Malignant fibrous histiocytomas of salivary glands

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SUMMARY The light microscopic, immunohistological and ultrastructural findings in two cases of malignant fibrous histiocytoma arising in salivary glands are presented and the features of seven previously reported cases are reviewed. This neoplasm is extremely rare in this site and may pose problems in diagnosis. It has to be distinguished from other spindled cell tumours, in particular from epithelial tumours of predominantly spindled cell pattern; immunohistological markers for histiocytic cells may be of value. The histogenesis of this neoplasm is controversial but our electron microscopic findings support an origin from mesenchymal cells which differentiate along a broad fibrohistiocytic spectrum.

Mesenchymal tumours of the salivary glands are rare and constitute < 5% of all primary salivary gland neoplasms in adults. Lipomas, haemangiomomas, lymphangiomomas, neurofibromas and neurilemmomomas form the bulk of these uncommon salivary gland tumours and malignant mesenchymal neoplasms of the salivary glands are of extreme rarity.

We report here two recently encountered examples of malignant fibrous histiocytoma arising in salivary glands, one occurring in the parotid gland and the other involving the submandibular gland.

Material and methods

Formalin-fixed, paraffin-embedded sections of biopsy material were stained with haematoxylin and eosin, Masson's trichrome, reticulin, Perls' stain, elastic van Gieson, periodic acid-Schiff (PAS), PAS after diastase digestion and phosphotungstic acid haematoxylin.

Staining for lysozyme (muramidase), alpha-1-antitrypsin (α,AT) and alpha-1-antichymotrypsin (α,ACT), used as histiocytic markers, was performed using the immunoperoxidase (PAP) technique. All antisera were obtained from Dako (Mercia Brocades, Surrey) and appropriate positive and negative controls were incorporated. Four randomly selected cases of fibrous histiocytoma occurring in other locations and four spindled cell variants of mixed salivary adenoma were also studied for these markers.

Tissue for electron microscopy had to be retrieved from paraffin-embedded blocks in both cases. Selected areas were dewaxed, post-fixed in osmium tetroxide and processed by standard methods. Ultrathin sections were stained with uranyl acetate and lead citrate and viewed with a Philips EM 301 electron microscope.

Case reports

CASE 1

A 28-year-old woman presented in May 1981 with a swelling in the left preauricular region of six months' duration. It had been an incidental finding on self palpation and there were no related symptoms. Examination revealed a poorly defined swelling 1-0 cm in diameter in the region of the left parotid gland. It was deeply fixed with no skin tethering and was not tender. The remainder of the physical examination was normal as were results of routine investigations.

A presumptive diagnosis of mixed salivary adenoma was made and exploration of the parotid gland and superficial parotidectomy carried out. A small branch of the facial nerve was found entrapped within the tumour and had to be sacrificed. Postoperatively she developed left sided facial paraesthesia and ptosis due to weakness of the orbicularis oculi; this however improved within a few days. At follow-up five months later there was no recurrence or lymphadenopathy.

Pathology

The resected parotid lobe measured 2 × 2 × 1 cm and was partially replaced by firm, grey white tissue.
Malignant fibrous histiocytomas of salivary glands

Microscopically a rim of normal parotid tissue surrounded a well defined but non-encapsulated spindled cell tumour. The spindled cells formed interlacing fascicles and whorls with a well marked storiform pattern in many areas (Fig. 1). A variable amount of collagenous stroma was present, most abundant at the periphery. Centrally the tumour was more cellular and the spindled cells much plumper. Scattered throughout the tumour, but predominant centrally, were multinucleated tumour giant cells often with a Touton-like appearance (Fig. 2). Slit-like vascular spaces were prominent in the central portion of the tumour and there was marked extravasation of red blood cells. Haemosiderin pigment, identified by iron stains, was abundant in this area. Mitotic figures were noted but the overall mitotic activity was low. At its margins the tumour infiltrated parotid tissue and there were focal lymphoid aggregates. A few residual ducts were entrapped within the tumour in this area but multiple sections did not reveal epithelial elements elsewhere in the tumour.

Immunoperoxidase studies showed granular brown staining for lysozyme, α₁AT and α₁ACT in tumour giant cells and in plump spindled cells in the central portion of the tumour. Spindled cells at the periphery of the tumour were mostly negative.

Electron microscopy

Tissue preservation was not optimal for electron microscopy but several cell types could be identified. Fibroblast-like cells were the most numerous and possessed indented nuclei and elongated cytoplasmic extensions. They contained abundant rough endoplasmic reticulum (RER), often with dilated...
cisternae filled with floccular material but other organelles were scanty (Fig. 3). Another cell type present had moderate amounts of RER and many compact bundles of myofilaments in their cytoplasm. Focal densities were present in some of these myofilament aggregates. Attachment plates were noted along the cell margins and were often associated with basal lamina-like material. These cells were interpreted as myofibroblasts and cells showing myogenic differentiation; typical smooth muscle cells were however, not found. Histiocyte-like cells had reniform nuclei and their cytoplasm contained a few cisternae of RER, free ribosomes, lysosomal bodies and empty fat vacuoles. Occasionally, cells showing features of both fibroblasts and histiocytes (fibrohistiocytes) were encountered. There were also a number of small cells with smooth cell surfaces, round nuclei and relatively clear cytoplasm in which organelles were very scanty (Fig. 4). These were considered to be undifferentiated mesenchymal cells. The extracellular space contained extravasated erythrocytes and collagen of normal periodicity.

CASE 2
A 65-year-old man with hepatosplenomegaly and a white cell count of 166 × 10⁹/l was diagnosed as having chronic lymphatic leukaemia (CLL) in March 1980. He was treated with prednisolone and cyclophosphamide and showed gradual clinical improvement. Four months later he presented with a swelling in the left submandibular region which had been rapidly enlarging over two months. He had first noticed a swelling in that area two years previously; it had decreased in size but apparently not completely disappeared with a course of antibiotics. His past medical history also included a basal cell carcinoma of the nose, successfully treated by radiotherapy in 1979, and herpes zoster at the level of D₂, the same year.

The submandibular swelling measured 5 cm in diameter and was extremely tender. The clinical impression was of a leukaemic deposit or lymphomatous transformation of CLL (Richter's syndrome). On surgical exploration a tumour mass was found within the submandibular salivary gland and the gland which was adherent to the mandible was

Fig. 3 Case 1: electron micrograph showing two fibroblast-like cells with irregular nuclei, elongated cytoplasmic extensions and abundant RER. Extravasated erythrocytes lie in the extracellular space. × 6250.
Excised. After surgery the mass recurred and he suffered considerable pain. A course of radiotherapy six weeks after the operation relieved the pain and produced some diminution of tumour size. A month later the mass was enlarging again and measured 12 x 10 cm; it now involved the left side of his face and also extended across the midline below the chin. There was skin ulceration and ulceration into the floor of the mouth. Antibiotics and chemotherapy with intravenous carminomycin produced little improvement. A chest x-ray at this time revealed an opacity considered to be a metastatic deposit in the midzone of the right lung. Terminally the tumour spread to involve the lips, mouth and right side of his face. The patient died at home with no identifiable acute event in January 1981. A necropsy was not performed.

Pathology
The excised submandibular salivary gland measured 7 x 5 x 4 cm. On section there was loss of the normal lobular pattern and replacement by grey haemorrhagic tissue surrounding a central necrotic and cystic area. Histologically a pleomorphic spindled cell tumour largely replaced the glandular parenchyma. A storiform pattern was evident in focal areas and there were frequent multinucleated tumour giant cells with abundant, eosinophilic cytoplasm (Fig. 5). Mitotic figures, often abnormal, were numerous. Small areas of necrosis were scattered throughout the tumour. At the periphery the tumour merged with residual ducts and acini of salivary gland tissue. A moderate degree of neutrophil polymorphonuclear and lymphocytic infiltration was present throughout the tumour. Trichrome stains demonstrated a variable production of collagen fibres.

Immunoperoxidase stains revealed coarse, brown granular staining for α,AT and α,ACT in both spindled and giant cells in several areas of the tumour (Fig. 6). With lysozyme finely granular staining was seen in only a few cells in focal areas of the tumour. Neutrophil polymorphs present stained strongly for lysozyme and α,AT.

Electron microscopy
Ultrastructurally the tumour was composed of a variable cell population, as in case 1. Histiocyte-like cells were abundant and had irregular nuclei with large nucleoli and peripheral heterochromatin. The

Fig. 4 Case 1: an undifferentiated cell with round nucleus and clear cytoplasm containing scanty organelles. A fibroblast-like cell to the right contains floccular material within dilated RER. × 11 250.
Benjamin, Wells, Fox, Reeve, Knox

cytoplasm contained numerous lysosomal bodies of varying size, fat vacuoles, laminated myelin figures and coiled RER (Fig. 7). Their cell borders had complex interdigitating processes. In occasional cells the cytoplasm was almost entirely filled by coalescent fat vacuoles producing a "foamy" (xanthomatous) appearance (Fig. 8). Fibroblast-like cells had lobulated nuclei, frequent nucleoli, abundant RER and a few fine cytoplasmic filaments. Undifferentiated cells similar to those in case 1 were also present as were fibrohistiocytes of rather immature appearance having variable amounts of RER, free ribosomes, lysosomal bodies and occasional cytoplasmic filaments. Tumour giant cells possessed multiple nuclei with prominent nucleoli, abundant dilated endoplasmic reticulum and a number of mitochondria.

Results of additional immunoperoxidase studies

The four fibrous histiocytomas studied (two subcutaneous malignant tumours, one malignant retroperitoneal tumour and one benign subcutaneous tumour) all showed granular brown staining for lysozyme and $\alpha$-AT in moderate to large numbers of tumour cells. Staining for $\alpha$-ACT was negative in one subcutaneous malignant tumour and in the benign fibrous histiocytoma but positive in the other two tumours.

The spindled cells of all four spindled cell variants of mixed salivary adenoma failed to stain the with lysozyme and $\alpha$-AT. With $\alpha$-ACT a variable number of spindled cells were positive in all tumours. Typical ductal structures, when present, stained positively for $\alpha$-ACT but less frequently for lysozyme and $\alpha$-AT.

Discussion

Seven previous cases of fibrous histiocytoma involving the salivary glands have been reported$^{3-8}$ and the main features of these, together with the two examples reported here, are summarised in the Table. Seven occurred in males and two in females, the ages of the patients ranging from 16 months to 69 yr: the maximum incidence was in the 6th and 7th decades. The time for which a mass had been present before surgical exploration varied from 6 wk to 30 yr and the parotid gland was the more common location than the submandibular gland (2:1). Four of these tumours were considered to be definitely malignant and three of these subsequently recurred: two also metastasised to the lungs and one patient (case 2 in our report) died at 5 months.

Case 2 of this report is of particular interest in that the patient had three malignant neoplasms diag-
Malignant fibrous histiocytomas of salivary glands

nosed over an 18-month period, a basal cell carcinoma, chronic lymphatic leukaemia and a malignant fibrous histiocytoma. Weiss and Enzinger,9 in their analysis of 200 cases of malignant fibrous histiocytoma, found that a second tumour occurred in 13% of cases; most of these were carcinomas but one patient developed acute myeloid leukaemia. It is also known that death from other malignant disease is common in cases of chronic lymphatic leukaemia and that the incidence is higher than can be accounted for by the predominance of elderly patients and may in fact be related to immunodeficiency.10 Lymphomatous transformation of chronic lymphatic leukaemia (Richter’s syndrome), characterised by a pleomorphic lymphoid infiltrate with tumour giant cells, had to be distinguished from malignant fibrous histiocytoma in this patient.

Considerable controversy surrounds the histogenesis of fibrous histiocytoma. The original concept that this family of neoplasms was derived from a tissue histiocyte which has the capacity to evolve into fibroblasts was based on histological and tissue culture studies.11 However, it is known that any tissue culture of mesenchymal cells can eventually transform into a fibroblastic culture12 and Alguacil-Garcia et al13 contend that in vitro transformation between cell types do not prove their origin but merely that they can assume alternate forms under certain conditions.

Perhaps the most impressive evidence to date for the histiocytic theory of origin of fibrous histiocytomas is that of a transplantable tumour in mice with the characteristic morphological features. This tumour has been shown to originate from peritoneal macrophages which have been thoroughly identified as histiocytes on the basis of histochemical, immunohistochemical, functional and ultrastructural studies.14

An alternative theory of histogenesis is that the neoplasm is derived from an undifferentiated mesenchymal cell which differentiates along a broad fibroblastic and histiocytic spectrum reflected by collagen synthesis and, occasionally, phagocytosis. Several recent electron microscopic studies have demonstrated in these tumours the presence of fibroblast-like, histiocyte-like, fibrohistiocytic and undifferentiated cells13 15-17 and it has been postulated that the mesenchymal stem cell may pass
Fig. 8  Case 2: part of a xanthomatous cell in which the cytoplasm is filled by fat vacuoles. A centriole, some lysosomes and a few mitochondria are also present. An adjacent histiocyte-like cell contains numerous lysosomes. × 22 750

through a stage (fibrohistiocyte) in which features of both main cell types are present. Our electron microscopic findings in both cases of a population of fibroblast-like, histiocyte-like, fibrohistiocytic and undifferentiated cells would support this theory, although morphology alone would be insufficient to prove it. In addition, cells showing myogenic differentiation were present in case 1. Myofibroblasts and cells showing myogenous features have been described in previous electron microscopic

Reported cases of salivary gland fibrous histiocytomas

<table>
<thead>
<tr>
<th>Author/case</th>
<th>Sex and age (yr)</th>
<th>Duration of mass</th>
<th>Location &amp; size of gland</th>
<th>Histological diagnosis</th>
<th>Initial treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Brien &amp; Stout (3)</td>
<td>M-69</td>
<td>30 yr</td>
<td>Submandibular 4-5 × 3-5 × 2 cm</td>
<td>Storiform fibrous xanthoma</td>
<td>Excision gland</td>
<td>Well at 5 months</td>
</tr>
<tr>
<td>O'Brien &amp; Stout (3)</td>
<td>M-65</td>
<td>5 months</td>
<td>Parotid 3-2 × 2-2 × 1-7 cm</td>
<td>Mixed fibrous xanthoma</td>
<td>Excision gland and neck nodes</td>
<td>Well at 9 months</td>
</tr>
<tr>
<td>Junaid et al (4)</td>
<td>M-50</td>
<td>2 yr</td>
<td>Right parotid 4-5 × 3-5 × 3 cm</td>
<td>Dermatofibrosarcoma protruberans of parotid</td>
<td>Partial parotidectomy</td>
<td>Recurrence at 6 yr with skin infiltration</td>
</tr>
<tr>
<td>Blitzer &amp; Lawson (5)</td>
<td>M-54</td>
<td>Not known</td>
<td>Right submandibular (size not known)</td>
<td>Malignant fibrous histiocytoma</td>
<td>Excision gland</td>
<td>Two recurrences and lung metastasis in 2 yr Well at 5 months</td>
</tr>
<tr>
<td>Nilsen &amp; Lind (6)</td>
<td>F-53</td>
<td>5 yr</td>
<td>Right parotid 2 × 2 cm</td>
<td>Benign fibrous xanthoma</td>
<td>Superficial parotidectomy</td>
<td>Not known</td>
</tr>
<tr>
<td>Shapshay et al (7)</td>
<td>M-16 months</td>
<td>6 wk</td>
<td>Right parotid 3 × 3 cm</td>
<td>Fibrous histiocytoma</td>
<td>Total parotidectomy</td>
<td>Well at 3 yr</td>
</tr>
<tr>
<td>Fayemi &amp; Ali (8)</td>
<td>M-46</td>
<td>&quot;many months&quot;</td>
<td>Left parotid 4 × 3-5 cm</td>
<td>Benign fibrous histiocytoma</td>
<td>Superficial parotidectomy</td>
<td>Well at 5 months</td>
</tr>
<tr>
<td>Present case 1</td>
<td>F-28</td>
<td>6 months</td>
<td>Left parotid 2 × 2 × 1 cm</td>
<td>Malignant fibrous histiocytoma</td>
<td>Superficial parotidectomy</td>
<td>Post-op recurrence and lung metastasis. Died with disease at 5 months</td>
</tr>
<tr>
<td>Present case 2</td>
<td>M-65</td>
<td>2 yr</td>
<td>Left submandibular 7 × 5 × 4 cm</td>
<td>Malignant fibrous histiocytoma</td>
<td>Excision gland</td>
<td></td>
</tr>
</tbody>
</table>
Malignant fibrous histiocytomas of salivary glands

Studies\textsuperscript{13-17,18} and probably represent a variation in mesenchymal differentiation.

Immunoperoxidase studies for lysozyme, $\alpha_1$AT and $\alpha_1$ACT described as markers of histiocytic cells\textsuperscript{19-21} showed positive staining cells in both cases. Staining was also consistently positive for lysozyme and $\alpha_1$AT in four randomly selected cases of fibrous histiocytoma but variable with $\alpha_1$ACT. Meister et al\textsuperscript{22} have studied a larger number of malignant fibrous histiocytomas using lysozyme and $\alpha_1$ACT. They found that staining for lysozyme was more selective but less frequently found whilst $\alpha_1$ACT was not found in all cells which on routine stains were compatible with histiocytes and was sometimes positive in non-histiocytic tumours. In our opinion positive staining with lysozyme and $\alpha_1$AT in combination with other diagnostic criteria, can be helpful in the diagnosis of fibrous histiocytomas. Alpha-1-antichymotrypsin, however, would appear to be an unreliable marker in these tumours.

The salivary gland adenomas of predominantly spindled cell pattern, attributed to the myoepithelial component,\textsuperscript{22} are the tumours for which fibrous histiocytomas are most likely to be mistaken.\textsuperscript{48} Epithelial structures may be scanty and unless multiple sections are taken, may be entirely missed. Four spindled cell variants of mixed salivary tumour studied for histiocytic markers were found to be negative for lysozyme and $\alpha_1$AT in contrast to the fibrous histiocytomas. Therefore in unusual locations, such as the salivary glands, these markers can be particularly useful in differential diagnosis.

Neurilemmoma, neurofibroma and leiomyoma are rare salivary gland tumours which might bear a superficial resemblance to a benign fibrous histiocytoma whilst various sarcomas, including rhabdomyosarcoma and fibrosarcoma, have to be distinguished from malignant fibrous histiocytoma. Electron microscopy has a valuable role to play in the precise diagnosis of these spindled cell neoplasms.

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Malignant fibrous histiocytomas of salivary glands

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