Virchows Arch A (1987) 410:423–431

Virchows Archiv A

Epithelioid sarcoma in children and adolescents

An immunohistochemical study*

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Summary. Six cases of epithelioid sarcoma were studied by conventional light microscopy and immunohistochemistry. The six cases account for 1.4% of the 417 cases of soft tissue sarcoma collected at the Paediatric Tumor Registry, Kiel. The average age of the five male and one female patient was 10.8 years (median: 13 years). Particular clinical findings included the location of the tumours; three were found in the pelvis, two in the head and neck, and one in the hand. Four patients are living without disease, and one patient died of disease three years after diagnosis.

Histologically, four of the six tumours revealed multinucleated giant cells. Immunohistochemically using a panel of mono- and polyclonal antibodies all cases stained positively for vimentin, cytokeratin, epithelial membrane antigen (EMA), and human milk fat globulin (HMFG-2). Five cases were positive for neuron specific enolase (NSE), and three stained positively for protein S-100. A positive reaction for alpha-1-antichymotrypsin was noted in two cases. These immunohistochemical findings attest to the multidirectional differentiating capabilities of epithelioid sarcoma and support the concept of derivation from a multipotent mesenchymal stem cell.

Key words: Epithelioid sarcoma – Immunhistochemistry – Differentiation – Histogenesis

Introduction

Epithelioid sarcoma is a unique soft tissue sarcoma occurring predominantly in the distal extremities (cf. Chase and Enzinger 1985). Despite numerous histopathological, ultrastructural and enzyme histochemical studies (Gabbiani et al. 1972; Santiago et al. 1972; Soule and Enriquez 1972; Frable et al. 1973; Seemayer et al. 1974; Küchemann 1975, Bloustein et al. 1976; Hajdu et al. 1977; Mackay 1977; Patchefsky et al. 1977; Tsuneyoshi et al. 1980; Mills et al. 1981; Cooney et al. 1982; Machinami et al. 1982; Miettinen et al. 1982b; Lombardi and Rilke 1984; Padilla et al. 1985) its histogenesis remains uncertain. There have been comparatively few immunohistochemical investigations (Blewitt et al. 1983; Chase et al. 1984; Meister 1984; Mukai et al. 1985). Most of them have demonstrated keratin in addition to vimentin intermediate filaments. Some authors have used antibodies against lysozyme, alpha-1-antitrypsin and alpha-1-anti-chymotrypsin which are said to be markers of neoplastic lesions of a histiocytic nature (Mukai et al. 1985; Padilla et al. 1985).

In the current study we investigated six cases of epithelioid sarcoma using a panel of mono- and polyclonal antibodies. We also included antibodies which were not expected to yield positive findings like anti-desmin. Their positive reactions in some of the cases raise questions on the value of immunohistochemical stains in the diagnosis and differential diagnosis of epithelioid sarcoma. Moreover, they provoke discussions on the histogenesis and differentiation of malignant soft tissue tumours in general as determined by immunohistochemical methods.

Materials and methods

Six cases of epithelioid sarcoma were identified among 417 cases of soft tissue sarcoma collected at the Paediatric Tumor Registry, Kiel over a period from 1980 to 1985. The age of the six patients varied from 43 months to 18.3 years with an average age of 10.8 years (median: 13 years). There were five males and one female. Three tumours were located in the

* This study was supported in part by a grant from the Bundesminister für Arbeit und Sozialordnung and the Deutsche Forschungsgemeinschaft (Schm 613/1-1)

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Table 1. Clinical data of patients with epithelioid sarcoma

Case No.	Age	Sex	Location	Treatment	Follow up
1	43 months	m	pelvis	Op., CHT	8 months, NED
2	5 years	m	pelvis	preop. CHT, Op., CHT	10 months, NED
3	12 years	m	head	Op.	6 months, NED
4	13 years	m	pelvis	Op., CHT, RT	3 years, 2 loc. rec., DOD
5	14 years	m	hand	Op.	14 months, NED
6	18 years	f	neck	CHT, RT	9 months, AWD

AWD = Alive with (progressive) disease; CHT = Chemotherapy; DOD = Died of disease; NED = No evidence of disease; Op. = Operation; RT = Radiotherapy

Table 2. Immunohistochemical reagents used in the study of cases of epithelioid sarcoma

Reagent	References	Source	Dilution
Anti-vimentin (P)	Ramaekers et al. (1983)	Euro diagnostics	1:10
Anti-keratin (P)	Ramaekers et al. (1983)	Euro diagnostics	1:100
Anti-keratin (55–57 Kd; KL 1; M)	Viac et al. (1983)	Dianova	1:100
Anti-desmin (P)	Ramaekers et al. (1983)	Euro diagnostics	1:50
Anti-epithelial membrane antigen (EMA; M)	Sloane and Ormerod (1981)	Dakopatts	1:100
Anti-human milk fat globulin-2 (HMFG-2; M)	Burchell et al. (1983)	Bios	1:100
Anti-neuron specific enolase (NSE; P)	Schmechel et al. (1979)	Dakopatts	1:300
Anti-protein S-100 (P)	Takahashi et al. (1981)	Dakopatts	1:100
Anti-lysozyme (P)	Mason and Taylor (1975)	Dakopatts	1:100
Anti-alpha-1-antitrypsin (P)	Isaacson et al. (1981)	Dakopatts	1:100
Anti-alpha-1-antichymotrypsin (P)	Meister and Nathrath (1980)	Dakopatts	1:100

(P) = Polyclonal; (M) = Monoclonal

deep soft tissues of the pelvis, two in the head and neck, and one in the dermis and subcutis of the hand. One of the two head and neck tumours occurred in the subcutis, the other in the deep soft tissues.

Four patients are living without evidence of disease, one is alive with disease, and one patient died of disease three years after diagnosis and two local recurrences (Table 1).

For conventional light microscopy 4 μm thick paraffin sections were stained with haematoxylin and eosin, Giemsa, periodic acid Schiff (PAS), silver impregnation according to Bielschowsky, and Goldner. Immunohistochemical studies were carried out on formalin fixed tissue. In one case alcohol fixed tissue was also available. Usually alcohol fixed tissue gives better results when intermediate filaments are studied (Altmannsberger et al. 1981), but we (Schmidt et al. 1986) and other authors (Altmannsberger et al. 1981; Osborn and Weber 1983; Ramaekers et al. 1983; Viac et al. 1983; Molenaar et al. 1985) have previously shown that intermediate filaments containing vimentin, desmin, (cyto-) keratin and glial fibrillary acid protein can also be demonstrated in formalin fixed tissue. The different antigens were demonstrated using the peroxidase-antiperoxidase (PAP) method according to Sternberger et al. (1970). Paraffin sections were dewaxed, rehydrated in a graded series of alcohol and incubated with the different types of primary mono- and polyclonal antibodies (Table 2). Proteolytic digestion was not employed.

For most antibodies incubation was carried out overnight at 4° C. Following incubation with the primary antibody the linking antibodies were applied (anti-rabbit Ig (1:25) for polyclonal antibodies, PAP conjugated rabbit anti-mouse Ig (1:25) for monoclonal antibodies). The PAP-complex was used in a dilution of 1:100. For the demonstration of vimentin-intermediate filaments the dilution of the PAP-complex had to be lowered to 1:40. As chromogen we used 3,3′-diaminobenzidine.

Negative controls were performed using phosphate buffered saline instead of primary antibody.

Results

The two tumors which were located in the dermis and subcutis of the head and hand, respectively, demonstrated a nodular arrangement of the constituent cells. The overlying epidermis was ulcerated. Degeneration and necrosis were apparent in the center of the nodules (Fig. 1). Areas of necrosis were also present in the tumors located in the deep soft tissues. In two cases necrosis was extensive resulting in a "geographical" pattern. The size and shape of the constituent cells varied. The predominant cells were small, round or polygonal and had twisted or indented nuclei and scanty cytoplasm. These cells merged imperceptibly with larger cells having round nuclei and prominent nucleoli. In addition to these small and large round cells there were fusiform cells. The large cells were particular-

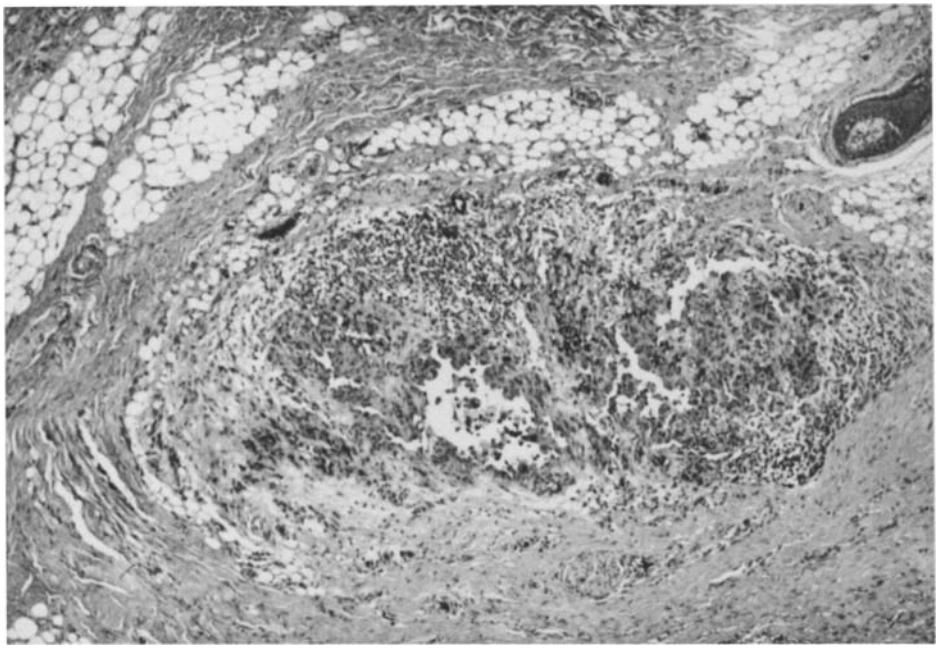

Fig. 1. Epithelioid sarcoma. Nodular arrangement of tumour cells with central necrosis and formation of pseudocystic spaces. Goldner, 56×

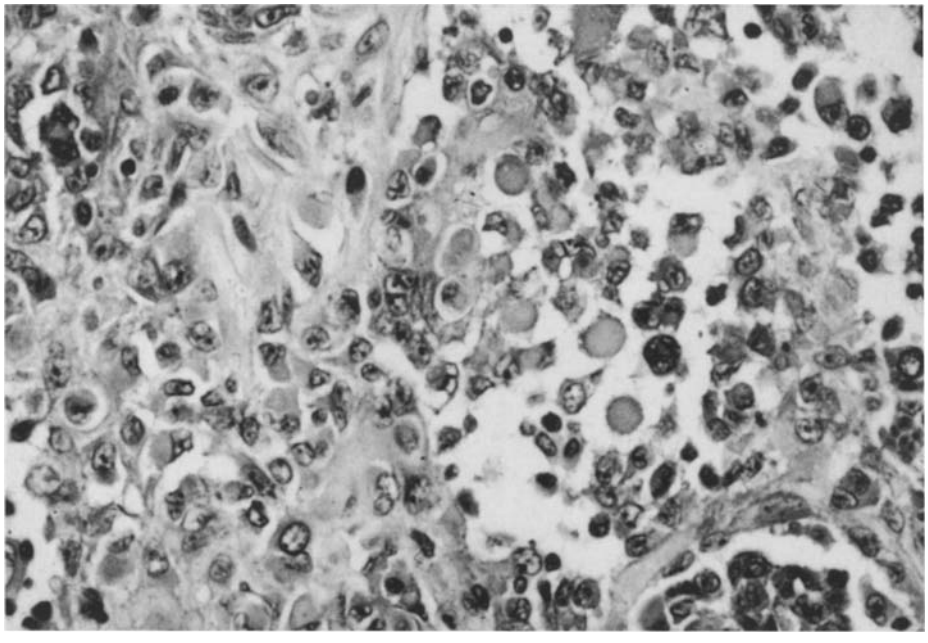

Fig. 2. Epithelioid sarcoma. Several cells in the pseudocystic space contain hyalin globules in their cytoplasm. HE, 350×

ly found in the vicinity and in the center of the necrotic areas. They had a deeply eosinophilic cytoplasm, and in two cases they contained hyalin, PAS-negative globules (Fig. 2). All tumours contained small amounts of glycogen. Multinucleated giant cells were observed in four of the six tumours, in one case corresponding to osteoclast-like giant cells. Between the neoplastic cells there was a prominent network of reticulin fibrils, and abundant hyalinized collagen was often seen. Large amounts of alcian blue-positive material were noted in the extracellular space. Mitotic activity was moderate.

All tumors stained positively for vimentin (see Table 3). Although the intensity of the reaction product varied, it was obvious that in five of the six cases more than 50% of the cells were positive including small, large and fusiform cells (Fig. 3). Keratin-positive cells were also found in all tumours. The most intensive staining was apparent

Table 3. Results of immunohistochemical stains in six cases of epithelioid sarcoma

Case No.	VIM*	KER*	KL 1**	NSE*	S-100*	EMA**	HMFG-2**	DESMIN*	LYS*	AAT*	ACT*
1	+++	+++	+++	(+)	∅	+++	+++	∅	∅	∅	∅
2***	+++	+++	+++	+++	∅	++	++	+	∅	∅	∅
3	++	+	+	+	∅	+++	+++	∅	∅	∅	++
4	+++	++	++	∅	++	++	++	∅	∅	∅	++
5	+++	++	++	(+)	+	+++	+++	∅	∅	∅	∅
6	+++	+	+	+++	+	+++	+++	∅	∅	∅	∅

(+) single cells; + < 10%; ++ 10–50%; +++ > 50% of all cells

VIM = Vimentin; KER = Keratin; KL 1 = Cytokeratin (55–57 kd); NSE = Neuron specific enolase; S-100 = Protein S-100; EMA = Epithelial membrane antigen; HMFG-2 = Human milk fat globulin-2; LYS = Lysozyme; AAT = Alpha-1-antitrypsin; ACT = Alpha-1-antichymotrypsin

* Polyclonal antibody; ** Monoclonal antibody; *** Alcohol fixed tissue available

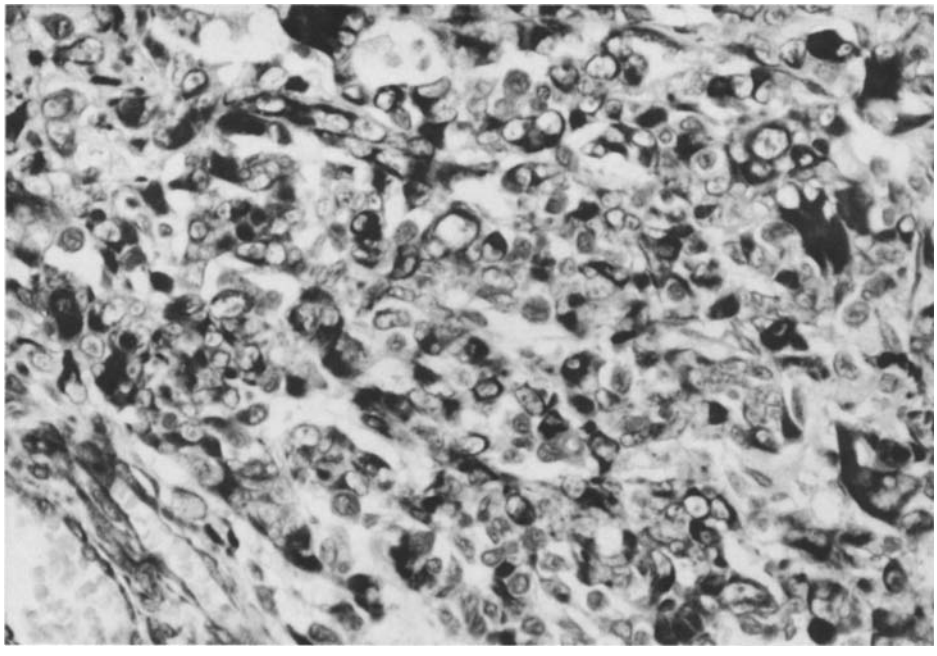

Fig. 3. Epitelioid sarcoma. Vimentin is present in many small cells, but also in some large cells. PAP-method, 350 ×

in the large cells, but many small and fusiform cells were also decorated. When the two antibodies were compared, more intensive staining was obtained using the monoclonal anti-keratin antibody KL 1 (Fig. 4). However, the number of positive cells labeled with the polyclonal antibody was almost identical. Positive reactions were also found using monoclonal antibodies against epithelial membrane antigen and human milk fat globulin-2 (HMFG-2). In four of the six cases virtually all cells demonstrated a positive reaction along the plasma membrane. Five cases revealed a positive staining for neuron specific enolase. In two of these cases more than 50% of the neoplastic cells were positive (Fig. 5). In the other cases mostly single positive cells were seen. Neuron specific enolase was found in both the small and large cells. Three cases demonstrated positivity for protein S-100, but the proportion of positive cells was low. In one case a positive reaction for desmin was observed in about 10% of the neoplastic cells. In this case the tumour tissue had been fixed in alcohol. There were large globular cytoplasmic inclusions frequently compressing the nuclei (Fig. 6). In two cases a positive granular reaction was found in the small and large cells for alpha-1-antichymotrypsin. Reactions for lysozyme and alpha-1-antitrypsin were consistently negative.

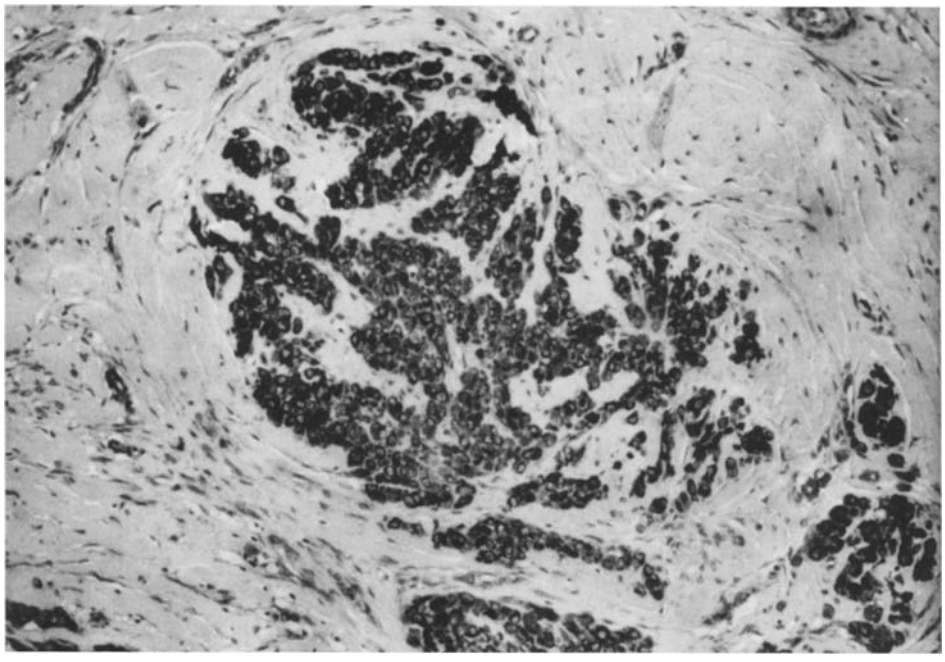

Fig. 4. Epithelioid sarcoma. Cluster of tumor cells stains positively for epidermal keratin (KL 1 antigen). PAP-method, 56×

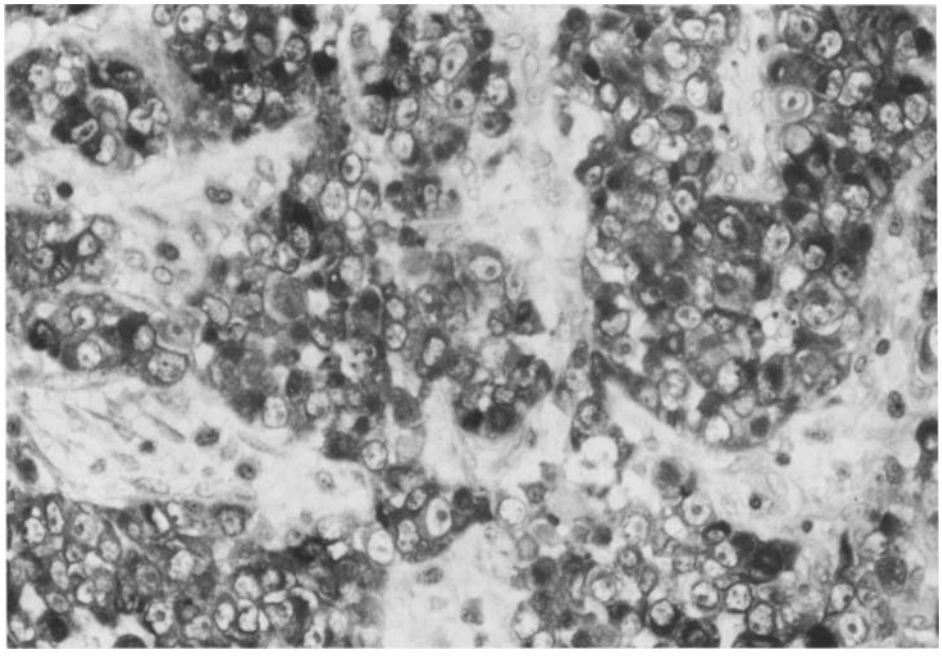

Fig. 5. Epithelioid sarcoma. Many cells reveal strong reactivity for neuron specific enolase. PAP-method, 350×

Discussion

In the current study six cases of epithelioid sarcoma were investigated by conventional light microscopy and immunohistochemistry using a panel of mono- and polyclonal antibodies. Five of the six tumours occurred in children less than 15 years of age at diagnosis, thus accounting for 1.2% of all soft tissue sarcomas collected at the Paediatric Tumour Registry, Kiel. This frequency is almost identical to that reported by Enjoji and Hashimoto (1984) who found one case of epithelioid sarcoma among 88 cases of soft tissue sarcoma in patients less than 15 years. By contrast, the anatomical distribution of our cases was different from that reported in the literature. Chase and Enzinger (1985) found that head and neck and pelvis, respectively, were very unusual sites. Ninety-five per cent of their 241 cases were located in the extremities. In comparison, among our six cases only one oc-

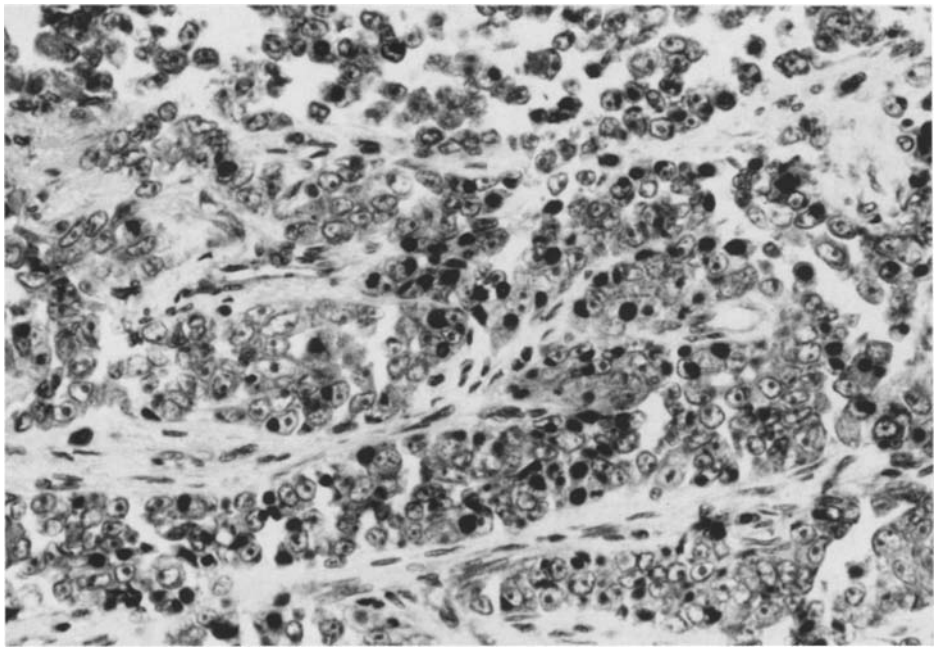

Fig. 6. Epithelioid sarcoma. Most cells have cytoplasmic inclusions which are positively stained for desmin. PAP-method, 350×

curred in the extremities, while the remaining five affected the head and neck and the pelvis, respectively. Thus, although the number of cases in the current study is low, especially compared with the series studied by Chase and Enzinger (1985), it is tempting to speculate whether epithelioid sarcoma in children is perhaps less frequently located in the extremities than in adults. Before this question can be answered more cases of epithelioid sarcomas in paediatric patients must be collected.

The overall histopathological appearance of our paediatric cases did not differ from that of epithelioid sarcomas in adolescents and adults. The only difference related to the presence of multinucleated giant cells. They were present in four of our six cases. By contrast, Chase and Enzinger (1985) point out that giant cells are a rare finding in epithelioid sarcoma, being present in only 5% of their cases (12/241). As in that study, the giant cells in our cases lacked the bizarre pleomorphism encountered in giant cells in malignant fibrous histiocytoma.

The main purpose of the current study was to evaluate the immunohistochemical features of epithelioid sarcoma. A panel of different mono- and polyclonal antibodies was therefore employed. Based on our experience from immunohistochemical studies on a large number of soft tissue sarcomas and non-sarcomatous tumours which not infrequently revealed surprising findings in their immunophenotypical features, we also used antibodies which were not expected to yield positive reactions including anti-desmin, anti-NSE and anti-protein S-100.

The polyclonal anti-desmin antibody yielded reliable results in our previous studies on rhabdomyosarcomas both of embryonal and alveolar subtypes (Schmidt et al. 1986). The same type of antibody was applied in immunohistochemical studies performed by Ramaekers et al. (1983) and Molenaar et al. (1985). Even poorly differentiated embryonal rhabdomyosarcomas could be identified using this antibody. It also proved useful in the diagnosis and differential diagnosis of spindle cell sarcomas, although a number of leiomyosarcomas did not stain. This finding, however, is not surprising, since it has been repeatedly stressed in the literature (Miettinen et al. 1982a, Meister 1984; Roholl et al. 1985). By contrast, it is questionable, whether "false" negative reactions occur in cases of rhabdomyosarcoma (Molenaar et al. 1985). This is probably more a problem of the definition what a rhabdomyosarcoma is. Nevertheless, it is clear that there are myogenous tumours which cannot be identified by immunohistochemical staining for desmin intermediate filaments.

Only Miettinen et al. (1982a) have reported "false" positive desmin staining in sarcomatous tumours. They found desmin positivity in one case of fibrosarcoma and malignant fibrous histiocytoma, respectively, and argued whether the positive cells might represent entrapped striated-muscle cells or represent muscle differentiation in malignant fibrous histiocytoma, which is assumed to be

derived from multipotential mesenchymal stem cells (Fu et al. 1975; Katenkamp and Raikhlin 1985). The possibility of entrapped skeletal muscle cells in the present case of epithelioid sarcoma focally positive for desmin can be excluded as the tumour was superficially located in the dermis without infiltration of voluntary muscle.

Moreover, the desmin-positive cells were indistinguishable from similar but desmin-negative cells in the other cases. Interestingly, desmin-positive cells were also labeled with antibodies against vimentin and keratin. These findings may be explained either by cross-reaction between different classes of intermediate filaments (and their respective antibodies) or by coexpression of the three different intermediate filament types. Unfortunately, tissue was not available for electron microscopic study or chemical analysis to elucidate this question further. It seems, however, that coexpression of two, three or even four types of intermediate filaments is a more common event than has previously been thought. For example, Gatter et al. (1986) found coexpression of different types of intermediate filaments in 40% of 94 pulmonary neoplasms. The possibility of shared epitopes between the different types of intermediate filaments could be excluded using two or three unrelated monoclonal antibodies for each intermediate filament class. From the findings of that study and of the current one as well as from our experience in other types of tumour it can be concluded that many neoplasms do not represent a homogeneous population of cells, but are composed of cells with varying properties. In addition to rather undifferentiated cells one can find cells with more or less obvious signs of differentiation.

This stem cell origin has also been proposed for epithelioid sarcoma (cf. Katenkamp and Raikhlin 1985), and accordingly, it is not surprising to find signs of muscle differentiation in this type of tumour. Likewise, it is not surprising to find epithelioid sarcomas which contain protein S-100- and/or NSE-positive cells. The finding of these so-called neural markers does not imply that epithelioid sarcoma is a neuroectodermally derived neoplasm, but merely demonstrates that neoplastic cells in epithelioid sarcoma are capable of multidirectional differentiation. This concept is further supported by our own findings and data from the literature that keratin-type intermediate filaments can be found in most cases (Nadji and Morales 1984; Chase et al. 1984; Mukai et al. 1985) and so-called histiocytic markers are expressed in a minor portion (Mukai et al. 1985; Padilla et al. 1985). Thus, epithelioid sarcoma is a remarkable example illustrating the problem of histogenesis and differentiation which has recently been excellently addressed by Gould (1986). Immunohistochemistry is also a useful tool in the differential diagnosis of epithelioid sarcoma from other types of soft tissue sarcoma, despite or because of its complex immunohistochemical properties. Except for epithelioid sarcoma and synovial sarcoma (Miettinen et al. 1982c) keratin has not been observed in any other type of soft tissue sarcoma including the malignant rhabdoid tumor of soft tissue. Otherwise, this type of tumour may present immunohistochemical features similar to those of epithelioid sarcoma (unpublished data), but in addition to the lack of keratin the younger age of the patient and the diffuse growth pattern enable this distinction. Interestingly, malignant rhabdoid tumour also contains eosinophilic cells with cytoplasmic inclusions. Like the eosinophilic cells in epithelioid sarcoma they are most frequent in areas which appear to undergo degenerative change. Thus, degeneration is most likely the reason of increased eosinophilia in both types of tumor. This view is supported by the finding that increased eosinophilia apparently corresponds to accumulation of intracytoplasmic filaments, and increase of intracytoplasmic filaments is well known from neoplastic and non-neoplastic conditions associated with degenerative change including Rosenthal fibres in astrocytic tumors (for review see Ghadially 1982). In epithelioid sarcoma there appears to be an increase in keratin intermediate filaments since most intensive staining with anti-keratin antibodies was obtained in the large eosinophilic cells close to or in the center of the degenerated areas.

In summary, our study has shown that epithelioid sarcoma in children and adolescents might occur in locations which are rarely affected in adults. Moreover, it demonstrates a diversity of immunohistochemical findings, which attest to its differentiating capabilities. It does not elucidate its histogenetic relationship, but allows its distinction from most other soft tissue sarcomas entering differential diagnosis.

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Accepted October 24, 1986