Virchows Archiv A Pathol Anat (1992) 420:359–366

Virchows Archiv A
Pathological Anatomy and Histopathology

Case report

Osteoclast-like giant cell tumour of the gallbladder

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Received April 24, 1991 / Received after revision August 14, 1991 / Accepted September 10, 1991

Summary. We describe a rare carcinoma of the gallbladder containing osteoclast-like giant cells. Well-differentiated adenocarcinoma was found in the mucosa of the fundus, and osteoclast-like giant cells were present mainly in a haemorrhagic mass protruding from the mucosal surface. The metastatic hepatic tumour was composed chiefly, if not exclusively, of osteoclastoma-like cells, but minute carcinomatous elements were also present. There was an apparent transition between the giant cells and tubular structures in both the gallbladder tumour and hepatic tumour. However, ultrastructural study did not reveal any evidence of epithelial differentiation in the giant cells. Immunohistochemical studies suggested that the mononuclear and giant cells were mesenchymal and histiocytic in nature (vimentin and factor XIIIa positive). A few exceptional giant cells transforming from the fine tubular structure were positive for epithelial membrane antigen. In conclusion, the osteoclast-like giant cell tumour component was thought to represent mesenchymal metaplasia in pre-existent adenocarcinoma.

Key words: Gallbladder – Osteoclast-like giant cell tumour – Vimentin

Introduction

Tumours histologically similar to giant cell tumours of bone have been reported in the pancreas (Trepeta et al. 1981; Fischer et al. 1988), breast (Holland and Van Haelst 1984; Athanasou et al. 1989), thyroid (Hashimoto et al. 1980), liver (Munoz et al. 1980; Kuwano et al. 1984), parotid gland (Eusebi et al. 1984; Balogh et al. 1985), urinary bladder (Holtz et al. 1972), heart (Dorney 1967), ovary (Prat and Scully 1979), small and large intestine (Eshun-Wilson 1973; Alpers and Beckstead 1985), kidney (Kimura et al. 1983), lung (Love and Darocca 1983), and soft tissue (Salon and Sissons 1972). In most cases the osteoclast-like giant cell component is intermingled with carcinomatous elements, but in some cases the tumour occurred as an apparently pure form of osteoclastoma. To our knowledge, three cases of giant cell tumour of the gallbladder have been described to date in the Armed Forces Institute of Pathology (AFIP) fascicles and Japanese literature (Edmondson 1967; Kimura et al. 1984; Albores-Saavedra and Henson 1986) but the suggested origin of the giant cell differed widely among the authors; opinions were divided between epithelial (Albores-Saavedra et al. 1981) and mesenchymal origin (Kimura et al. 1984). The osteoclast-like giant cell tumour of the gallbladder has never been the subject of a detailed immunohistological study and we have examined such a tumour in order to investigate its immunohistological and ultrastructural features and to attempt to elucidate its origin.

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Case report

A 74-year-old Japanese man was admitted to National Nagasaki Central Hospital in February 1990 with a right upper abdominal mass and pain in the right upper quadrant. Ultrasound examination and computed tomography showed multiple gallstones and a 1.3 × 1.0 cm tumour in the bladder fundus indicative of gallbladder cancer. Ultrasound examination coincidentally revealed a 1.0 × 1.5 cm solid mass in the right inferior lobe (S4 section) of the liver, which was later shown to be a haemangioma-like hypervascular tumour by coeliac angiography. Hepatitis B surface antigen was negative, and the serum level of alpha-fetoprotein was not elevated. The patient underwent surgery on 12 March 1990 with a clinical diagnosis of gallstones, gallbladder cancer and hepatic hemangioma. Wedge resection of the right hepatic lobe and cholecystectomy were performed. Negative radiographic findings and the absence of any symptoms of bone tumour ruled out the possibility of liver metastasis of giant cell tumour of the bone.

Pathological findings

The gallbladder contained 20 small gallstones and an organized haematoma-like tumour (Fig. 1) measuring 4 × 4 × 7 cm and locat-

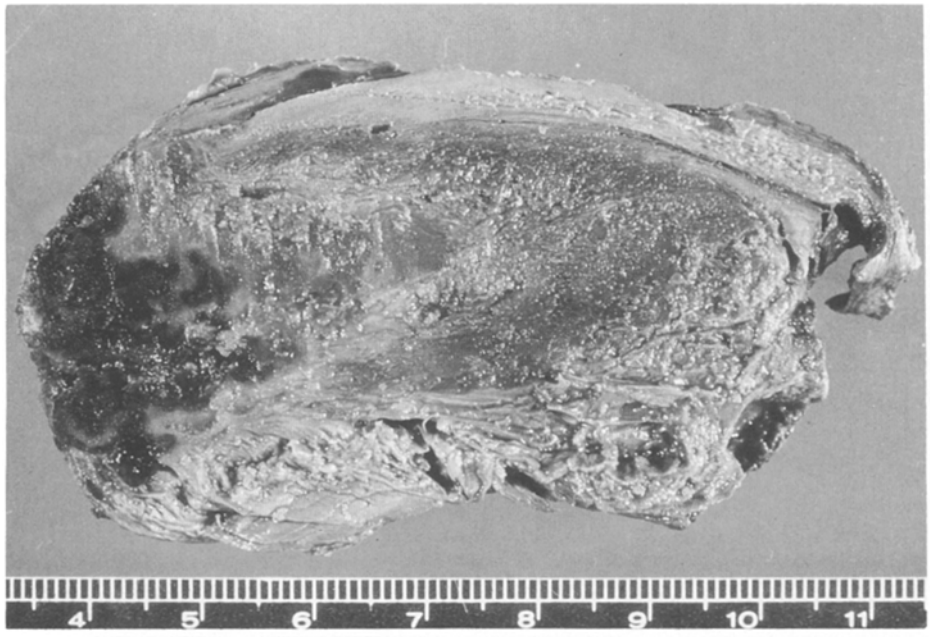


Fig. 1. Gross appearance of the haemorrhagic tumour in the gallbladder. Osteoclast-like giant cells are present in the left marginal portion of the tumour

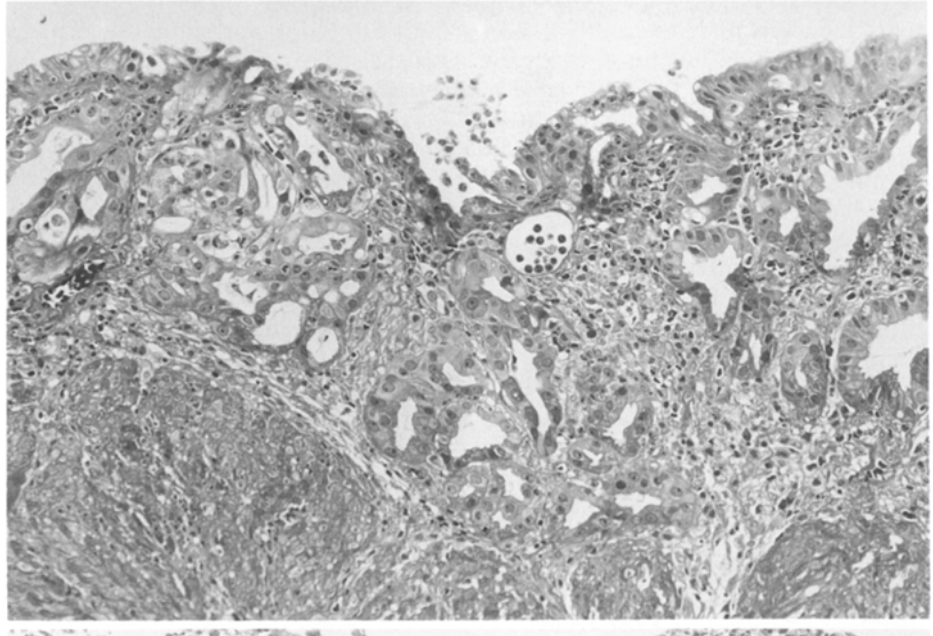


Fig. 2. Well-differentiated adenocarcinoma is present mostly in the mucosa of the gallbladder. H&E, ×165

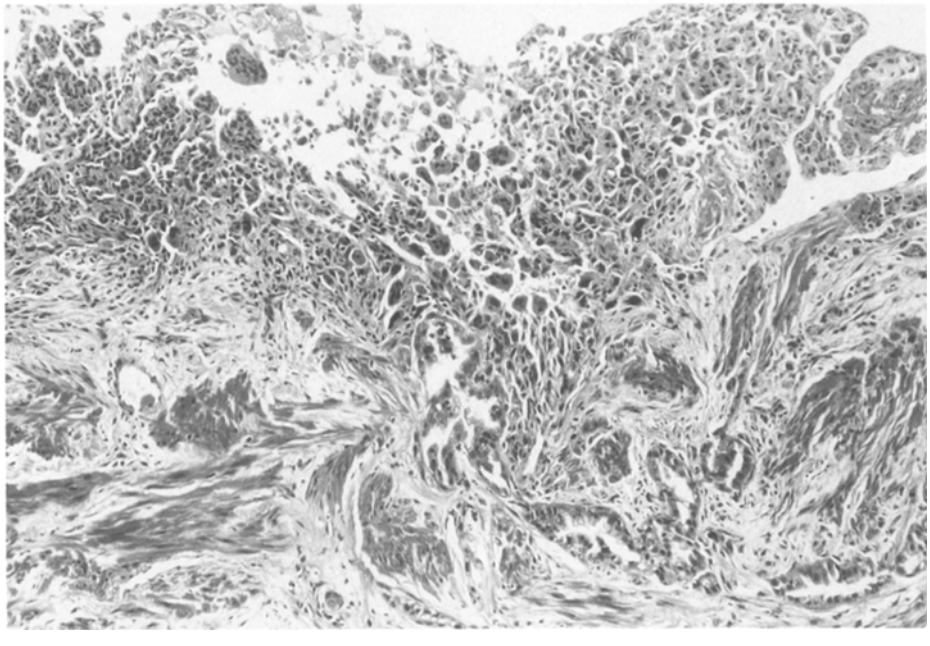


Fig. 3. There are two distinct tumour elements of osteoclast-like giant cells and tubular adenocarcinoma with a transition zone in the mucosa of the gallbladder. H&E, ×110

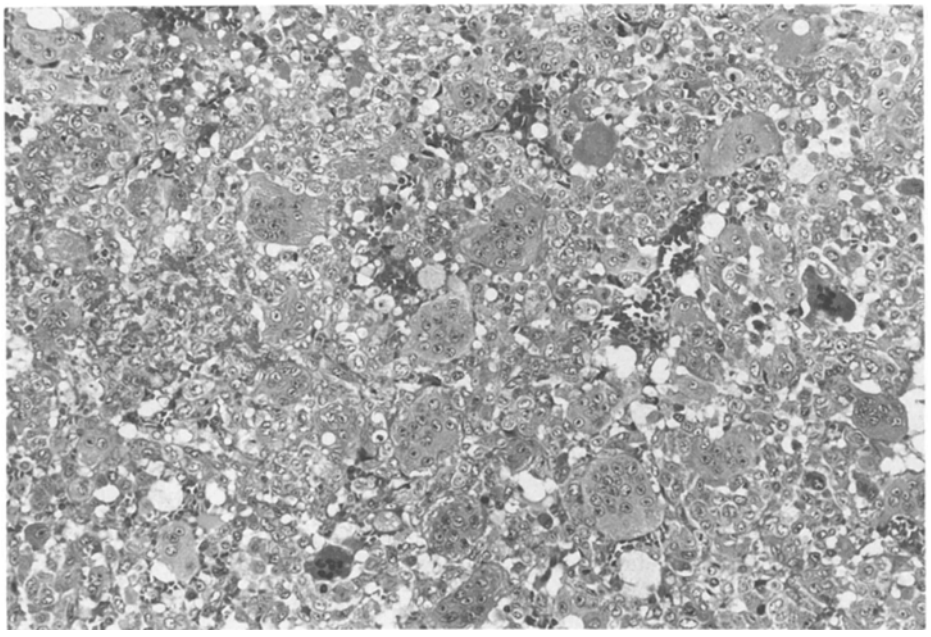


Fig. 4. Various sizes and forms of multinucleated giant cells intermingling with epithelioid mononuclear tumour cells. The giant cells have a benign appearance. Characteristic giant cells with numerous large nuclei are interspersed among mononuclear cells. H&E, ×165

ed in continuity with the mucosal surface. Multiple small papillary tumours were present in the fundus of the gallbladder. Generally, the gallbladder mucosa was atrophic and multifocally erosive. A well-circumscribed mass measuring 1.0 × 1.2 cm with multiple haemorrhagic foci was present on the edge of the inferior right hepatic lobe (segment 4). The surrounding hepatic tissue seemed normal.

All the gallbladder and hepatic tumour specimens were fixed in formalin and embedded in paraffin. Paraffin blocks containing the element of osteoclast-like giant cells were cut serially in 3-μm sections, and at least 60 sections per block were processed for light microscopic observation.

Histologically, the papillary gallbladder tumours were well-differentiated tubular adenocarcinomas and were confined mostly to the mucosal layer of the fundus, partly invading the muscle layer (Fig. 2). The haematoma-like mass consisted mainly of coagulation necrosis of tumour elements, red blood cells and fibrinous exudate, but also contained the osteoclast-like giant cell tumour component in that portion of the mucosal adenocarcinoma where the carcinomatous invasion of the muscle layer was observed. At this site adenocarcinoma merged with osteoclast-like giant cells to form a transition zone (Fig. 3). This tumour was very similar to giant cell tumour of the bone: the most characteristic components were multinucleated giant cells with an appearance similar to benign osteoclasts and pleomorphic or polygonal mononuclear cells. Measuring 100 μm in diameter, the osteoclast-like giant cells contained as many as 70 nuclei and possessed prominent nucleoli. The nuclei were situated centrally and varied little in size. The abundant cytoplasm stained finely granular, homogeneous or deep eosinophilic with haematoxylin and eosin (H&E). The giant cells contained no mitotic figures. A few had phagocytosed neutrophils and cell debris. The second component (mononuclear cells) was made up of polygonal or spindle-shaped cells with eosinophilic or vesicular cytoplasm and irregular round or elongated nuclei with large clumps of chromatin. Abnormal mitoses were numerous in this cell population and suggested malignancy. Very few glandular structures were encountered in the middle of the osteoclast-like giant cell component.

The hepatic mass was a solid tumour with multiple foci of a haemorrhage. The solid, highly cellular portion was composed mainly, but not entirely, of the same giant cell tumour component as that in the gallbladder (Figs. 4, 6). Under close scrutiny, a few clearly demonstrable tubular or acinar structures were encountered in the hepatic tumour. A transition was observed between these tubules and osteoclast-like giant cells and was confirmed by serial sectioning (Fig. 5). Some giant cells were formed by fusion of mononuclear tumour cells in the serial sections. There was occasional vascular invasion by the tumour, with mononuclear and giant cells in the marginal area.

Immunohistological reactions were detected using either the avidin-biotin peroxidase complex (ABC) method or the peroxidase-anti-peroxidase (PAP) method on formalin-fixed material for both the gallbladder and the hepatic tumour. The following mouse monoclonal primary antibodies were used with an appropriate dilution: vimentin, epithelial membrane antigen (EMA), cytokeratin, S-100α protein, and S-100β protein. The following polyclonal primary antibodies were also used with an appropriate dilution: α_1-antitrypsin, α_1-antichymotrypsin, factor XIIIa, lysozyme, S-100 protein, desmin, factor-VIII-related antigen, carcinoembryonic antigen (CEA), keratin, and α-fetoprotein. The source and dilution

Table 1. Sources and dilutions of the applied antibodies

Antibody	Dilutions	M/P	Source
Vimentin	1:10	M	Dakopatts (Copenhagen, Denmark)
α_1AT	1:100	P	Ortho Diagnostic (New Jerwey, USA)
α_1ACT	1:100	P	Ortho Diagnostic
Factor XIIIa	1:100	P	Diagnostica Stago (Asnières, France)
Lysozyme	1:100	P	Dakopatts
EMA	1:100	M	Dakopatts
CEA	1:200	P	Kyowa (Tokyo, Japan)
α-Fetoprotein	1:100	P	Dakopatts
Keratin	1:400	P	Dakopatts
Cytokeratin	1:200	M	Labsystem (Helsinki, Finland)
Factor VIII	1:100	P	Ortho Diagnostic
S-100	1:200	P	Dakopatts
S-100α	1:800	M	Dakopatts
S-100β	1:400	M	Dakopatts
Desmin	1:100	P	Ortho Diagnostic

α_1AT, α_1-antitrypsin; α_1ACT, α_1-antichymotrypsin;
EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen;
M, monoclonal; P, polyclonal

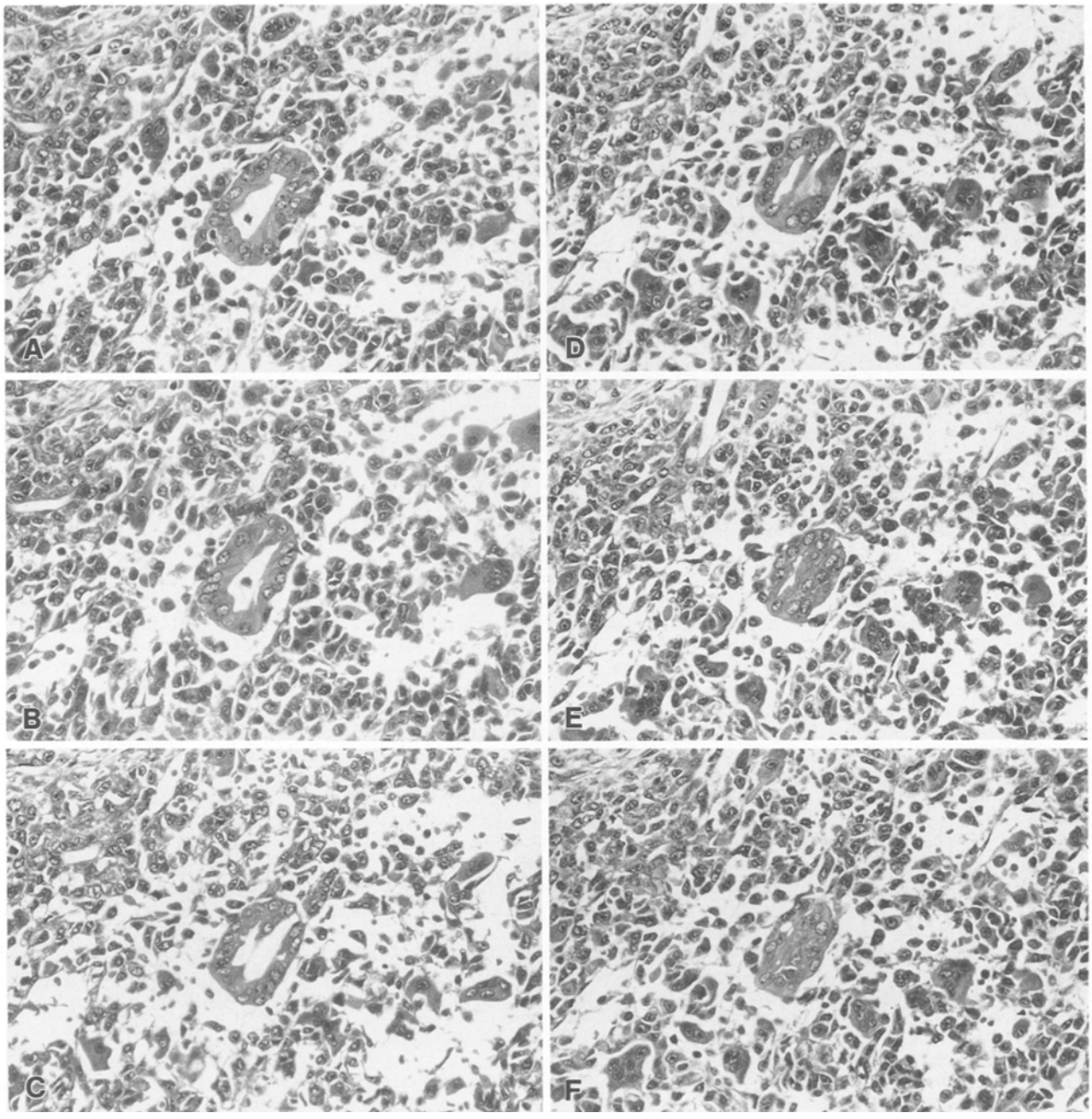
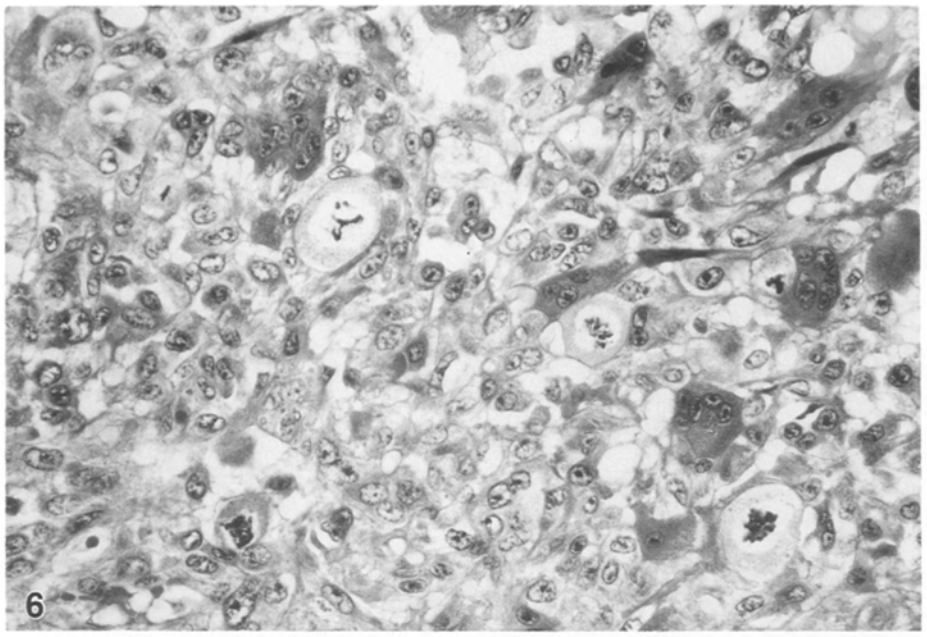
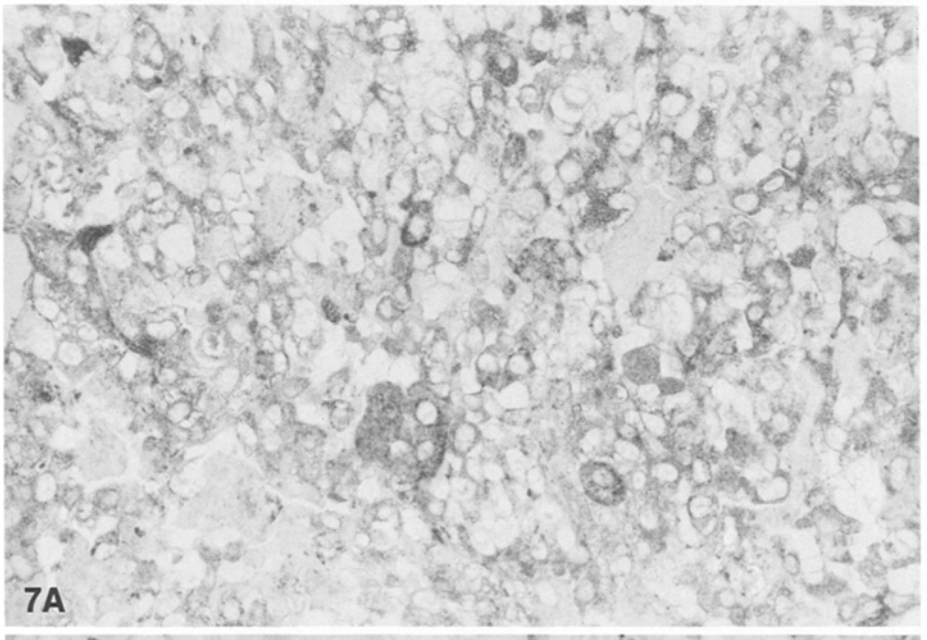


Fig. 5. The transition between a multinucleated giant cell and a minute tubule was observed in the serial sections of the hepatic tumour (**A–F**). H&E, ×165

of antisera used in the immunohistochemical study are summarized in Table 1. The mononuclear tumour cells and the giant cells were strongly positive for vimentin (Fig. 7A). Immunoperoxidase reaction for histiocytic markers α_1-antitrypsin, α_1-antichymotrypsin, and factor XIIIa (Nemes and Thomazy 1988) was positive in a high percentage of mononuclear tumour cells and a few giant cells (Fig. 7B). There was a negative reaction for lysozyme, cytokeratin, CEA, α-fetoprotein, S-100 protein, desmin, and factor-VIII-related antigen in both osteoclast-like giant cells and mononuclear tumour cells. Although most giant cells were negative for EMA; a few of those transformed from tubular structures were positive for EMA (Fig. 8A, B). The minute tubules observed in the hepatic and gallbladder tumours were consistently positive for EMA but negative for other epithelial, mesenchymal and histiocytic markers. The gallbladder tumour and hepatic tumour displayed the same immunoreactivity.

For electron microscopical examination, small samples were obtained from the formalin-fixed hepatic tumour. These were refixed in glutaraldehyde, postfixed in 1% osmium tetroxide, embedded in epoxy resin after dehydration in graded alcohols and propylene oxide, and processed for viewing with an electron microscope (Hitachi H-600, Tokyo). The ultrastructural features of the multinucleated giant cells included an abundance of cytoplasmic organelles and numerous oval nuclei with prominent nucleoli. The multinucleated giant cells contained abundant mitochondria, small amounts of rough endoplasmic reticulum, free ribosomes and irregularly arranged intermediate filaments (Fig. 9). Scanty lysosomal bodies were encountered in a few of the giant cells. There were two types of mononuclear cells, the majority being similar to the giant cells and containing numerous cytoplasmic organelles and microfilament bundles, whilst a small number had lysosomal bodies of various sizes in addition to abundant organelles. No cell attachment structures or surface microvilli were present in either cell population.





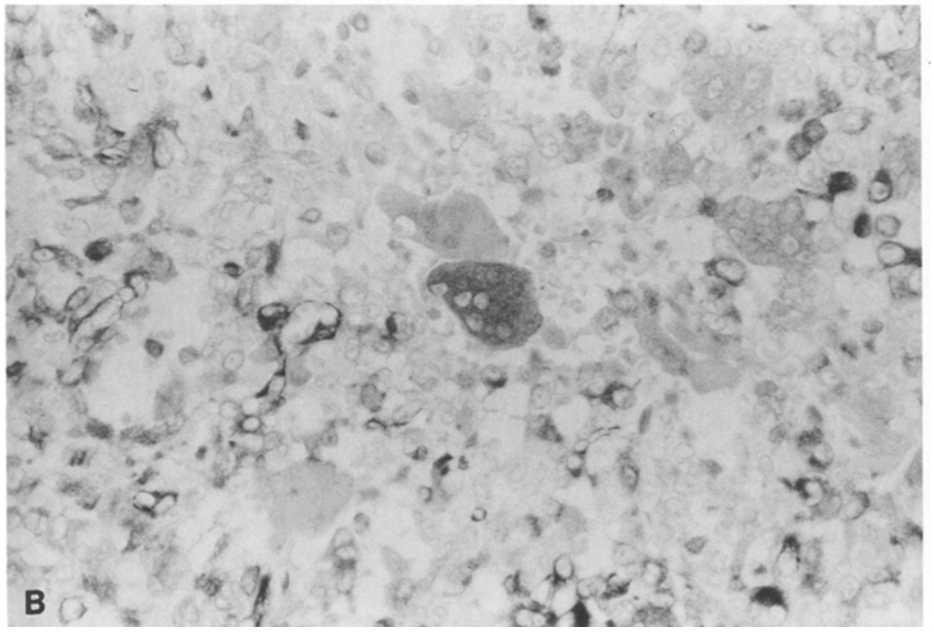


Fig. 6. Atypical mitosis was observed only in the mononucleated cell populations. H&E, ×330

Fig. 7A, B. Immunohistochemical features of vimentin and factor XIIIa. **A** Mononuclear cells and giant cells were markedly immunoreactive for vimentin. ABC, ×330. **B** Factor XIIIa was positive among mononuclear and giant cells. ABC, ×330

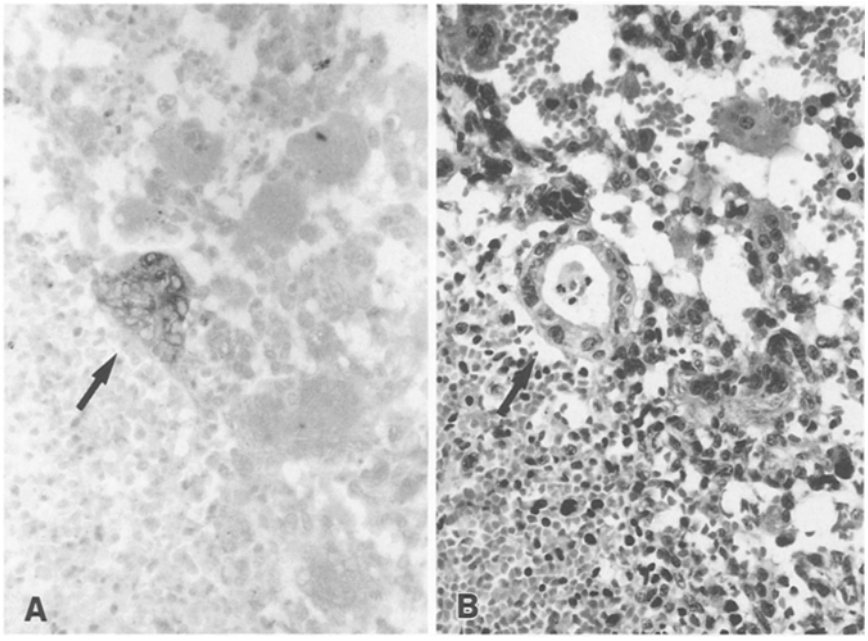


Fig. 8 A, B. Epithelial membrane antigen (EMA) staining of giant cells. **A** EMA was strongly positive in the giant cell (*arrow*) transformed from a minute gland represented in **B. A** and **B** are in the serial sections. Other giant cells were negative. ABC, ×165. **B** Carcinomatous glandular structure (*arrow*) was present in the middle of the gallbladder tumour. H&E, ×165

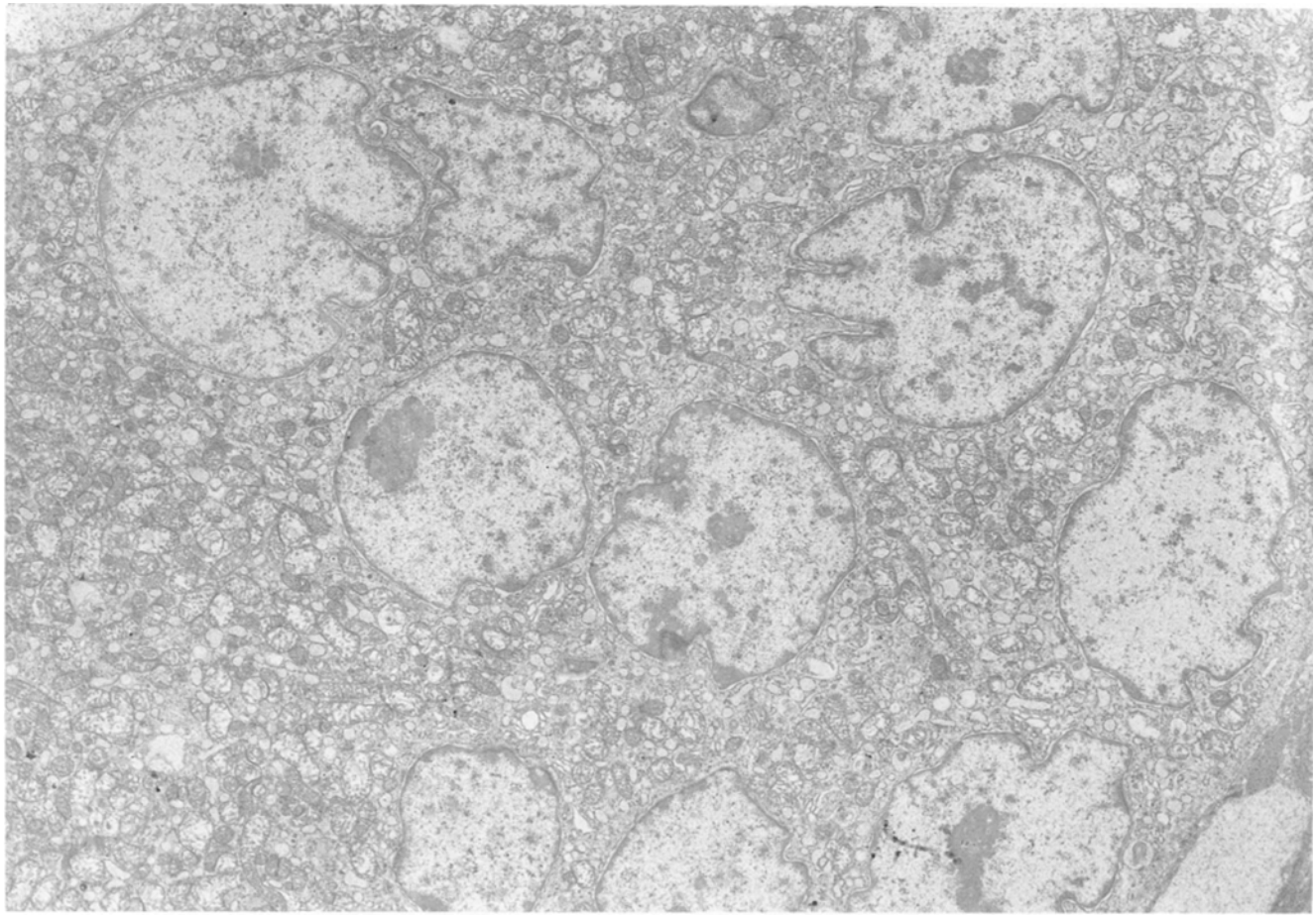


Fig. 9. Electron micrograph of a multinucleated giant cell showing well-developed mitochondria and small amounts of endoplasmic reticulum and free ribosomes similar to those of mononuclear tumour cells. Uranyl acetate and lead citrate, ×4600

Discussion

Although rare, extraosseous tumours containing osteoclast-like giant cells have been described in several sites of the body. The osteoclast-like giant cell tumours of the gallbladder is very rare; only three cases have been reported to date. The first was described by Edmondson in the AFIP series in 1967. The patient was a 56-year-old woman with haemorrhagic masses in the fundal portion of the gallbladder exhibiting round to oval stromal cells and multinucleated giant cells. Many faceted calculi were present. She died 6 months after surgery as a result of intra-abdominal recurrence. Edmondson classified this tumour under the category of "sarcoma". The second description was published in the AFIP fascicle by Albores-Saavedra and Henson (1986). One gallbladder tumour collected by the authors displayed an osteoclast-like giant cell element in pleomorphic adenocarcinoma. They considered this lesion to be a variant of pleomorphic carcinoma because in some areas the usual pattern of pleomorphic adenocarcinoma was present, including glands. The third case was reported by Kimura et al. (1984). This tumour consisted of a giant-cell component devoid of carcinoma, and the authors suspected a mesenchymal cell origin on the basis of negative keratin immunoreactivity.

Pleomorphic giant-cell adenocarcinoma accounts for 13.2% of all malignant tumours of the gallbladder and commonly exhibits large bizarre nuclei and prominent nucleoli (Albores-Saavedra et al. 1981). In contrast, osteoclast-like giant cells of the kind encountered in our case show apparently benign multiple nuclei, suggesting that this tumour may differ from giant cell (anaplastic) carcinoma of the gallbladder.

The origin and nature of these giant cells are subjects of controversy. The confusion is largely due to the fact that ultrastructural findings and immunohistological studies have produced conflicting or uncertain results. Three hypotheses have been proposed: (1) that the lesion is a true sarcomatous giant cell tumour arising from the mesenchymal component; (2) that the cells represent a host reaction to a primary tumour; and (3) that it is metaplastic reaction within a carcinoma cell line with mesenchymal features.

Two cases of "pure osteoclastoma" have been reported in the heart (Dorney 1967) and liver (Munoz et al. 1980), and the authors suggested a mesenchymal origin. Some authors (Hashimoto et al. 1980; Kuwano et al. 1984; Alpers and Beckstead 1985) have suggested that the giant cells are non-neoplastic, reactive cells of the macrophage system. A similar suggestion has been made for the multinucleated giant cells of giant cell tumour of bone (Brecher et al. 1986). However, in the present case the morphological features, namely the locally aggressive behaviour and numerous mitoses, support the hypothesis of a true neoplastic proliferation with malignant potential rather than a host reaction.

Most authors presume an epithelial derivation for these neoplasms on the grounds that the microstructure includes microvilli and cell junctions, immunoreactivity for epithelial markers, and a morphological transition from a carcinomatous element into an osteoclast-like giant cell. These ultrastructural findings are not definitive evidence of epithelial origin; microvilli and cell junctions are non-specific and can be seen in a variety of cell types, including those of mesenchymal origin (Eusebi et al. 1984). Furthermore, the lack of an epithelial antigenic marker has been reported in many papers. In contrast, vimentin, α_1-antitrypsin and α_1-antichymotrypsin cannot be regarded as key markers for mesenchymal and histiocytic cell origin, since they may be present within some kinds of poorly or undifferentiated carcinoma (Ramaekers et al. 1983; Roholl et al. 1985). Also the identification of morphological "transitions" between epithelial tissues and those with a mesenchymal appearance is a highly subjective interpretation for the epithelial origin of a giant cell tumour (Eusebi et al. 1984).

The concept of mesenchymal metaplasia for this kind of tumour was first proposed by Oyasu et al. (1977) and has been supported by many authors (Kobayashi et al. 1987; Fischer et al. 1988). A metaplastic reaction within a carcinomatous cell line may lead to the acquisition of mesenchymal characteristics.

With regard to mononuclear tumour cells, many authors (Factor et al. 1977; Robinson et al. 1977; Kobayashi et al. 1987) have pointed out a number of similarities in nuclear and cytoplasmic characteristics between mononuclear tumour cells and giant cells using morphological data obtained by light and/or electron microscopy. They have suggested that the osteoclast-like giant cells were formed by fusion of mononuclear tumour cells.

In the present case, transition between a giant cell tumour and tubular adenocarcinoma was demonstrated in the gallbladder and in a hepatic tumour. The results of our immunohistological studies suggest that the mononuclear tumour cells and giant cells were mesenchymal (vimentin) and histiocytic (α_1-antitrypsin, α_1-antichymotrypsin, and factor XIIIa) in nature; evidence of epithelial features in the mononuclear cells and most of the giant cells was obtained neither ultrastructurally nor immunohistochemically. Hence, mesenchymal metaplasia is the most convincing interpretation for the transition of two diverse tumour components. We conclude that the element of the osteoclast-like giant cell tumour probably represents the mesenchymal metaplasia of pre-existent adenocarcinoma of the gallbladder and an epithelial origin.

Acknowledgements. We would like to express sincere thanks to Mr. B. Burke-Gaffney for editorial assistance and to Mr. T. Kawada for preparing the photographs.

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