Osteoclast-type giant cell tumour of the pancreas

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SUMMARY A case of osteoclast-type giant cell tumour of the pancreas is described and the features of eight other previously reported patients are reviewed. Characteristically, these neoplasms are large at presentation and show focal haemorrhage and necrosis, but seem slow to give rise to metastases. Histological examination reveals numerous osteoclast-like giant cells set in a sarcomatous stroma, the appearances being similar to those seen in giant cell tumours of bone. They are distinct from pleomorphic giant cell carcinomas of the pancreas and may have a slightly better prognosis after resection than ordinary adenocarcinomas. The histogenesis of these rare tumours is unknown.

Primary neoplasms containing numerous osteoclast-like giant cells and bearing a striking histological resemblance to giant cell tumours of bone have been reported in various organs and tissues other than the skeletal system, but they are rare.¹⁻¹¹ Rosai¹² was the first to describe osteoclast-type giant cell tumours in the pancreas, (two cases), since when, to our knowledge, only six other examples have been reported in the literature.¹³⁻¹⁷ Two of the studies have included electron microscopical examinations^{12,16} and these are contradictory in terms of the ultrastructural features observed and the interpretation of the histogenesis. We present a ninth case of this tumour which we also studied with the electron microscope.

Case report

A 55-year-old Caucasian man presented with a two week history of fever and weight loss followed by obstructive jaundice. Ultrasound examination revealed common bile duct obstruction which was shown on endoscopic retrograde cholangiopancreatography to be due to extrinsic compression.

At laparotomy, a firm tumour was palpable in the head of the pancreas and this was locally invasive. A needle biopsy was taken. No metastatic spread to the peritoneum, liver or lymph nodes was discerned. Only bypass surgery was considered feasible and a cholecystojejunostomy was fashioned.

The patient remained well for four months when he again developed obstructive jaundice with anorexia and anaemia. Palliative treatment was

given including transfusion and insertion of a common bile duct catheter. Five weeks later he developed ascites, recurrent gastrointestinal bleeding and anaemia. He died seven months from the date of presentation.

At necropsy the head of the pancreas was found to be replaced by a firm tumour 10 cm in diameter which was occluding the pancreatic duct and infiltrating through the adjacent duodenal wall. The cholecystojejunostomy was occluded by fibrosis but the common bile duct catheter was patent.

The liver showed several circumscribed deposits of metastatic tumour measuring up to 2 cm in diameter. No other evidence of metastatic spread was found on naked-eye examination.

Material and methods

The needle biopsy specimen and representative necropsy blocks of the tumour and liver metastases were fixed in 10% formol saline and embedded by routine techniques in paraffin wax. Sections were stained with haematoxylin and eosin and selected sections with periodic acid Schiff (PAS), PAS/diastase, alcian blue, mucicarmine, phosphotungstic acid haematoxylin (PTAH) and Gordon and Sweet's reticulin. Frozen sections of formalin-fixed tissue were stained with Oil-Red-O.

For electron microscopy small pieces of the formalin-fixed necropsy blocks were post fixed in glutaraldehyde followed by osmium tetroxide and block-stained with uranyl acetate. Dehydration was performed through graded acetones to propylene oxide and the blocks embedded in Spurr resin. Sections (1 μ m) were stained with toluidine blue.

Fig. 1 Photomicrograph of pancreatic tumour showing osteoclast-type multinucleated giant cells and pleomorphic stromal cells. Haematoxylin and eosin $\times 300$.

Ultrathin sections were collected on copper grids, stained with Reynold's lead citrate and carbon coated before being viewed in a Philips 300 electron microscope.

Results

LIGHT MICROSCOPY

The tumour was composed of multinucleate giant cells in a stroma of pleomorphic spindle cells (Fig. 1). The giant cells had abundant eosinophilic cytoplasm and between five and 40 nuclei.

The nuclear chromatin was finely distributed and one or two prominent nucleoli were present. No mitoses were found in these cells and they closely resembled osteoclasts in appearance. A few of the stromal cells showed similar features to the giant cells except for the presence of a single nucleus but many were oval or spindle-shaped with enlarged, hyperchromatic nuclei and occasional mitotic figures. Prominent areas of necrosis and haemorrhage were present within the tumour. Examination of multiple blocks revealed no evidence of adenocarcinoma anywhere in the neoplasm and there were no foci of calcification nor bone formation. The cytoplasm of the osteoclast-like giant cells and of a few stromal cells showed weak, patchy positivity with PAS, PAS/diastase and alcian blue.

The stromal background was also slightly alcian blue positive. Mucicarmine and PTAH were negative. The Oil-Red-O stain for neutral fat showed occasional positive droplets within the cytoplasm of a few giant cells. There was a rich reticulin network in the tumour, with fine fibrils surrounding single and small groups of cells.

Tumour was found in three small lymph nodes adjacent to the head of the pancreas and these metastases and those in the liver were histologically the same as the primary tumour.

The needle biopsy taken at laparotomy showed an infiltrating malignant tumour which at the time had proved impossible to classify. Review of the sections after the necropsy showed the appearance to be similar to the stromal component of the neoplasm and a few small osteoclast-like giant cells were also found.

ELECTRON MICROSCOPY

As expected from necropsy material, preservation was very poor but it could be seen that the giant cell cytoplasm contained large numbers of mitochondria, many of which exhibited dense granules in their matrix, and moderate amounts of rough endoplasmic reticulum (RER) (Fig. 2). Occasional dilated cisternae of RER contained fluffy electron dense material but no clearly defined granules were

Fig. 2 Electron micrograph of part of a multinucleate giant cell showing cytoplasm containing numerous mitochondria with dense matrix granules (large arrows). Small profiles of RER are also seen (thin arrows). N = nuclei. $\times 14\,000$.

identified. No microvilli or ruffled membranes were seen but at the edge of one cell an amorphous zone of cytoplasm was noted (Fig. 3). The stromal cells in the area examined had similar ultrastructural cytoplasmic appearances to the giant cells. No desmosomes were found between the cells.

Discussion

Giant cell tumours of the pancreas in which the giant cells appear benign and resemble osteoclasts should be distinguished from pleomorphic carcinomas containing bizarre multinucleated giant cells.¹⁴⁻¹⁸ These two types of tumour have been somewhat confused in the literature¹³⁻¹⁹⁻²⁰ but it appears that there are eight other well documented osteoclast-type giant cell tumours. The features of our case and of these eight are summarised in Tables 1 and 2.

Microscopically all these tumours showed a remarkable resemblance to giant cell tumours of bone with the osteoclast-like giant cells being set in a pleomorphic sarcomatous stroma. Focal haemor-

rhage was noted in all the tumours and similar results were obtained with special stains where these were performed. The giant cells showed weak patchy staining with alcian blue, PAS and PAS/diastase but mucicarmine staining was negative. Occasional fat droplets were found in cells adjacent to areas of necrosis and there was a prominent reticulin network around the tumour cells.

Cases 1 and 7 were studied with the electron microscope.¹²⁻¹⁶ In case 1 both the giant cells and the stromal cells showed plentiful RER with dilated cisternae containing dense granules of protein. Microvilli were present on the surface of the giant cells and numerous desmosomes were seen between the stromal cells. These features were interpreted as indicating that the tumour derived from pancreatic acinar cells.¹² In contrast, in case 7, the most prominent feature in the giant cell cytoplasm was the presence of numerous mitochondria. The RER was much less conspicuous and the cell surfaces showed ruffled membranes. Two types of stromal cells were identified; type A had a structure similar to the giant

Fig. 3 Amorphous area of cytoplasm at edge of giant cell (arrows). ×22 000.

Table 1 Osteoclast-type giant cell tumours of pancreas

Case	Author	Age (yr)	Sex	Site of tumour	Presenting complaints
1	Rosai (1968)	82	F	Tail	Fatigue; weight loss; abdominal mass
2	Rosai (1968)	74	F	Head	Anorexia; weight loss; gastrointestinal bleeding
3	Freund (1973)	32	F	Head	Jaundice; abdominal pain; vomiting
4	Cubilla and Fitzgerald (1979)	45	M	Head	Not given
5	Alguacil-Garcia and Weiland (1977)	49	M	Head	Abdominal pain; anorexia
6	Alguacil-Garcia and Weiland (1977)	95	F	Not given	Not given
7	Robinson, Damjenov and Brezina (1977)	63	M	Not given	Abdominal mass
8	Posen (1981)	45	F	Body and tail	Abdominal pain; vomiting
9	This report	55	M	Head	Jaundice; weight loss

cells and type B resembled fibroblasts. Only occasional desmosomal junctions were seen. These authors note the similarities between these ultrastructural features and those described for giant cell tumours of bone.¹⁶

The EM findings in our case most closely resemble those of Robinson *et al.*,¹⁶ with prominent mitochondria in both giant cells and stromal cells. Although no ruffled borders were identified this could be attributed to the late fixation of this autopsy material. The amorphous zone (Fig. 3) noted in one cell could represent the homogeneous layer free of organelles which is seen in osteoclasts and in the giant cells of giant cell tumours of bone.²¹

Extraskelatal osteoclast-type giant cell tumours have been described in a number of other sites including soft tissue,^{5,6} heart,⁴ orbit³ myometrium^{9,11} and dermis² as well as in several sites in which epithelial tumours predominate including breast,¹ thyroid⁸ and colon.⁷ The histogenesis of such tumours occurring in the pancreas, and in other sites, is unknown.

Some authors have suggested that they derive from epithelium,^{12,15,17} whilst others favour an origin from some mesenchymal cell.¹³ The EM features found by Robinson *et al.*¹⁶ and ourselves certainly resemble those of giant cell tumours of bone. However, this does not preclude an epithelial origin for

Osteoclast-type giant cell tumour of the pancreas

Table 2 Osteoclast-type giant cell tumours of pancreas

Case	Size of tumour	Extent of extrapancreatic spread at laparotomy	Treatment	Clinical course
1	10.5 × 12 × 13 cm	Stomach, splenic and mesenteric veins. Microscopically, tumour in 2 of 16 parapancreatic nodes	Subtotal pancreatectomy, splenectomy	Alive and well 4 months postoperatively
2	7.5 × 8 × 4 cm	Duodenum	Whipples	Alive and well 10 months postoperatively
3	7 cm diam	None	Pancreatico-duodenectomy	Died 17 months after presentation. Local recurrence at necropsy. No lymph node, liver or distant metastases
4	7 × 6 cm	None	Whipples	Developed pulmonary metastases. Died after 4 years. No necropsy.
5	8 cm diam	None	Total pancreatectomy	Alive and well 15 years postoperatively
6	Large	Not given	Exploration and biopsy only	Died 10 months after presentation. No necropsy
7	15 cm diam	Posterior abdominal wall	Biopsy then radiation therapy	Developed pulmonary metastases. Died 4½ months after presentation. No necropsy
8	Giant cell tumour was a 4 cm diam nodule within a 14 cm diam cystadenocarcinoma	Giant cell tumour component was partially encapsulated and confined to pancreas	Resection of tumour	Still alive at time of case report; length of follow up not given
9	10 cm in diam	Duodenum	Palliative cholecysto-jejunostomy	Died 7 months after presentation. Large pancreatic tumour extending into duodenum. Microscopic tumour deposits in parapancreatic lymph nodes and multiple liver metastases at necropsy.

the neoplasm since mesenchymal differentiation has been shown in epithelial tumours such as spindle cell squamous carcinomas.²² On the other hand, the ultrastructural features observed by Rosai¹² cannot be regarded as specific for epithelial tumours. Microvilli have been observed in giant cell tumours of bone^{23,24} and electron dense condensations in RER cisternae have been described in a number of situations including the stromal cells of osteogenic sarcoma.²⁵ Desmosome-like junctions have also been described in a number of mesenchymal cell types and tumours.²⁶

In this case, only tissue fixed in formol saline was available for study. This precluded the successful use of modern immunocytochemical techniques. In the future, however, investigation of osteoclast-type giant cell tumours of the pancreas with a range of monoclonal antibodies may help to delineate the precise cell of origin. At the present time of more importance is the identification of features which distinguish osteoclast-type giant cell tumours from pleomorphic and other adenocarcinomas of the pancreas. Osteoclast-type giant cell tumours tend to be large at initial presentation and have a predilection for local spread. Lymph node metastases are uncommon and blood-borne secondary spread tends to be a late event. This is in contrast to pleomorphic giant cell and ordinary carcinomas in which metastatic deposits, especially in lymph nodes, are a com-

mon early finding.^{27,28} The small number of cases reported so far precludes accurate comment upon the prognosis of osteoclast-type giant cell tumours although the evidence to date (Table 2) suggests that the outcome after resection may be more favourable than for pancreatic adenocarcinoma. The latter claims the lives of the majority of patients within six months of presentation and shows a five year survival rate of less than 6% even after apparently successful resection.²⁹⁻³¹

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