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ORIGINAL ARTICLE

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Malignant mesenchymomas of soft tissue associated with numerous osteoclast-like giant cells mimicking the so-called giant cell variant of "malignant fibrous histiocytoma"

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Abstract Three cases of malignant mesenchymoma with numerous osteoclast-like giant cells, arising in deep soft tissue, and which mimicked the so-called giant cell variant of "malignant fibrous histiocytoma" have been studied. All three neoplasms arose in adults; two patients were male and one was female. Two tumours arose in the thigh, and one in the right shoulder. Two patients died within 2 years of the primary excision while the third is alive and well at 2.5 years. Histologically, one case showed leiomyosarcoma plus liposarcoma, one leiomyosarcoma plus osteosarcoma, and one tumour consisted of liposarcoma plus osteosarcoma; all components were assessed morphologically as high-grade malignant. All three cases showed prominent osteoclast-like giant cells in the leiomyosarcomatous or osteosarcomatous areas, thereby closely mimicking the phenotype of so-called giant cell variant of "malignant fibrous histiocytoma". We discuss briefly differences in soft tissue sarcomas demonstrating this distinctive osteoclast-rich phenotype.

Key words Mesenchymoma · Osteoclast · Giant cell Malignant fibrous histiocytoma · Immunohistochemistry

Introduction

Malignant mesenchymoma, a concept first described formally by Stout in 1948 [12], is defined by the presence of at least two separate and distinctive lines of malignant mesenchymal differentiation, proved morphologically and supported by immunohistochemistry where appropriate. Fibrosarcomatous areas, myxofibrosarcomas, unclassifiable and undifferentiated sarcomas, or specific sarcomas showing "dedifferentiation" are not accepted within the most recent definition [10]. Similarly, areas resembling pleomorphic "malignant fibrous histiocytoma" ("MFH") and malignant heamangiopericytoma are also not included because these patterns are common features of a wide variety of soft tissue sarcomas and may be present also sometimes in undifferentiated carcinomas and lymphomas [3, 4, 10, 15]. Traditionally, malignant peripheral nerve sheath tumours showing heterologous differentiation, malignant Triton tumours, and malignant ectomesenchymomas are also excluded. Malignant mesenchymomas show most often an admixture of liposarcomatous, rhabdomyosarcomatous and/or osteo/chondrosarcomatous elements [10]. Other combinations, such as a leiomyosarcomatous component, occur but appear to be less frequent [2, 13]. We report three cases of malignant mesenchymoma with prominent osteoclast-like giant cells, arising in deep soft tissue, and which mimicked closely the so-called giant cell variant of "MFH".

Materials and methods

Two cases were identified in the consultation files of CDMF (see Acknowledgements) and the third case in the surgical files of St Thomas's Hospital. In all cases, tissue was fixed in 10% formaldehyde, routinely processed and embedded in paraffin wax. Four micron thick sections were cut and stained with haematoxylin and eosin and by the Masson's trichrome and periodic-acid Schiff techniques. For immunohistochemical studies, representative sections were examined by the avidin-biotin-peroxidase complex technique using appropriate positive and negative controls throughout. Monoclonal antibodies for pan-keratin (MNF 116, dilution 1: 50, Dakopatts), CD 68 (KP1, 1: 50, Dakopatts), muscle actin (HHF 35, 1: 25000, Enzo Diagnostics), alpha-smooth muscle actin (IA 4, 1/16000, Sigma), desmin (D 33, 1: 300, Dakopatts), and fast myosin (MY 32, 1: 400, Sigma), and polyclonal antibodies for S-100 protein (1: 300, Dakopatts) were used. The mitotic rate was expressed as the average mitotic count present in ten high power fields (HPF, one HPF=0.159 mm^2 on the microscope used); 50 HPF were counted in each case.

Each component or line of differentiation was defined by the same detailed criteria as we have published previously (Newman and Fletcher 1991, Fletcher 1992).

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Case histories

The first case was a 37-year-old woman who presented with an enlarging, deep-seated mass on her right shoulder of 8 months preoperative duration. After an incomplete initial excision, a radical re-excision of the right deltoid muscle and postoperative local radiotherapy were carried out. There has been no evidence of local recurrence or metastasis for 30 months after the first operation.

The second case was a 71-year-old man who underwent resection of an intramuscular lesion in his left upper leg, which had rapidly enlarged in the preceeding 8 weeks. The tumour was excised widely along with parts of rectus femoris and vastus medialis and postoperative local radiotherapy was carried out. A local recurrence and a solitary pulmonary metastasis were excised 8 and 9 months later respectively. The patient died of disseminated tumour 22 months after initial excision.

The third case was an 82-year-old man who was admitted to hospital because of an intramuscular mass in his left thigh. The mass was surgically shelled-out. The tumour recurred locally with considerable oedema of the leg and local radiotherapy was carried out. Two years after initial treatment the patient died with further local recurrence and a pulmonary metastasis in the left upper lobe. Postmortem examination revealed bronchopneumonia as the immediate cause of death.

Pathological findings

The initial specimen from case 1 measured 7 × 3 × 4 cm and was described as a lobulated, soft, white/yellow mass firmly attached to skeletal muscle at one edge. Histologically, a high grade sarcoma demonstrating a biphasic pattern was evident. The bulk of the lesion was composed of short fascicles of pleomorphic spindle cells with abundant palely eosinophilic cytoplasm and blunt-ended or polygonal vesicular nuclei; these cells had the morphological features of smooth muscle differentiation. In one area, however, smaller round and spindle-shaped tumour cells, dispersed in a more myxoid background and intermixed with numerous multivacuolated lipoblasts were demonstrated (Fig. 1a). Peripherally, adjacent to the spindle-celled (leiomyosarcomatous) area, a cellular rim was noted, in which round and fusiform tumour cells with eosinophilic cytoplasm were intermixed with numerous osteoclast-like giant cells and pleomorphic multinucleated tumour giant cells in a giant cell "MFH"-like pattern (Fig. 1b). The mitotic count ranged from 5 to 12 mitoses per ten HPF in different tumour areas. Immunohistochemically, the spindled and pleomorphic tumour cells stained, at least focally, strongly positive for alpha-smooth muscle actin and cells were also immunoreactive for desmin (Fig. 1c). The osteoclast-like giant cells were weakly positive for CD68 but failed to stain with myogenic markers. The diagnosis made was malignant mesenchymoma composed of pleomorphic leiomyosarcoma and liposarcoma.

The excision specimen from case 2 revealed a tumour mass, approximately 6 cm in its greatest diameter, with a pale haemorrhagic cut surface and focal cystic degeneration. Microscopically, the lesion was composed mainly of ill-defined nodules of polygonal, spindle-shaped or round eosinophilic and fuchsinophilic tumour cells with pleomorphic vesicular nuclei, intermixed with prominent osteoclast-like giant cells (Fig. 2a). In some areas short spindle cell fascicles, with typical features of leiomyosarcoma, were noted. A distinctive feature was the presence, in several foci, of partially calcified osteoid being laid down by pleomorphic malignant cells (Fig. 2b). Frequent mitoses (up to 55 per ten HPF), extensive tumour necrosis and widespread vascular invasion were observed. The spindle and round tumour cells stained strongly positive for alpha-smooth muscle actin and desmin (Fig. 2c). Both myogenic markers were negative in the cytologically benign osteoclast-like giant cells, which stained intensely positive for CD68. The diagnosis made was malignant mesenchymoma composed of pleomorphic leiomyosarcoma and osteosarcoma.

The primary neoplasm in case 3 consisted of a pseudoencapsulated, lobulated tumour of about 15 cm in diameter, which demonstrated a pinkish-grey or cream-coloured cut surface. Histologically, the lesion was characterised by a biphasic pattern. In one part of the tumour consisted of multivacuolated lipoblasts with prominent lipid droplets in the cytoplasm and pleomorphic hyperchromatic nuclei (Fig. 3a). The mitotic figures in this area numbered between 8 and 10 per ten HPF. Mono- and multinucleated tumour cells intermixed with numerous osteoclast-like giant cells and arranged in a multinodular pattern (Fig. 3b) formed the second tumour component. Additionally, widespread small foci of malignant osteoid (Fig. 3c) were noted in this area. The tumour cells in these multinodular areas displayed marked pleomorphism with high mitotic activity (up to 45 mitoses per ten HPF). Extensive vascular invasion and large areas of tumour necrosis were noted. The tumour cells were not immunoreactive for any applied marker; only few bland osteoclast-like giant cells stained weakly positive for CD68. The recurrent tumour demonstrated the features of the multinodular poorly differentiated osteosarcomatous component, whereas the appearance in the pulmonary metastasis was more in keeping with unclassifiable pleomorphic and spindle cell sarcoma. Tumour cell emboli in larger pulmonary arterioles were noted. The diagnosis made was malignant mesenchymoma composed of pleomorphic liposarcoma and poorly differentiated osteosarcoma.

Discussion

Malignant mesenchymoma is a rare tumour which arises most often in the retroperitoneum and the thigh of elderly people [2]. The three cases presented herein fulfil the strict diagnostic criteria for malignant mesenchymoma [3, 10]; one tumour consisted of leiomyosarcoma plus liposarcoma, one of leiomyosarcoma plus osteosarcoma, and the third of liposarcoma plus osteosarcoma. All the different mesenchymal components were morphologically of high-grade malignancy in each case. In two of our three cases, one of the tissue components was morphologically and immunohistochemically proven pleomorphic leiomyosarcoma. This element has been reported,

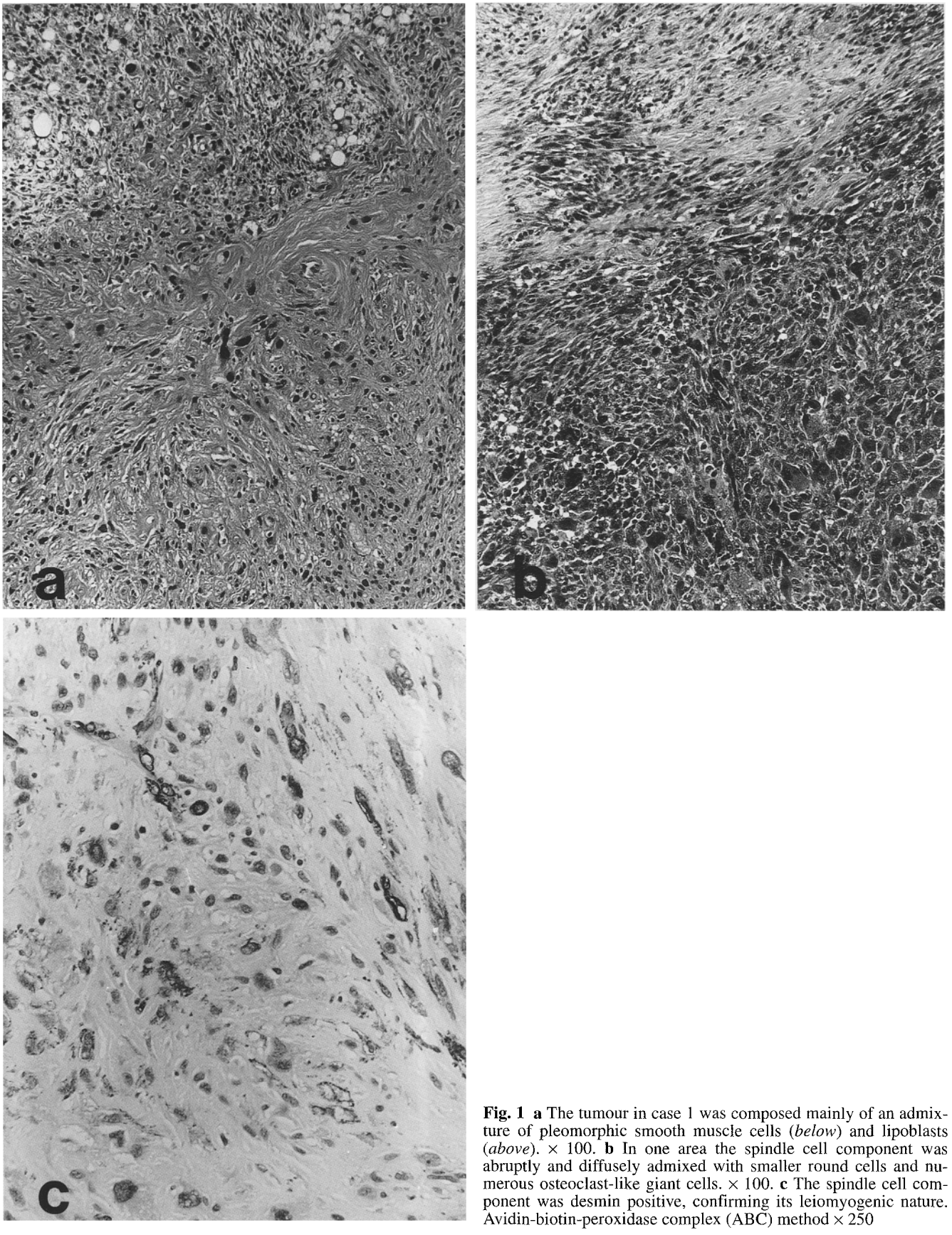

Fig. 1 **a** The tumour in case 1 was composed mainly of an admixture of pleomorphic smooth muscle cells (*below*) and lipoblasts (*above*). × 100. **b** In one area the spindle cell component was abruptly and diffusely admixed with smaller round cells and numerous osteoclast-like giant cells. × 100. **c** The spindle cell component was desmin positive, confirming its leiomyogenic nature. Avidin-biotin-peroxidase complex (ABC) method × 250

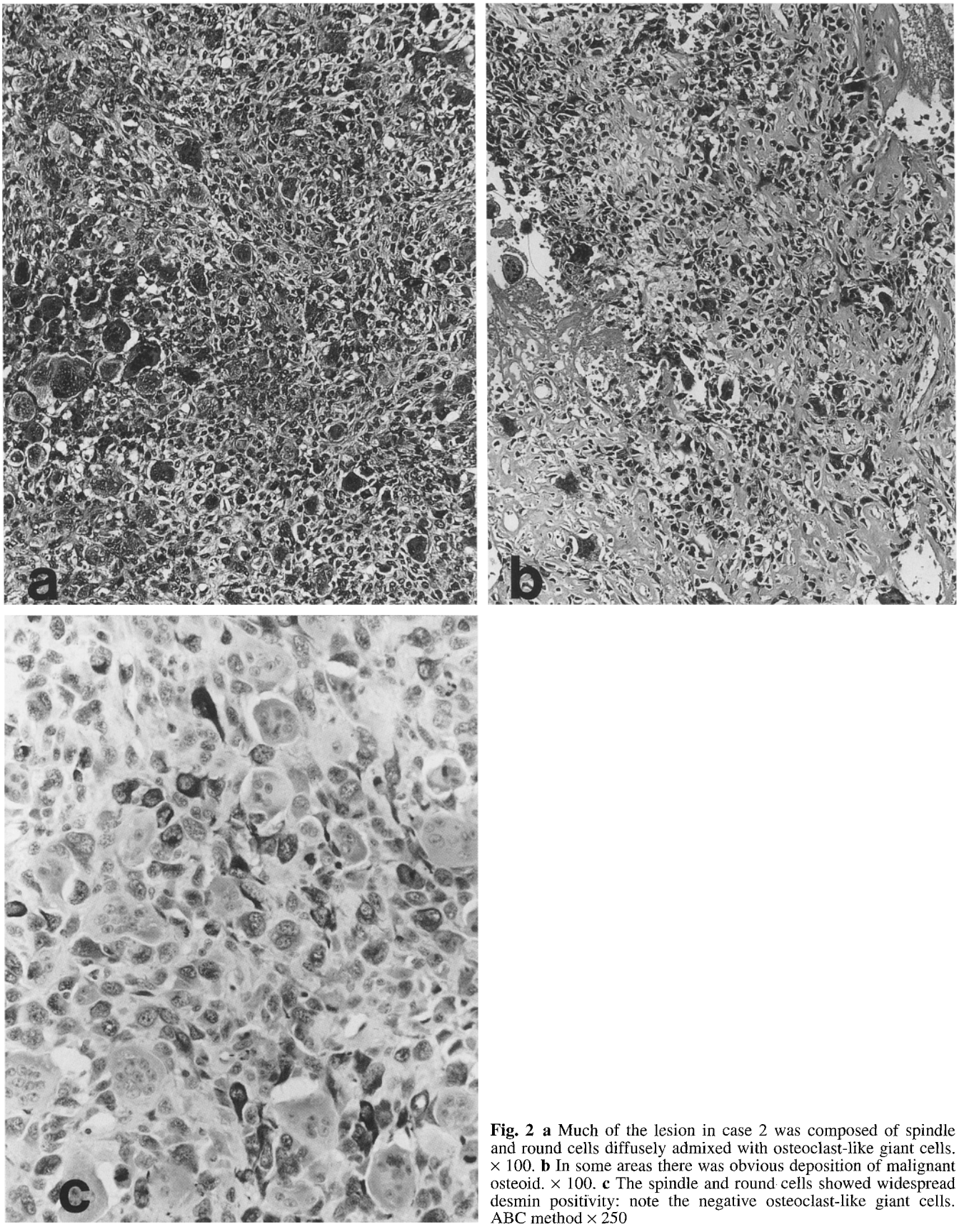

Fig. 2 **a** Much of the lesion in case 2 was composed of spindle and round cells diffusely admixed with osteoclast-like giant cells. × 100. **b** In some areas there was obvious deposition of malignant osteoid. × 100. **c** The spindle and round cells showed widespread desmin positivity: note the negative osteoclast-like giant cells. ABC method × 250

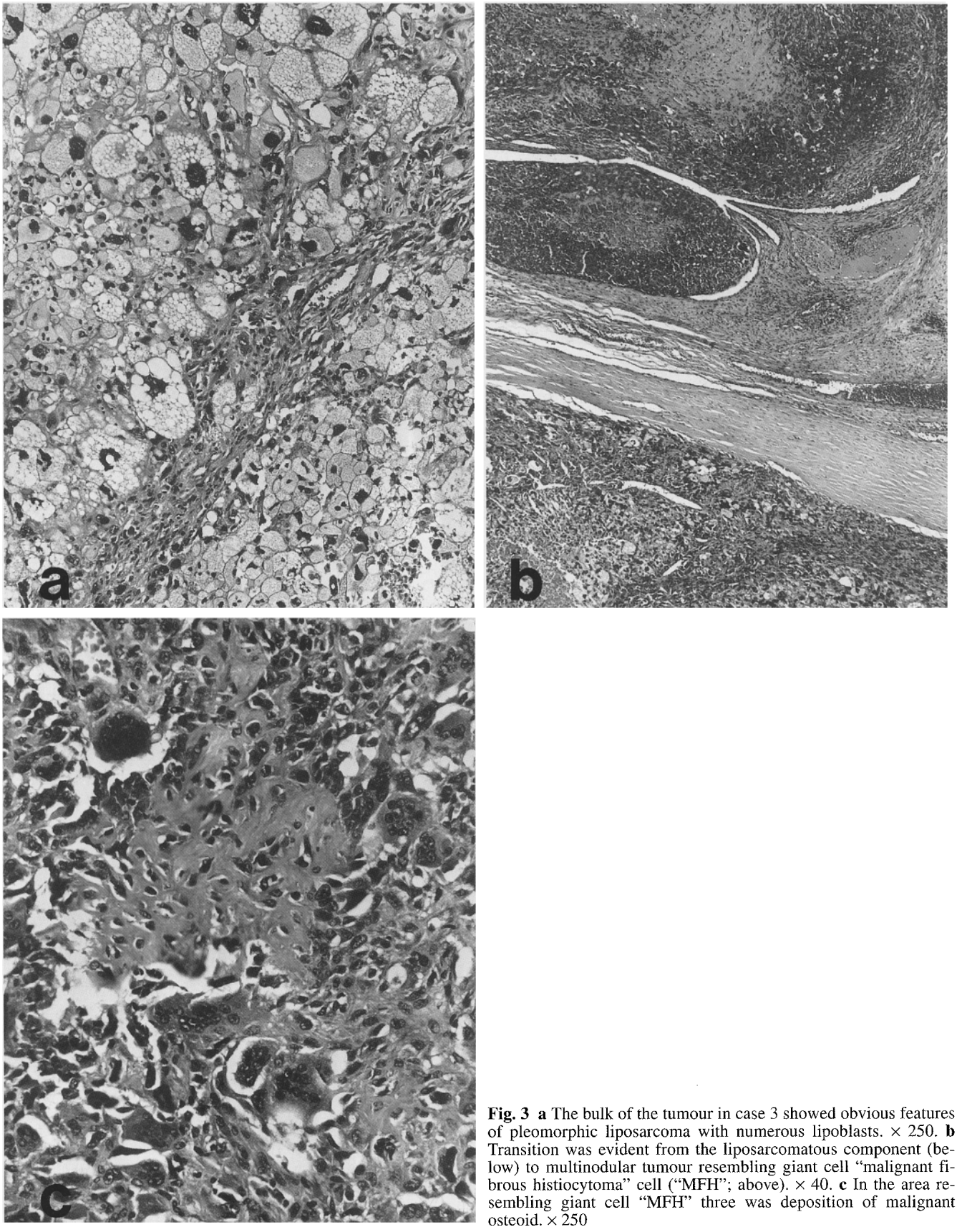

Fig. 3 **a** The bulk of the tumour in case 3 showed obvious features of pleomorphic liposarcoma with numerous lipoblasts. × 250. **b** Transition was evident from the liposarcomatous component (below) to multinodular tumour resembling giant cell "malignant fibrous histiocytoma" cell ("MFH"; above). × 40. **c** In the area resembling giant cell "MFH" three was deposition of malignant osteoid. × 250

but is relatively uncommon, in malignant mesenchymomas [2, 6]. Interestingly, in one previous case report of a malignant mesenchymoma, comprising leiomyoblastic, chondroblastic, and osteoblastic elements, a few areas with multinucleated, osteoclast-like giant cells were also described [7].

We wish to distinguish our cases from the recently reported dedifferentiated liposarcoma with divergent myosarcomatous differentiation [14], in which the initial tumours had been diagnosed as well-differentiated liposarcoma, with myosarcomatous elements being noted only when dedifferentiation occurred. Our cases are also different from the recently reported lesions showing an admixture of well-differentiated lipo- and leiomyosarcomatous components [13], since the tumours reported herein are frankly high grade throughout.

The unusual feature in our cases was the intimate admixture of the leiomyosarcomatous and/or osteosarcomatous components with numerous osteoclast-like giant cells in a multinodular growth pattern, thereby mimicking the so-called giant cell variant of "MFH".

Classically, giant cell "MFH", also known as malignant giant cell tumour of soft parts, is characterized by a multinodular proliferation of osteoclast-like giant cells, pleomorphic tumour cells, fibroblasts, and histiocyte-like cells. As was described in the first properly documented series [5], it is our experience also (unpublished results), that more than 50% of all cases with this phenotype show formation of neoplastic osteoid, bone or cartilage. We believe that it is more logical to regard this largest subgroup of cases as examples of a giant cell-rich variant of soft tissue osteosarcoma. More recently, we have reported 10 leiomyosarcomas with prominent osteoclast-like giant cells displaying a close resemblance to giant cell MFH and noticed that osteoclast-like giant cells are associated with around 10% of leiomyosarcomas arising in deep soft tissue [8]. We believe that these leiomyosarcomas represent the second largest subgroup of lesions among the heterogenous family of lesions which presently are classified as giant cell "MFH". A further subgroup of lesions closely resembling giant cell tumour of bone, but which also had been diagnosed initially as giant cell "MFH", has recently been reviewed by Nascimento [9], who suggested low-grade malignant behavior for this group of cases, which he believed were best classified as giant cell tumour of soft tissue.

The cases reported herein of malignant mesenchymoma associated with osteoclast-like giant cells expand the range of lesions which may show a giant cell "MFH"-like pattern, thereby further suggesting that the latter is a non-specific, heterogeneous phenotype and not a specific entity. We believe that tumours showing this morphological pattern are classified best on the basis of their more specific or definable line of differentiation, in the same manner as pleomorphic "MFH" [3].

The clinical relevance of subclassifying lesions showing the phenotype of so-called giant cell "MFH" hopefully should be established in future studies. Whereas extraskeletal osteosarcoma and retroperitoneal or soft tissue leiomyosarcoma are accepted commonly as high-grade malignant neoplasms [1, 11, 16], low-grade malignant behaviour for giant cell tumour of soft tissue has been suggested [9]. Interestingly, the clinical behaviour of those cases of giant cell "MFH" containing neoplastic osteoid or bone is not as consistently aggressive as that of conventional extraskeletal osteosarcoma [1, 5]. Despite unequivocally high-grade areas in previously reported malignant mesenchymomas, Newman and Fletcher [10] suggested, that their prognosis, as a group, is probably much better than originally believed. However, the cases reported herein do not support this hypothesis. The reasons for this are unclear but seem unlikely to be related to the presence of prominent osteoclast-like giant cells. It seems more likely that this discrepancy reflects simply the small number of carefully defined malignant mesenchymomas with follow-up which have been analysed in the recent literature. With the passage of time and increasing experience, it may be that prognostic subgroups will be defined among malignant mesenchymomas. It is to be hoped that the application of consistent diagnostic criteria for histological subclassification of sarcomas increasingly will aid more precise prognostication.

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