Malignant fibrous histiocytomas of salivary glands

E BENJAMIN, S WELLS, H FOX, NL REEVE, F KNOX

From the Departments of Pathology, University of Manchester, Manchester M13 9PT, and Stepping Hill Hospital, Stockport, Cheshire

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.¹ Lipomas, haemangiomas, lymphangiomas, neurofibromas and neurilemmomas 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_1 AT) and alpha-1-antichymotrypsin (α_1 ACT), used as histiocytic markers, was performed using the immunoperoxidase (PAP) technique.² 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 spindle cell tumour. The spindle 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 spindle 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, α_1 AT and α_1 ACT in tumour giant cells and in plump spindle cells in the central portion of the tumour. Spindle 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

Fig. 2 Case 1: multinucleate giant cells and vascular channels in central part of tumour. Haematoxylin and eosin $\times 460$

Fig. 1 Case 1: malignant fibrous histiocytoma of parotid gland showing a well marked storiform pattern and entrapment of residual ducts by tumour. Haematoxylin and eosin $\times 50$

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. $\times 6250$.*

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 $166 \times 10^9/l$ 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 D₃, 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. 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. $\times 11\,250$.

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 12×10 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 $7 \times 5 \times 4$ 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_1 AT and α_1 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_1 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. 5 Case 2: pleomorphic spindled and tumour giant cells and a diffuse inflammatory cell infiltrate. Haematoxylin and eosin $\times 160$

Fig. 6 Case 2: (a) tumour cells showing coarse granular staining for α_1 ACT. Immunoperoxidase $\times 350$. (b) Granular cytoplasmic staining of tumour giant cells for α_1 AT. Immunoperoxidase $\times 350$

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 α_1 AT in moderate to large numbers of tumour cells. Staining for α_1 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 with lysozyme and α_1 AT. With α_1 ACT a variable number of spindled cells were positive in all tumours. Typical ductal structures, when present, stained positively for α_1 ACT but less frequently for lysozyme and α_1 AT.

Discussion

Seven previous cases of fibrous histiocytoma involving the salivary glands have been reported³⁻⁸ 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-

Fig. 7 Case 2: electron micrograph of a histiocyte-like cell containing lysosomes, empty fat vacuoles and coiled RER. $\times 33\,700$

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 al*¹³ 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 cells¹⁵⁻¹⁷ 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. $\times 22\,750$

through a stage (fibrohistiocyte) in which features of both main cell types are present.¹⁵ 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

Author/ case	Sex and age (yr)	Duration of mass	Location & size of gland	Histological diagnosis	Initial treatment	Follow-up
O'Brien & Stout (3)	M-69	? 30 yr	Submandibular 4.5 $\times$ 3.5 $\times$ 2 cm	Storiform fibrous xanthoma	Excision gland	Well at 5 months
O'Brien & Stout (3)	M-65	5 months	Parotid 3.2 $\times$ 2.2 $\times$ 1.7 cm	Mixed fibrous xanthoma	Excision gland and neck nodes	Well at 9 months
Junaid <i>et al</i> (4)	M-50	2 yr	Right parotid 4.5 $\times$ 3.5 $\times$ 3 cm	Dermatofibrosarcoma protuberans of parotid	Partial parotidectomy	Recurrence at 6 yr with skin infiltration
Blitzer & Lawson (5)	M-54	Not known	Right submandibular (size not known)	Malignant fibrous histiocytoma	Excision gland	Two recurrences and lung metastasis in 2 yr
Nilsen & Lind (6)	F-53	5 yr	Right parotid 2 $\times$ 2 cm	Benign fibrous xanthoma	Superficial parotidectomy	Well at 5 months
Shapshay <i>et al</i> (7)	M-16 months	6 wk	Right parotid 3 $\times$ 3 cm	Fibrous histiocytoma	Total parotidectomy	Not known
Fayemi & Ali (8)	M-46	"many months"	Left parotid 4 $\times$ 3.5 cm	Benign fibrous histiocytoma	Superficial parotidectomy	Well at 3 yr
Present case 1	F-28	6 months	Left parotid 2 $\times$ 2 $\times$ 1 cm	Malignant fibrous histiocytoma	Superficial parotidectomy	Well at 5 months
Present case 2	M-65	2 yr	Left submandibular 7 $\times$ 5 $\times$ 4 cm	Malignant fibrous histiocytoma	Exision gland	Post-op recurrence and lung metastasis. Died with disease at 5 months

Malignant fibrous histiocytomas of salivary glands

studies^{13 17 18} and probably represent a variation in mesenchymal differentiation.

Immunoperoxidase studies for lysozyme, α_1 AT and α_1 ACT described as markers of histiocytic cells¹⁹⁻²¹ showed positive staining cells in both cases. Staining was also consistently positive for lysozyme and α_1 AT in four randomly selected cases of fibrous histiocytoma but variable with α_1 ACT. Meister *et al*²⁰ have studied a larger number of malignant fibrous histiocytomas using lysozyme and α_1 ACT. They found that staining for lysozyme was more selective but less frequently found whilst α_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 α_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,²² are the tumours for which fibrous histiocytomas are most likely to be mistaken.^{4*} 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 α_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.

References

- ¹ Thackray AC, Sobin LH. Histological typing of salivary gland tumours. Geneva: World Health Organisation, 1972;7:25.
- ² Sternberger LA, Hardy PH, Cuculus JJ, Meyer HG. The unlabelled antibody enzyme method of immunohistochemistry. Preparation and properties of the soluble antigen-antibody complex (horseradish peroxidase anti-horseradish peroxidase) and its use in identification of spirochetes. *J Histochem Cytochem* 1970;18:315-33.

- ³ O'Brien JE, Stout AP. Malignant fibrous xanthoma. *Cancer* 1964;17:1445-55.
- ⁴ Junaid TA, Ani AN, Ejeckam GC. Dermatofibrosarcoma protuberans in the parotid gland — a case report. *Br J Oral Surg* 1975;12:298-301.
- ⁵ Blitzer A, Lawson W, Biller HF. Malignant fibrous histiocytoma of the head and neck. *Laryngoscope* 1977;87:1479-99.
- ⁶ Nilsen R, Lind O. Benign fibrous xanthoma of the parotid gland: a case report. *Br J Oral Surg* 1978;79;16:111-4.
- ⁷ Shapshay SM, Wingert RH, Davis JS. Fibrous histiocytoma of the parotid gland. *Laryngoscope* 1979;89:1808-12.
- ⁸ Fayemi AO, Ali M. Fibrous histiocytoma of the parotid gland. *Mt Sinai J Med (NY)* 1980;47:290-2.
- ⁹ Weiss SW, Enzinger FM. Malignant fibrous histiocytoma. An analysis of 200 cases. *Cancer* 1978;41:2250-66.
- ¹⁰ Hoffbrand AV, Lewis SM. *Postgraduate haematology*. 2nd ed. London: William Heinemann Medical Books Ltd, 1981:484.
- ¹¹ Ozello L, Stout AP, Murray MR. Cultural characteristics of malignant histiocytomas and fibrous xanthomas. *Cancer* 1963;16:331-44.
- ¹² Jacob F. *Cells and tissues in culture: methods, biology and physiology*. London and New York: Academic Press, 1965;2:78.
- ¹³ Alguacil-Garcia A, Unni KK, Goellner JR. Malignant fibrous histiocytoma. An ultrastructural study of six cases. *Am J Clin Pathol* 1978;69:121-9.
- ¹⁴ Yumoto T, Morimoto K. Experimental approach to fibrous histiocytoma. *Acta Pathol Jpn* 1980;30:767-78.
- ¹⁵ Fu YS, Gabbiani G, Kaye GI, Lattes R. Malignant soft tissue tumours of probable histiocytic origin (malignant fibrous histiocytomas): general considerations and electron microscopic and tissue culture studies. *Cancer* 1975;35:176-98.
- ¹⁶ Taxy JB, Battifora H. Malignant fibrous histiocytoma. An electron microscopic study. *Cancer* 1977;40:254-67.
- ¹⁷ Harris M. The ultrastructure of benign and malignant fibrous histiocytomas. *Histopathology* 1980;4:29-44.
- ¹⁸ Churg AG, Kahn LB. Myofibroblasts and related cells in malignant fibrous and fibrohistiocytic tumours. *Hum Pathol* 1977;8:205-18.
- ¹⁹ Mason DY, Taylor CR. The distribution of muramidase (lysozyme) in human tissues. *J Clin Pathol* 1975;28:124-32.
- ²⁰ Meister P, Konrad EA, Nathrath W, Eder M. Malignant fibrous histiocytoma: histological patterns and cell types. *Pathol Res Pract* 1980;168:193-212.
- ²¹ Isaacson P, Jones DB, Millward-Sadler GH, Judd MA, Payne S. Alpha-1-antitrypsin in human macrophages. *J Clin Pathol* 1981;34:982-90.
- ²² Merino MJ, Li Volsi VA. Pleomorphic adenomas of the parotid gland resembling mesenchymal tumours. *Oral Surg* 1977;44:405-10.

Requests for reprints to: Professor H Fox, Department of Pathology, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, England.