protein).

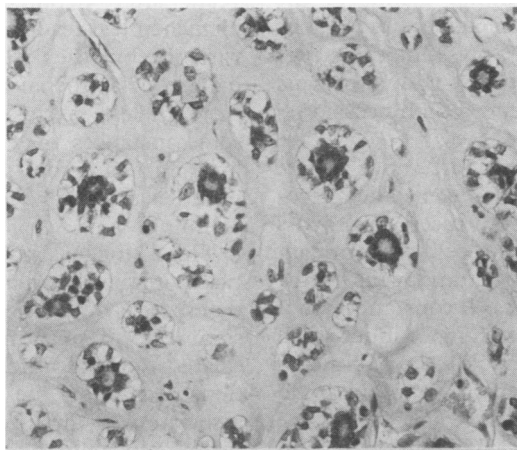


Figure 3 Case 4: sclerotic area, showing relatively sparse double lined ducts separated by hyalinised stroma (haematoxylin and eosin).

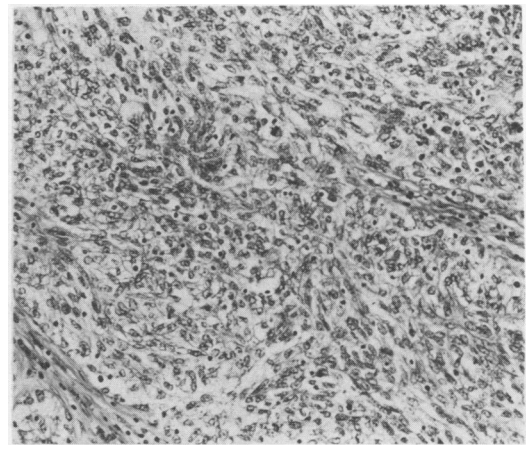


Figure 6 Case 3: recurrence showing a solid mass of cells with increased pleomorphism and mitotic activity (haematoxylin and eosin).

clear cell predominant areas (fig 8), where the inner ductal cells were often difficult to identify. The dedifferentiated areas in the recurrent tumour in case 3 showed a patchy reaction with cytokeratins, HMFG 1 and 2 and CEA, but negative staining for S100 protein and all other markers.

Discussion

Epithelial-myoepithelial carcinoma is a rare tumour accounting for slightly fewer than 1% of salivary gland neoplasms.⁹ Our four cases among 280 salivary tumours (1.4%) indicated a broadly similar relative incidence.

Previous studies have shown that it is some-

Figure 7 Case 3: mainly basal positive staining of the outer cell layer (S100 protein).

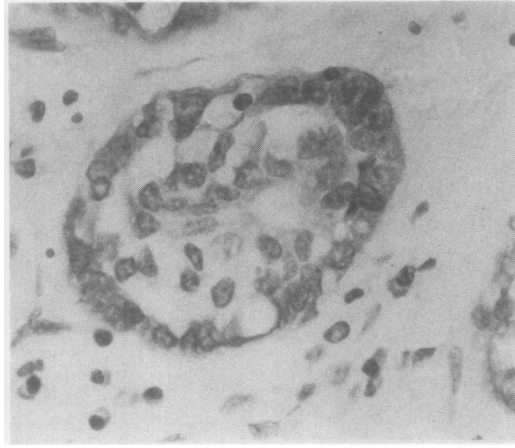
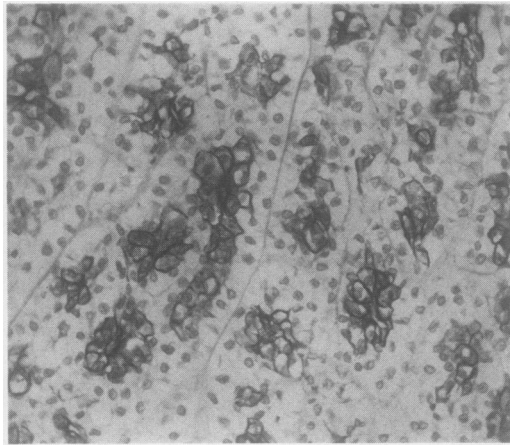


Figure 8 Case 1: positive staining of inner cells in a clear cell predominant area (AE1).



what more prevalent in women, and that the mean age at presentation is about 60 years, with a range of 27 to 103, the latter being our case 3. Most tumours arise in the major salivary glands, especially the parotid, but cases have been described in the minor glands of the mouth, and even in the maxillary sinus.⁸ The history is typically that of a mass enlarging over several months or even years. Pain and facial nerve palsy have been reported on occasion,¹³ but were not noted in our cases.

The tumours are solitary and range in size from 2 to 8 cm maximal diameter. The microscopic appearances, as in our cases, encompass classic, sclerotic, and clear cell predominant patterns, and any particular tumour may show one or more of these zones. A constant feature is the double layer ductal lining of inner small epithelial cells and outer clear myoepithelial cells. Immunohistochemistry can help to identify the two layers when they are morphologically indistinct. We found AE1 and S100 protein to be the best combination of markers for this. Electron microscopical examination has confirmed the inner epithelial and outer myoepithelial differentiation.^{14 15} Although the tumours are locally invasive, they do not exhibit nuclear pleomorphism or a high mitotic rate, an exception being the recurrent tumour in our case 3 which resembled a malignant spindle cell myoepithelioma.¹⁶

The morphological features of epithelial-myoeplithelial carcinoma are generally quite distinct from other salivary tumours. Mono-

morphic or pleomorphic adenomas do not invade locally, and the latter often contain abundant alcian blue positive stromal mucin. Salivary duct adenocarcinoma⁸ is aggressive and resembles ductal carcinoma of the breast. Terminal duct carcinoma⁸ (or polymorphous low grade adenocarcinoma) is a locally invasive tumour arising almost always in minor salivary glands, and is characterised by cytological uniformity and histological diversity; single-lined ducts often with intraluminal papillae are typical, but a biphasic ductal lining is not a feature.

The clear cell predominant pattern of epithelial-myoeplithelial carcinoma, however, can be confused with other clear cell tumours. Monomorphic clear cell carcinoma is found in minor salivary glands and lacks S100 positive myoeplithelial differentiation.¹⁷ The clear cells of mucoepidermoid carcinoma contain neutral epithelial mucin (PAS positive), and squamous differentiation is also, by definition, a feature of these tumours. Sebaceous carcinoma is composed of "foamy," lipid-rich clear cells, and sometimes intracytoplasmic mucin.¹⁸ A salivary gland oncocytoma may be composed largely of clear cells, although scattered typical oncocytes are usually present to betray its true nature. The clear cells often have faintly granular cytoplasm with some diastase resistant PAS positive granules, and numerous mitochondria are seen on electron microscopical examination.¹⁹ The clear cells in some acinic cell carcinomas are generally considered to represent a fixation artefact, and it is not thought that a true clear cell variant exists^{20 21} as a careful search will show foci with the characteristic secretory granules of normal acinar cells. A parotid mass may be the first manifestation of metastatic carcinoma, particularly from the kidney, and this can also occur up to nine years after nephrectomy.²² The immunohistochemical reactions of renal carcinoma are variable, but they will not show the biphasic pattern of epithelial-myoeplithelial carcinoma. Nevertheless, exclusion of this possibility in some instances may still require the use of imaging techniques such as abdominal ultrasound examination and computed tomography scanning.

The histogenesis of epithelial-myoeplithelial carcinoma is uncertain. It has been suggested that there is bidirectional differentiation from a stem cell to form myoeplithelial and intercalated ductal epithelial cells.¹⁵ Our observations highlight the constant and intimate association of these two cell types, but do not further elucidate the histogenesis.

Although originally thought to be benign, it is now apparent that epithelial-myoeplithelial carcinoma is a genuine low grade malignancy. In a review of 35 cases⁸ 37% had recurrences and 17% lymph node metastases. Three patients developed distant metastatic spread and died nine months, 10 years, and 27 years after initial diagnosis.

Information on the effectiveness of different treatments is scanty. In one series of nine patients¹⁵ seven were initially treated by surgical excision alone and five later developed

one or more recurrence. In contrast, both patients treated with surgical excision plus immediate postoperative radiotherapy remained tumour free after nine years. In the present study all four patients were treated with surgical excision, including the one who later had a recurrence. Of the other three, only one had received a course of radiation shortly after surgery.

The prognostic value of other factors is also not established. The histological differentiation (cellular anaplasia and mitotic activity) is said not to matter,⁹ but tumour size may. In one series⁹ the recurrence rate was higher in tumours larger than 4 cm. In another¹⁵ none of the tumours smaller than 3 cm in maximum diameter recurred, while all the larger ones did. Among our cases the recurrence happened in the largest tumour, but in case 1, a carcinoma of 5 × 4 × 3.5 cm failed to recur in over eight and a half years (initial treatment included radiotherapy).

In conclusion, epithelial-myoepithelial carcinoma of salivary glands is a low grade malignancy with a distinct histological appearance. It deserves wider recognition.

We are most grateful to Messrs P Beasley, A J Knox, and T T Irvin, and Drs A H Ridler, M J W Slot, and J A G Benson for additional clinical information on their patients. We also thank all the technical staff of the Histopathology Department in Exeter, especially Brian Moores, Farid Moshtael, and Derek Boustred. We are also most grateful to Louise Parkhouse for secretarial help.

- 1 Thackray AC, Sobin LH. Histological typing of salivary gland tumours. *International Histological Classification of Tumors No 7*. Geneva: World Health Organisation, 1972.
- 2 Donath K, Seifert G, Schmitz R. Zur diagnose und ultrastruktur des tubulären speichelgangcarcinoms: epithelial-myoepitheliales schaltstückcarcinom. *Virchows Arch (Pathol Anat)* 1971;356:16-31.
- 3 Corridan M. Glycogen-rich clear-cell adenoma of the parotid gland. *J Pathol Bacteriol* 1956;72:623-6.
- 4 Feyrter F. Über das glykogenreiche retikulierte adenom der speicheldrüsen. *Zeitschrift für Krebsforschung* 1963; 65:446-54.
- 5 Saksela E, Tarkkanen J, Wartiovaara J. Parotid clear-cell adenoma of possible myoepithelial origin. *Cancer* 1972; 30:742-8.
- 6 Goldman RL, Klein HZ. Glycogen-rich adenoma of the parotid gland: an uncommon benign clear-cell tumor resembling certain clear-cell carcinomas of salivary origin. *Cancer* 1972;30:749-54.
- 7 Thackray AC, Lucas RB. Tumors of the major salivary glands. *Atlas of Tumor Pathology. 2nd series. Fascicle 10*. Washington, DC: Armed Forces Institute of Pathology, 1974:62-3.
- 8 Luna MA, Batsakis JG, Ordóñez NG, Mackay B, Tortoledo ME. Salivary gland adenocarcinomas: a clinicopathologic analysis of three distinctive types. *Semin Diagnost Pathol* 1987;4:117-35.
- 9 Hamper K, Brugmann M, Koppermann R, et al. Epithelial-myoepithelial duct carcinoma of salivary glands: a follow-up and cytophotometric study of 21 cases. *J Oral Pathol* 1989;18:299-304.
- 10 Main JHP, Orr JA, McGurk FM, McComb RJ, Mock D. Salivary gland tumors: review of 643 cases. *J Oral Pathol* 1976;5:88-102.
- 11 Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. *J Pathol* 1985;146: 51-8.
- 12 Palmer RM. Epithelial-myoepithelial carcinoma: an immunocytochemical study. *Oral Surg Oral Med Oral Pathol* 1985;59:511-15.
- 13 Daley TD, Wysocki GP, Smout MS, Slinger RP. Epithelial-myoepithelial carcinoma of salivary glands. *Oral Surg* 1984;57:512-19.
- 14 Luna MA, Ordóñez NG, Mackay B, Batsakis JG, Guillaumondegui O. Salivary epithelial-myoepithelial carcinomas of intercalated ducts: a clinical, electron microscopic, and immunocytochemical study. *Oral Surg Oral Med Oral Pathol* 1985;59:482-90.
- 15 Corio RL, Sciubba JJ, Brannon RB, Batsakis JG. Epithelial-myoepithelial carcinoma of intercalated duct origin: a clinicopathologic and ultrastructural assessment of sixteen cases. *Oral Surg* 1982;53:280-7.
- 16 Dardick I, van Nostrand AWP. Myoepithelial cells in salivary gland tumors—revisited. *Head Neck Surg* 1985;7:395-408.
- 17 Simpson RHW, Sarsfield PTL, Clarke TJ, Babajews AV. Clear cell carcinoma of minor salivary glands. *Histopathol* 1990;17:433-8.
- 18 Batsakis JG, El-Naggar AK. Pathology consultation: sebaceous lesions of salivary glands and oral cavity. *Ann Otol Rhinol Laryngol* 1990;99:416-18.
- 19 Ellis GL. "Clear cell" oncocytoma of salivary gland. *Hum Pathol* 1988;19:862-7.
- 20 Echevarria RA. Ultrastructure of the acinic cell carcinoma and clear cell carcinoma of the parotid gland. *Cancer* 1967;20:563-71.
- 21 Batsakis JG. Clear cell tumors of salivary glands. *Ann Otol* 1980;89:196-7.
- 22 Melnick SJ, Amazon K, Dembrow V. Metastatic renal cell carcinoma presenting as a parotid tumor: a case report with immunohistochemical findings and a review of the literature. *Hum Pathol* 1989;20:195-7.