Virchows Arch (2000) 436:305–311

ORIGINAL ARTICLE

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Sclerosing, pseudovascular rhabdomyosarcoma in adults

Clinicopathological and immunohistochemical analysis of three cases

Received: 22 October 1999 / Accepted: 8 December 1999

Abstract Rhabdomyosarcoma in adults represents a rare soft tissue neoplasm which is seen most frequently in its pleomorphic subtype in this age group. Very rarely, clear cell and spindle-cell variants have been reported. In this study we describe three cases of rhabdomyosarcoma in adult patients, characterised by prominent hyaline sclerosis and a pseudovascular growth pattern. All cases were identified in the consultation files of one of the authors and routinely processed. Immunohistochemical studies were performed on paraffin sections with the alkaline phosphatase–antialkaline phophatase method. The patients, two women and one man, were 40, 41, and 56 years old. One developed a deep-seated soft tissue mass in the left lower leg, and one, a tumour of the left upper jaw. In one patient a bone tumour in the proximal body of the sacrum without extension into soft tissues was seen. The patients were treated by wide excision, piecemeal excision and incomplete excision in one case each; additional radiotherapy was performed in all three cases, and chemotherapy in two patients. In one patient multiple pulmonary metastases were noted, which showed progression despite systemic chemotherapy. Histologically, the neoplasms were composed of round/polygonal and spindle-shaped tumour cells including typical rhabdomyoblasts. In all cases a pseudovascular pattern and prominent hyaline sclerosis of the intercellular matrix was seen. Immunohistochemically, tumour cells stained positively for desmin and muscle actin (HHF35) and also for markers of striated muscle differentiation (myogenin, MyoD1, fast myosin). In this paper an unusual morphological variant of rhabdomyosarcoma arising in adult patients is described, which should be added to the morphological spectrum of these neoplasms.

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Key words Rhabdomyosarcoma · Soft tissue tumours · Adults · Immunohistochemistry

Introduction

Rhabdomyosarcomas comprise about two-thirds of soft tissue sarcomas in children; in adolescents and young adults they are more infrequent; and in patients older than 40 years these tumours are very rare. Recently, the Intergroup Rhabdomyosarcoma Study proposed a new classification for rhabdomyosarcomas in children and adolescents [13]. In this classification three prognostically significant subtypes were recognised. Botryoid and the recently delineated spindle-cell form of embryonal rhabdomyosarcoma [2, 8] are associated with a better prognosis than either of the other subtypes, embryonal rhabdomyosarcoma is characterised by an intermediate prognosis, and alveolar rhabdomyosarcoma, including its solid variant, is associated with a poor clinical outcome.

In adults rhabdomyosarcoma occurs in two main histological forms. In addition to rare cases of the juvenile histological types, rhabdomyosarcoma in adults is seen most frequently as pleomorphic rhabdomyosarcoma [6]. Pleomorphic rhabdomyosarcomas in adults commonly arise in deep soft tissues of the extremities of middle-aged or older patients; they have a male predominance and follow a very aggressive clinical course [5]. Most recently, cases of clear-cell [1] and spindle-cell rhabdomyosarcoma [17] have been described as rare morphological forms in adult patients. We report three cases of rhabdomyosarcoma in adults, characterised morphologically by prominent hyaline sclerosis and a pseudovascular pattern, which represents an additional morphological variant and may be a potential diagnostic pitfall.

Materials and methods

All three cases were identified in the consultation files of one of the authors (D.K.). In each case, tissue was fixed in 10% buffered

Table 1 Antibodies used for immunohistochemical analysis (*ASMA* alpha smooth muscle actin, *EMA* epithelial membrane antigen, *NSE* neuron-specific enolase)

Antigen	Clone	Dilution	Source
Vimentin	V 9	1:40	Dako, Glostrup, Denmark
Desmin	D33	1:50	Dako
ASMA	1A4	1:80	Dako
Muscle actin	HHF35	1:300	Dako
MyoD1	5.8.A	1:30	Novocastra, Newcastle, UK
myf 4	L026	1:30	Novocastra
Fast myosin	MY-32	1:400	Sigma, Deisenhofen, Germany
Myoglobin	Polyclonal	1:40	Dako
CD 31	JC/70A	1:30	Dako
CD 34	QBEND10	1:100	Dianova, Hamburg, Germany
CD99	O13	1:50	Signet, Dedham, Mass.
F VIII-antigen	F8/86	1:50	Dako
S-100 protein	Polyclonal	1:2000	Dako
Pancytokeratin	MNF 116	1:50	Dako
EMA	E29	1:50	Dako
NSE	BBS/NC/VI-H14	1:100	Dako

Table 2 Clinical details in three cases of sclerosing, pseudovascular rhabdomyosarcoma (*M* male, *F* female, *RT* radiotherapy, *CT* chemotherapy, *NSR* no sign of recurrence)

Case no.	Age/Sex	Site	Size (cm)	Follow-up
1	40/M	Left lower leg	5 cm	Postoperative RT, NSR at 11 months
2	41/F	Left upper jaw	"Bean-sized"	Postoperative RT, local recurrence at 8 months, additional RT and CT
3	56/F	Proximal body of the sacrum	3×2×2	Presented with four pulmonary metastases; postoperative RT and CT (progression of pulmonary metastases); patient is alive with tumour at 7 months

formalin, conventionally processed and embedded in paraffin wax. Sections 4 µm thick were stained with haematoxylin and eosin, periodic acid–Schiff reaction (PAS), and Goldner trichrome. Representative slides of all cases were studied by immunohistochemistry with the alkaline phosphatase–antialkaline phosphatase method (APAAP) using appropriate positive and negative controls throughout. The antibodies used and their dilutions and sources are listed in Table 1. The mitotic rate was expressed as the average mitotic count present in 10 high-power fields (HPF; 1 HPF=0.159 mm^2 on the microscope used). Clinical details and follow-up information were obtained if possible from the hospital records, the laboratory request forms, and the referring pathologists (see Acknowledgements).

Results

Clinical findings

The clinical data are summarised in Table 2. The age of the patients at operation was 40, 41, and 56 years; two patients were women. In case 1 a trauma of the left tibia 10 years before tumour development was reported. From this region a 5-cm deep-seated soft tissue lesion was excised in a piecemeal excision. The patient received postoperative radiotherapy and developed an ulceration in this region 8 months later. No signs of recurrence or metastases were noted within the next 11 months. The patient in case 2 developed a bean-sized intramuscular neoplasm in the region of the left upper jaw. The tumour was widely excised and additional radiotherapy was performed. A local recurrence was noted clinically at 8 months, and the patient received additional radio- and chemotherapy. The patient in case 3 presented with a lesion in the first vertebrosacral body with extension into the spinal canal. MRI scanning showed no extension into paravertebral soft tissues. The neoplasm was incompletely excised, and at the time of presentation four pulmonary metastases were evident; no other primary was detected by careful clinical and radiological investigation. The patient received additional radio- and chemotherapy. Despite chemotherapy the pulmonary metastases progressed, and 7 months after incomplete excision of the primary the patient still has metastases but is alive.

Histological findings

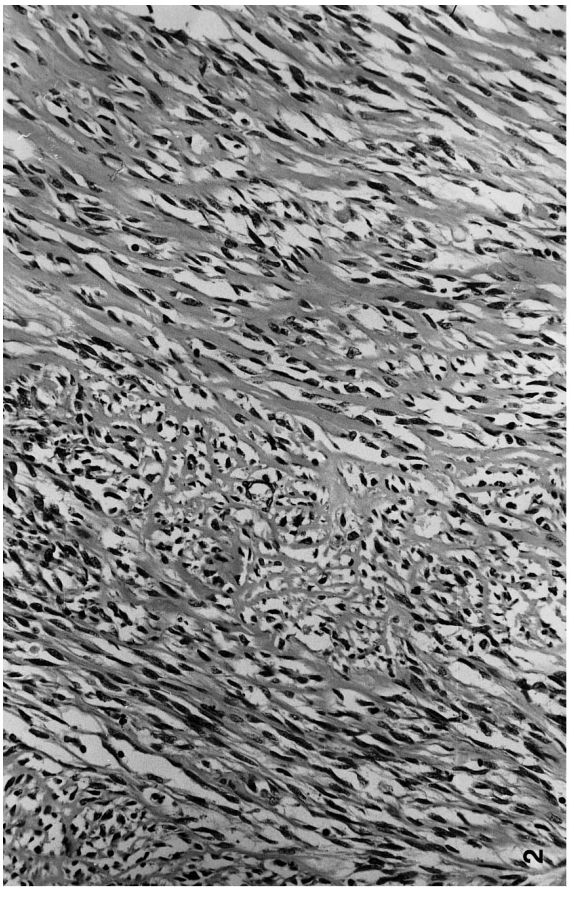
Histologically, all neoplasms were composed of elongated spindle-shaped or polygonal tumour cells containing a varying amount of eosinophilic cytoplasm and enlarged, atypical nuclei, which were either hyperchromatic with irregular borders or vesicular with small nucleoli.

Fig. 1 Case 1. Anastomosing spaces lined by tumour cells with hyperchromatic nuclei are seen. Note small papillary tufts. H&E ▶

Fig. 2 Case 1. Focally, a fascicular growth pattern of spindle-shaped tumour cells was found. H&E

Fig. 3 Case 1. Numerous rhabdomyoblasts (*arrows*) with abundant eosinophilic cytoplasm and eccentrically placed nuclei were evident. H&E

Fig. 4 Case 2. Note tumour cells with enlarged nuclei and cytoplasmic vacuoles (spider-web rhabdomyoblasts) mimicking lipoblasts. H&E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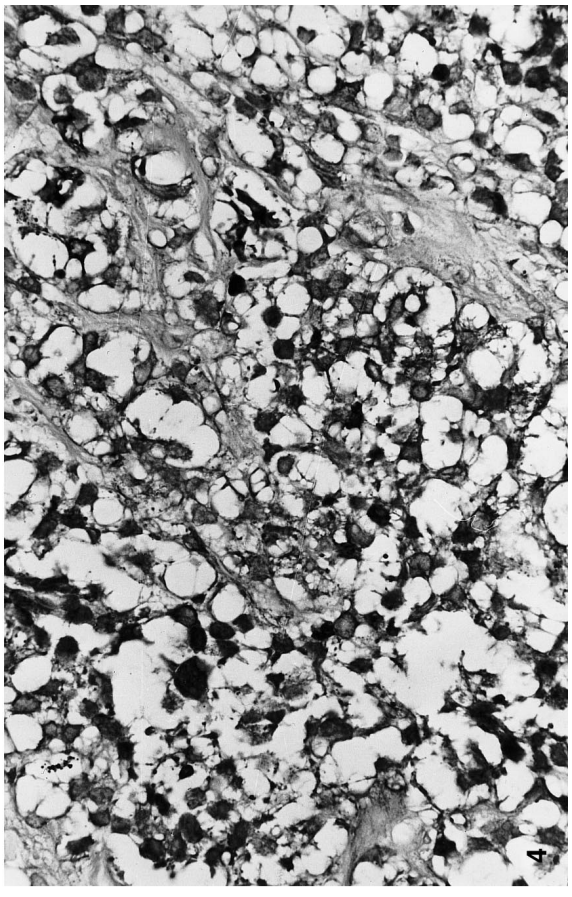
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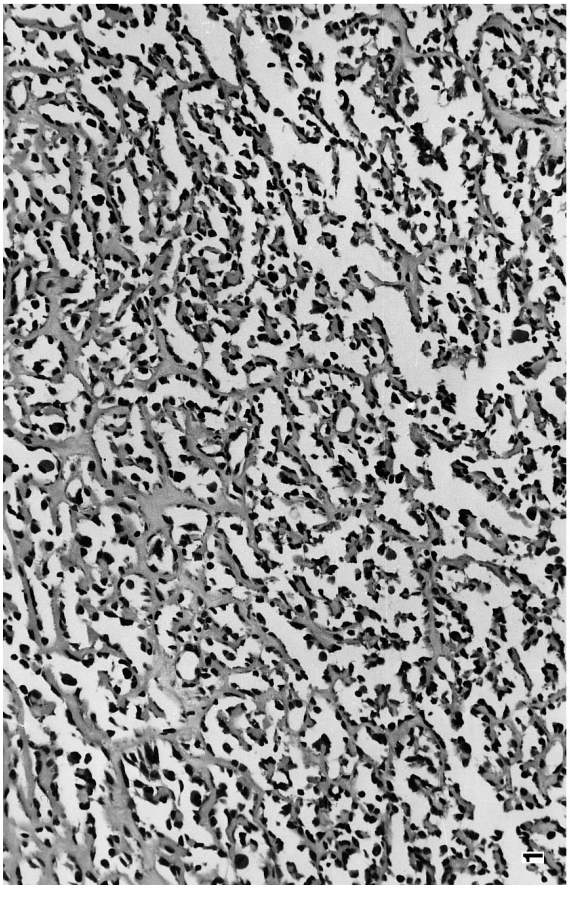
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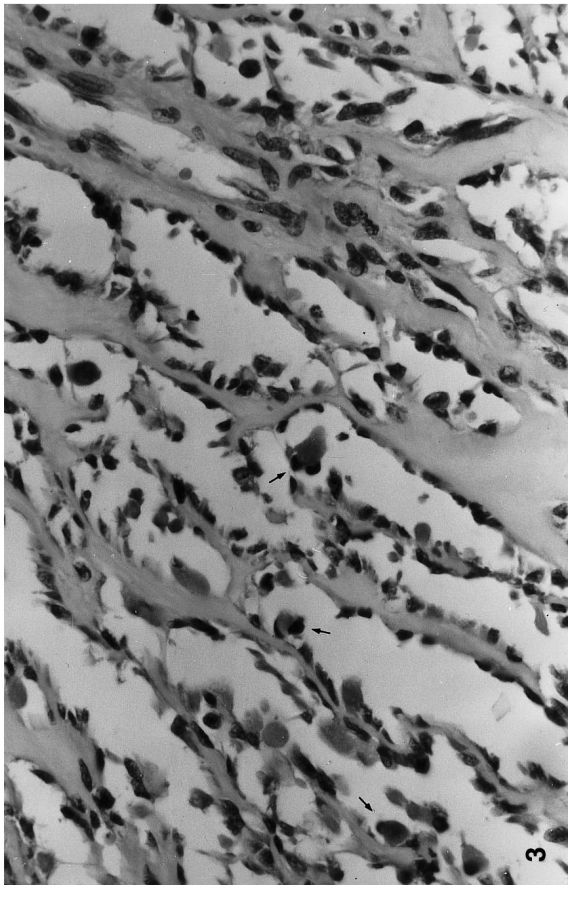
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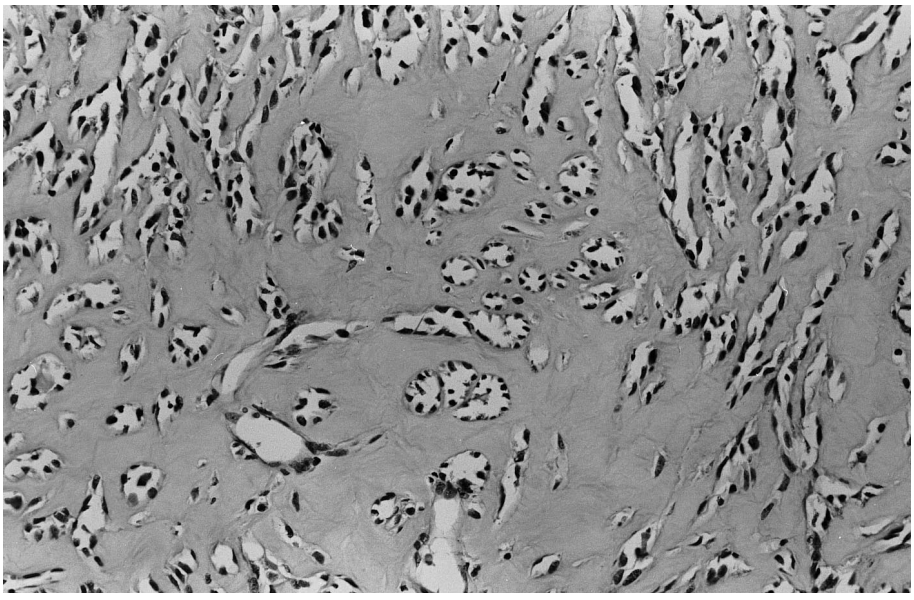

Fig. 5 Case 3. In all cases abundant intercellular collagen showing prominent hyaline sclerosis was seen. H&E

Table 3 Results of immunohistochemical studies (+ positive, – negative, (+) focal or weak positivity of tumour cells, NV not available)

	Case 1	Case 2	Case 3
Vimentin	+	+	NV
Desmin	+	(+)	+
ASMA	(+)	–	NV
Muscle actin	+	+	(+)
MyoD1	–	(+)	+
myf 4	+	+	–
Fast myosin	+	(+)	NV
Myoglobin	(+)	NV	NV
CD 31	–	–	NV
CD 34	–	–	NV
CD99	–	–	NV
F VIII-antigen	–	NV	NV
S-100 protein	NV	–	–
Pancytokeratin	–	NV	–
EMA	–	NV	NV
NSE	NV	–	NV

Most of the tumour area examined in case 1 was composed of irregularly anastomosing spaces lined by atypical cells with small papillae, and tufts creating a pseudovascular pattern were noted (Fig. 1). In other areas of this neoplasm a more fascicular growth pattern of rather elongated spindle-shaped tumour cells with atypical fusiform nuclei was seen (Fig. 2). In addition, scattered medium-sized, round or polygonal, tumour cells with abundant eosinophilic cytoplasm and eccentrically placed atypical nuclei resembling typical rhabdomyoblasts were identified (Fig. 3).

Pre-existing fibrofatty tissue and skeletal muscle were diffusely infiltrated by round and polygonal tumour cells in case 2. In addition to tumour cells with pale eosinophilic cytoplasm, scattered tumour cells with a central and large nucleus and numerous intracytoplasmic vacuoles containing PAS-positive glycogen (so-called spider-web rhabdomyoblasts) were noted in this neoplasm (Fig. 4). Few tumour cells showed nuclear pseudoinclusions. Pseudovascular spaces similar to the appearance in case 1 were found.

In case 3 numerous tissue fragments containing enlarged, round or polygonal tumour cells were identified. Most neoplastic cells resembled rhabdomyoblasts with abundant eosinophilic cytoplasm and enlarged, peripherally placed nuclei occasionally containing nuclear pseudoinclusions and lined pseudovascular clefts at least focally.

The intercellular stroma in all cases was composed of abundant collagen showing prominent hyaline sclerosis (Fig. 5). Small aggregates of inflammatory cells were seen in case 2. The mitotic rate ranged from 2 (case 3) to 4 (case 1) mitoses in 10 HPF.

Immunohistochemical findings

The results of immunohistochemical stainings are summarised in Table 3. Tumour cells in all cases tested stained positively for vimentin, desmin (Fig. 6) and muscle-specific actin (HHF45), whereas alpha smooth muscle actin was only focally positive in case 1. In addition, rhabdomyoblasts were positive for myogenin (myf 4) in cases 1 and 2 (Fig. 7), for MyoD1 in cases 2 and 3, for fast myosin in case 1 (Fig. 8), and at least focally for myoglobin in case 1. Cells lining anastomosing and pseudoglandular spaces were negative for endothelial and epithelial markers. All tumours tested were entirely negative for S-100 protein, CD99 and NSE.

Discussion

Rhabdomyosarcoma in adults is a very rare and clinically aggressive neoplasm, and morphologically the pleomorphic subtype predominates in this age group [5]. Pleomorphic rhabdomyosarcoma can display a broad va-

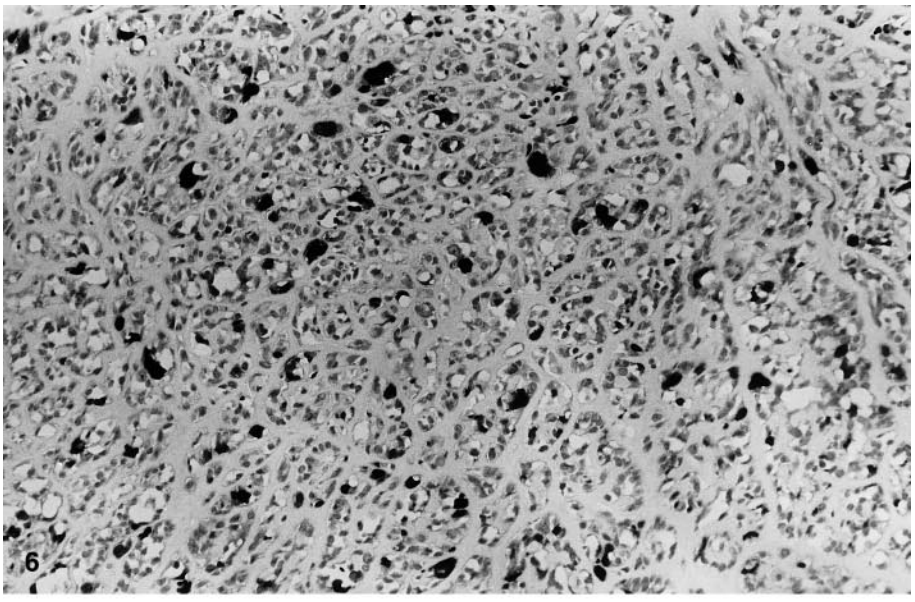

Fig. 6 Tumour cells in all cases (case 1) stained positively for desmin. APAAP

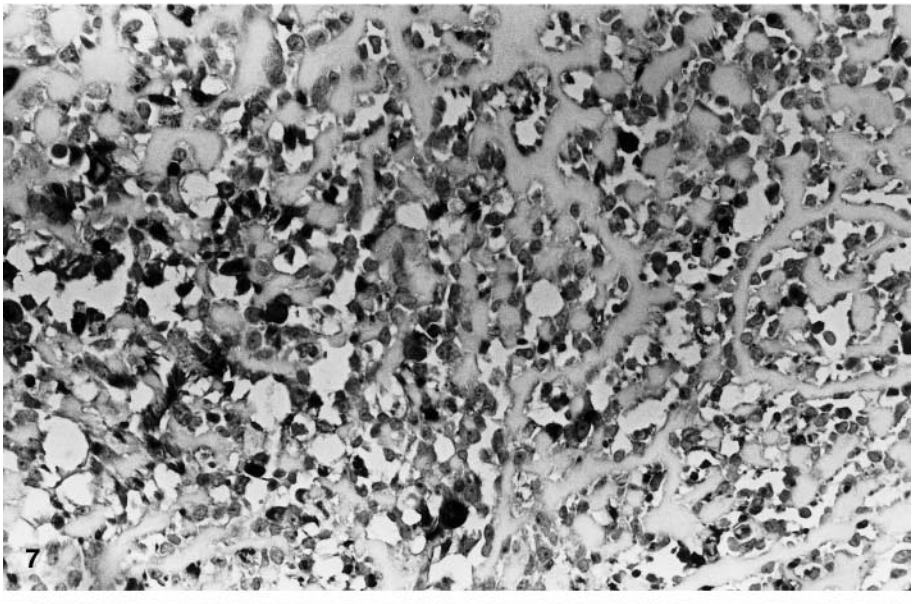

Fig. 7 Case 2. Note rhabdomyoblasts showing positive nuclear staining for myogenin (myf 4). APAAP

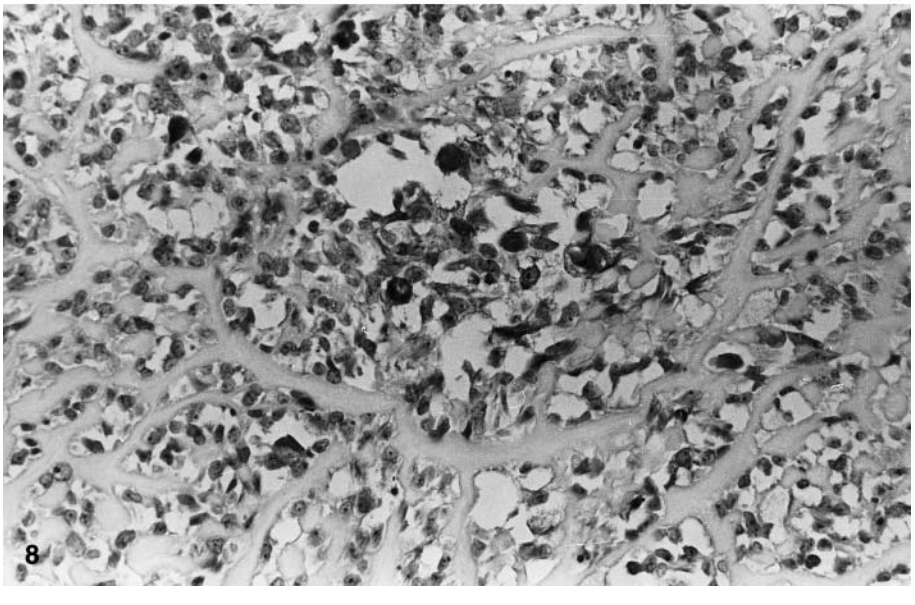

Fig. 8 Case 2. Scattered tumour cells stained positively for fast myosin. APAAP

riety of histological features. Fascicles of spindle-shaped tumour cells may suggest the diagnosis of leiomyosarcoma or fibrosarcoma in many cases. Therefore, the demonstration of rhabdomyoblasts is indispensable for the exact diagnosis of these neoplasms, and in the past different forms, including strap and tadpole rhabdomyoblasts, were described. Unfortunately, light-microscopic features of these tumour cells are not diagnostic in the absence of cytoplasmic cross-striations (which it is difficult or impossible to find in most cases). Therefore, a tentatively suggested diagnosis of rhabdomyosarcoma needs ultrastructural and/or immunohistochemical confirmation. With the benefit of these ancillary techniques and the availability of newly developed immunohistochemical antibodies against antigens involved in the regulation of skeletal muscle differentiation (MyoD family) [3], rhabdomyosarcoma in adults has been more frequently diagnosed in the last years [5]. Nowadays, rhabdomyosarcomas can be clearly distinguished from so-called malignant fibrous histiocytomas, with which they may easily be confused in conventional H&E sections.

In addition to rare cases of the juvenile histological types and the usual pleomorphic type, rare morphological variants, including clear-cell [1] and spindle-cell rhabdomyosarcoma [17], have been described.

We would like to extend the list of morphological variants and forms of rhabdomyosarcoma in adults reported hitherto by the addition of these three cases characterised by a pseudovascular pattern of neoplastic cells and prominent hyaline sclerosis of intercellular matrix. Usually, there is no prominent collagenous background in rhabdomyosarcoma, and collagen is confined to intervening fibrous septa in alveolar rhabdomyosarcoma. However, in rare cases prominent desmoplasia has been shown [4].

The presence of anastomosing spaces lined with atypical tumour cells in all cases and of small papillae and tufts in case 1 closely resembled morphological features of angiosarcoma. In contrast, immunohistochemistry revealed clear positivity for myogenic markers of tumour cells in all cases that stained negatively for endothelial markers. A further neoplasm with pseudovascular spaces, which may metastasise to deep soft tissue in rare cases, is acantholytic or pseudovascular squamous carcinoma [12]. In these neoplasms extreme acantholysis is accompanied by the development of pseudovascular spaces. However, existence of a primary tumour somewhere and positive staining of tumour cells for epithelial markers allow distinction from the cases reported in this paper.

Do the cases reported represent an unusual form of alveolar rhabdomyosarcoma occurring in older patients than expected? Alveolar rhabdomyosarcoma is characterised by an alveolar architecture and does not show pseudovascular, anastomosing spaces lined by a single layer of neoplastic cells with papillae and tufts. In addition, multinucleated (wreath-like) rhabdomyoblasts were not found in our cases. In case 1 representative material was available for molecular investigations (see Acknowledgements). No chimeric RNA transcripts due to t(1;13) or t(2;13) translocation characteristic of alveolar rhabdomyosarcoma were found by RT-PCR.

Further neoplasms which may be considered in the differential diagnosis include leiomyosarcoma, myofibroblastic sarcoma, triton tumour, and the recently characterised epithelioid fibrosarcoma [10]. Leiomyosarcoma is easily excluded by the histological and immunohistochemical evidence of rhabdomyoblastic differentiation in our cases (immunopositivity for myf 4, MyoD1, myoglobin and fast myosin). Because of prominent stromal hyalinisation and focal spindle-cell morphology of tumour cells (especially in case 1), which stained positively for desmin and muscle actin, sarcomas showing myofibroblastic differentiation (myofibrosarcomas) [11] must also be considered in the differential diagnosis. Tumour cells in myofibroblastic sarcomas contain a paler eosinophilic cytoplasm and are negative for myf 4, MyoD1, myoglobin and fast myosin. Malignant peripheral nerve sheath tumours with heterologous rhabdomyoblastic differentiation (triton tumours) are composed of elongated tumour cells with tapered nuclei showing perivascular whorling and histological and/or immunohistochemical/ultrastructural neural differentiation. Sclerosing epithelioid fibrosarcoma is characterised by round to ovoid epithelioid tumour cells and prominent hyaline sclerosis. Loss of cellular cohesion resulting in an alveolar pattern was observed in some cases. However, in contrast to the neoplasms described in this paper, all cases of sclerosing epithelioid fibrosarcoma were negative for muscle markers.

The cases reported are also unusual in their clinical presentation. In case 1 previous trauma was reported, and in cases 2 and 3 the tumours arose in unusual anatomical locations. In contrast to childhood rhabdomyosarcoma, most cases of rhabdomyosarcoma in adults are seen within the skeletal musculature of the limbs [6]. In case 2 rhabdomyosarcoma was located in deep soft tissue of the upper jaw, and in case 3 a primary rhabdomyosarcoma of bone was noted. There are only single case reports of rhabdomyosarcomas in bone in children [9] and adults [7, 14, 15], and they have to be distinguished from dedifferentiated chondrosarcoma with rhabdomyosarcomatous differentiation [16].

In summary, we describe three cases of rhabdomyosarcoma in adults, all showing unusual morphological features which represent a potential diagnostic pitfall. Their knowledge is not only mandatory for the exact diagnosis but may also be important for the treatment. Despite the limited number of cases, it has been said that rhabdomyosarcoma in adults responds better to chemotherapy than do other sarcomas [17].

Acknowledgements The authors are very grateful to the following pathologists for providing case material and clinical information when available: Dr. Peters, Hamburg, Germany (case 1), Professor Dr. Hill and Dr. Steinmann, Hamm, Germany (case 2), and Dr. Lüftner, Meiningen, Germany (case 3). In addition, we are very grateful to Professor Dr. C.D.M. Fletcher, Boston, Mass., who contributed to the right diagnosis in case 1, and to Professor Dr. D. Harms and Dr. M. Krams, Kiel, Germany, who kindly performed molecular investigations in case 1.

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