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Case report

Epithelioid sarcoma mimicking angiosarcoma: the value of immunohistochemistry in the differential diagnosis*

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Summary. Epithelioid sarcoma (ES) is a rare malignant tumour of young adults, usually presenting as a skin ulcer or subcutaneous nodule in the distal portion of the upper limb. Multiple recurrences and late metastases are typical, leading to fatality in a third to one-half of all cases. The slow evolution of the tumour is one reason for its delayed recognition. The other is its frequent histological misinterpretation, in particular, as a peculiar granulomatous reaction. In our case, the primary tumour presented a variant morphological pattern so closely mimicking a cavernous angiosarcoma as to mislead several reputable opinions. Later recurrences and metastases were typical of ES, while a focal angiomatoid pattern was maintained. The morphology and immunoreactivity to a wide spectrum of tumour markers is compared with that of six file cases of classical ES. Retrospectively, all neoplastic lesions in our patient were ES. In young adults, lesions of the upper extremity, even when angiomatoid or haemorrhagic, should raise a suspicion of ES. Once epithelioid sarcoma is suspected, the differential diagnosis can be elucidated on immunohistochemical grounds. Early diagnosis provides the best opportunity for radical surgery at a stage when the tumour has not spread locally or disseminated systemically.

Key words: Epithelioid sarcoma – Soft tissue sarcoma – Immunohistochemistry – Marker co-expression

Introduction

Since epithelioid sarcoma (ES) was first defined as a distinct clinico-pathological entity in 1970 (Enzinger 1970), its typical biological behaviour and morphological features have been described in several series (Bos et al. 1988; Bryan et al. 1974; Chase and Enzinger 1985; Prat et al. 1978; Santiago et al. 1972; Schmidt and Harms 1987).

Arising most often in the distal upper extremity of young adults, ES commonly presents as an ulcerating skin lesion or as a nodule in proximity to fascial or tenosynovial tissues. The origin is obscure. If excised locally, it will recur repeatedly and widely in about 80% of all cases and in nearly 50% will go on to metastasize, mainly to lymph nodes and lungs. The prognosis is better in younger patients and in females and worse if the tumour arises in proximal or deep sites, measures more than 2 cm, or is associated with increased necrosis, mitotic activity, haemorrhage or vascular invasion (Bos et al. 1988; Chase and Enzinger 1985; Prat et al. 1978). Early recognition and radical excision are thus essential for effective therapy. The histological appearance of ES, however, can be misleading, suggesting other malignancies (synovial sarcoma, melanoma, epithelioid haemangioendothelioma, metastatic carcinoma), or perhaps a non-neoplastic fibro-histiocytic or granulomatous reaction (Enzinger 1970).

We have witnessed the evolution of a typical ES from an initial morphology so closely mimicking a cavernous type of angiosarcoma that several renowned specialists in mesenchymal pathology were misled. This angiomatoid variant is a further morphological guise under which ES may elude recognition and appropriate therapy. Its immunoreactivity is compared to six file cases of bona fide ES. Once ES is suspected, immunohistochemical screening should lead to the correct diagnosis.

Materials and methods

Histological slides or paraffin blocks of six cases of ES examined at our institutions were reviewed. They had originally been diagnosed on the basis of morphological criteria as described by Enzinger (1970) and Chase and Enzinger (1985). Material from our collected cases and from the one presented below was subjected

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to immunohistochemical screening using the avidin-biotin-complex (ABC) method (Guesdon et al. 1979) with the reagents listed in Table 1.

Pertinent clinical data on our total of seven patients with ES are summarized in Table 2. One patient (case 1) is presented in more detail below.

Table 1. Antibodies used against tumour cells in immunohistc chemical reactions in this study

	Clonal	Source
Epithelial		
LU-5	M	Hoffmann-LaRoche, Basel
CK-61[a]	M	Institute of Pathology, Zurich
EMA	M	Dakopatts, Copenhagen
CAM 5.2	M	Becton Dickinson, Mountainview, Calif
Mesenchymal and others		
Vimentin	M	Dakopatts, Copenhagen
CIV-22[b]	M	Institute of Pathology, Zurich
Desmin	M	Amersham International
AT	P	Dakopatts, Copenhagen
ACT	P	Dakopatts, Copenhagen
F III-RAG	M	Dakopatts, Copenhagen
UEA-1		E-Y Labs. Inc. San Mateo, Calif.
Neural		
S-100	P	Dakopatts, Copenhagen
NSE	P	Dakopatts, Copenhagen

LU-5/CK/CAM, Cytokeratin markers;
EMA, epithelial membrane antigen;
CIV-22, type IV collagen;
NSE, neuron specific enolase;
F VIII-RAG, factor VIII related antigen;
UEA-1, Ulex Europaeus agglutinin;
AT, alpha-1-antitrypsin;
ACT, alpha-1-antichymotrypsin

[a] Lang et al. (1986)
[b] Odermatt et al. (1984)

Case report

At age 26, a female born in 1947 underwent partial resection of a "dysplastic" diaphyseal segment of the right radius (Fig. 1) with iliac bone grafting. Consolidation was good and the operative field unremarkable upon removal of the metal plate 2 years later. After 3 years, in 1978, there appeared a slowly growing, fluctuating sub-

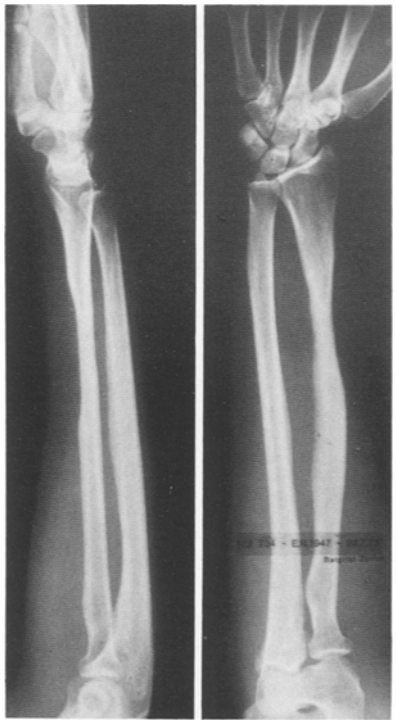

Fig. 1. Case 1. Radiograph at presentation (1973) interpreted as showing the result of a growth disorder affecting the distal radial diaphysis. Histology revealed increased remodelling with sclerosis and fatty marrow. Records do not comment on whether periosteum and the soft tissue sleeve were examined

Table 2. Clinical data on 7 patients with epithelioid sarcoma

Case	Time to biopsy	Location	Age at biopsy (years)	Sex	Diagnosis at biopsy	Treatment	Follow-up	Duration of evolution
1	>2 years	Forearm	32	F	Angiosarcoma	Excision Radiation Amputation	Dead from metastases	9 years
2	9 months	Index Hand	24	M	Synovial sarcoma	Excisions Amputations	Suicide upon recurrence with chest wall infiltration	5 years
3	4 years	Hand	29	M	Fibromatosis Nodular synovitis	Excisions	Alive with wide-spread local recurrences	16 years
4	"Chronic"	Index	30	F	Epithelioid sarcoma	Excision	Lost to follow-up	
5	Months	Finger	27	F	Glomus tumor	Excision	Alive with local recurrences	3 years
6	?	Thumb	27	M	Epithelioid sarcoma	Amputation	Dead from metastases	5 years
7	2 years	Forearm	22	F	Epithelioid sarcoma	Excision	Alive with residual tumour	2 years

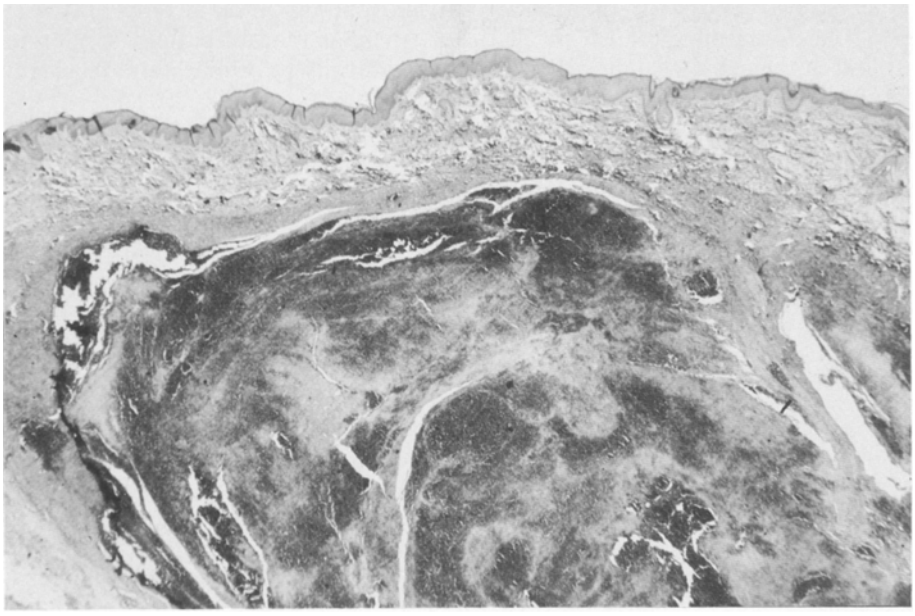

Fig. 2. Case 1. Primary lesion: large cavernous blood-filled tumour in the dermis of the forearm. ×10

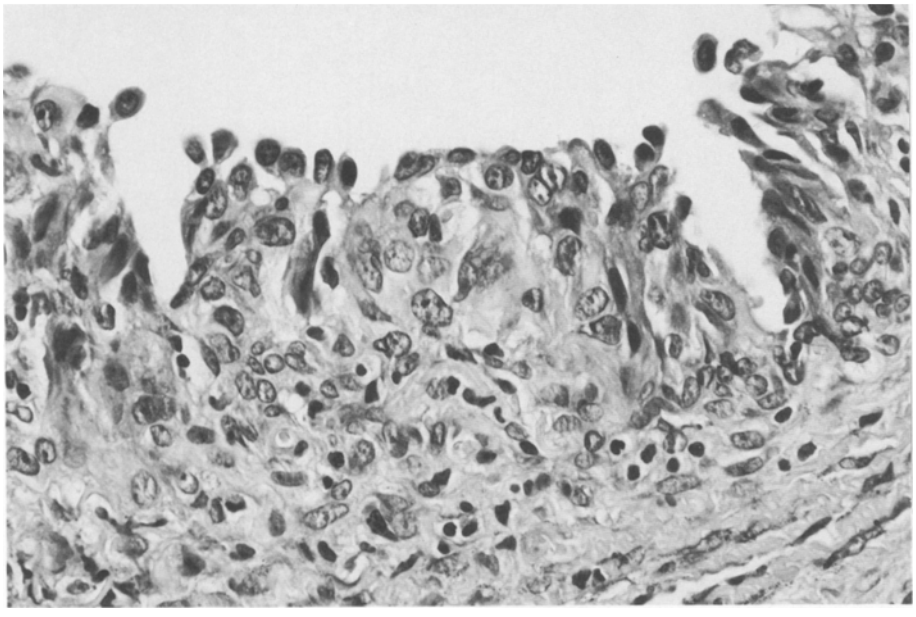

Fig. 3. Case 1. Primary lesion: neoplastic cells lining the cavernous lesion take on a "hobnail" appearance and project into the lumen, suggesting an endothelial neoplasm. ×360

cutaneous swelling near the scar. On excisional biopsy, in January 1979, the lesion was found to infiltrate. The histological diagnosis was malignant haemangioendothelioma. Postoperatively, 6500 cGy was applied to the site. The subsequent course was marked by lymphoedema and fracture of the radius in 1983, treated by external fixation and complicated by osteomyelitis with fistulous drainage. Debridement with insertion of a gentamicin chain and soft tissue reconstruction were undertaken. Biopsies of recurring skin ulcers (Fig. 4) proved to be infiltrated by tumour. CT scans suggested metastases in lungs, pleura, kidney and pancreas. Nevertheless, due to persisting osteomyelitis and the patient's increasing inability to use her forearm and hand, an above-elbow amputation and axillary lymph node dissection were carried out by the end of 1987. Two cycles of chemotherapy (ifosfamide, adriamycin, DTIC) were administered. The response was poor and the patient died from pulmonary metastases complicated by severe pneumonia 9 years after diagnosis of malignancy.

Results

In case 1 the first excisional biopsy showed a polycystic, cavernous lesion filled largely with blood and lined by layers of neoplastic cells (Fig. 2), some of which projected into the lumen in a "hobnail" fashion (Fig. 3). The presence of some erythrocytes within the cytoplasm suggested erythrophagocytosis. There was no delimiting basement membrane, but a meshwork of reticulin fibres was seen, investing cells closest to the stroma. Later biopsy specimens revealed a nodular granulomatous pattern: serpiginous bands of epithelioid polyhedral cells walling off areas of necrosis (Fig. 5). Focally there was a tendency for cell clusters to exhibit lumen formation, producing a capillary angiomatoid pattern (Fig. 6).

The amputation specimen (Fig. 7) contained one large tumour mass in the soft tissues of the forearm (Fig. 8). Smaller tumour nodules were found in the subcutaneous tissues and as ulcerated cutaneous lesions. Moreover, there was extensive miliary seeding within tendons and along fascial planes (Fig. 9). Axillary lymph nodes were free of tumour. Post-mortem revealed metastases to lungs, pleura, liver, and the retroperitoneum involving kidney, adrenal and the pancreatic tail. An angiomatoid pattern was again present focally (Fig. 10).

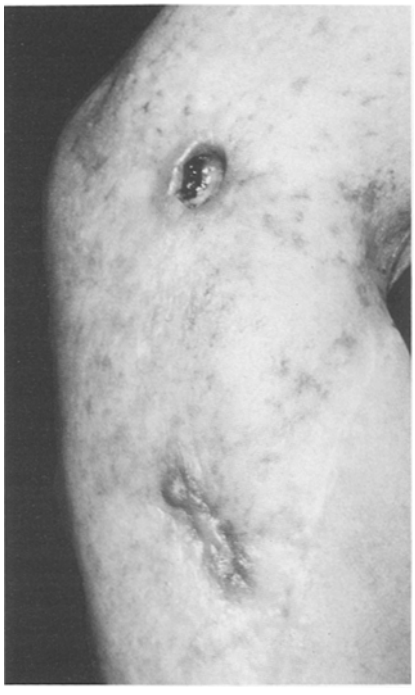

Fig. 4. Case 1. Recurrent tumour manifesting as chronic punched-out ulcers with indurated margins, several months after soft tissue reconstruction

In cases 2–7 the morphological features were typical of ES in all cases. An angiomatoid pattern similar to that in Fig. 6 was seen focally in primary and recurrent lesions of one patient (case 2).

The results of immunohistochemical reactions are summarized in Table 3. Reaction profiles of recurrent tumours and primaries were the same. The bivalent response to epithelial markers and to vimentin (Fig. 11) was strikingly consistent in all cases. Epithelial markers were strongly positive. Epithelial membrane antigen (EMA) generally gave the weaker response but in one case was expressed more strongly than cytokeratins. Type IV collagen was expressed in three cases examined. Aside from being prominent around vessels, it stained slender fibrils between epithelioid cells. Alpha-1-antichymotrypsin (ACT) and neuron-specific enolase (NSE) were positive in a majority of cases, alpha-1-antitrypsin (AT) and desmin in some, while vascular markers and S-100 protein gave no reaction. In our presented case, positivity to epithelial antigens and to vimentin was similarly expressed in both the primary tumour, originally considered to be endothelial sarcoma, and in all later recurrences.

Discussion

Our seven patients illustrate the typical clinical setting of ES (Bos et al. 1988; Chase and Enzinger 1985). All tumours were located in the distal parts of the upper extremity, five in the hand or a finger. Evolution is slow, the presence of a subcutaneous nodule or ulcerative lesion having preceded the first operation by months to years. At least three patients underwent multiple excisions and resections/amputations for recurrences over many years. Of five patients in whom follow-up can be evaluated, two are alive with tumour. In one, however, tumour has spread throughout the arm 16 years

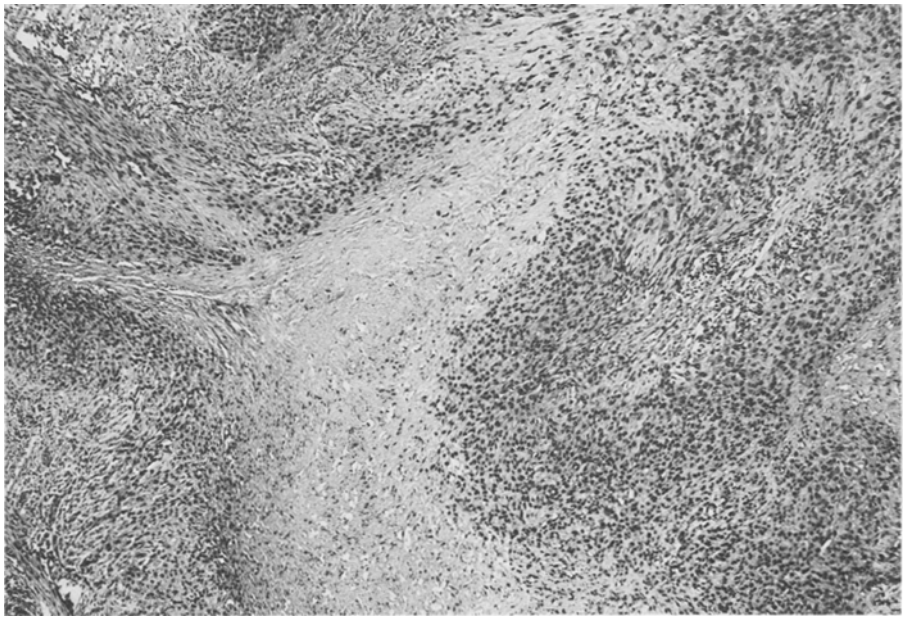

Fig. 5. Case 1. Recurrence: serpiginous band of neoplastic cells around an area of necrosis marks the granulomatous form of epithelioid sarcoma. ×40

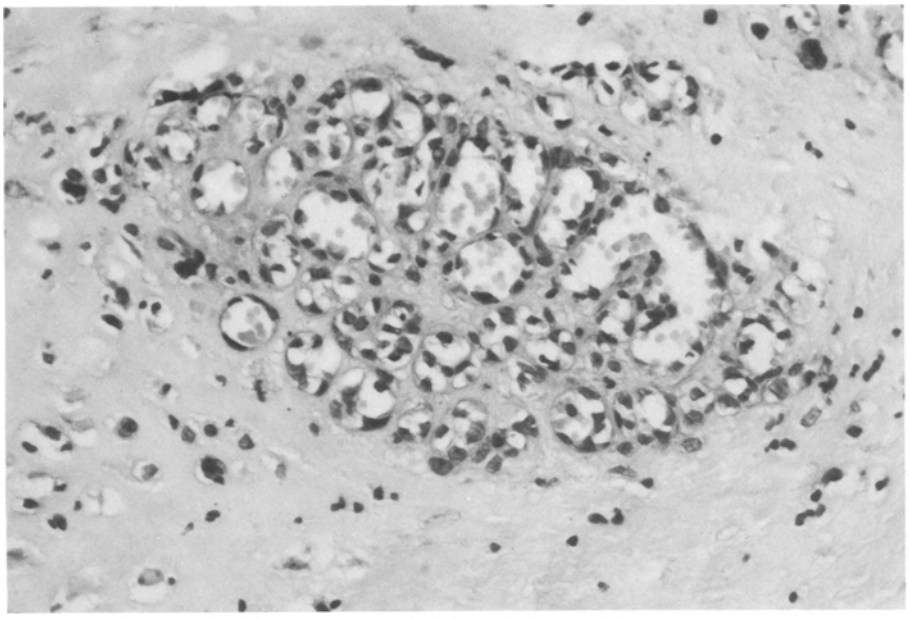

Fig. 6. Case 1. Recurrence: group of tumour cells in an angiomatoid pattern imitating capillary proliferation replete with intraluminal erythrocytes. This cell group proved positive to cytokeratin antibodies on immunostaining. ×250

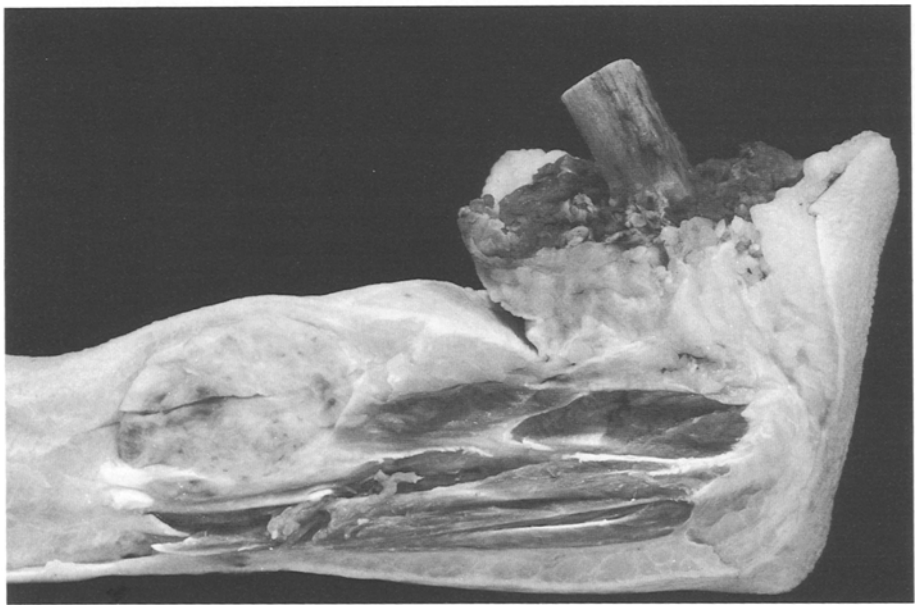

Fig. 7. Case 1. Above-elbow amputation specimen displayed a large tumour recurrence in the forearm

after the onset of symptoms. Two patients died from metastases 5 and 9 years after the first clinical manifestation. Another committed suicide when, following piecemeal resections and amputation of the extremity, yet another recurrence involved his chest wall. These findings underscore the typically slow but relentless course, characterized by recurrences in nearly 80%, metastases in about 50% and tumour-related fatality in a third of all patients (Chase and Enzinger 1985). In the case of our index patient, it may be wondered whether the X-ray at the time of presentation (Fig. 1) did not display the signs of bone atrophy due to an enveloping neoplasm in periosteal location rather than dysplasia.

Response to chemotherapy or radiation therapy has not been encouraging (Bos et al. 1988; Chase and Enzinger 1985). In our patient 6500 cGy did not eradicate the neoplasm, but led to severe complications. Aggressive surgical management remains the treatment of choice. The high recurrence rate, reflecting the difficulty in determining radical surgical margins, is explained by the the fact that while the tumour may be confined initially, it recurs as multiple nodules that invade tendons and fascial structures in a miliary fashion (Enzinger 1970; Prat et al. 1978). For treatment to be radical, it must be early (Prat et al. 1978): hence the importance of early recognition. ES, however, is often misinterpreted histologically as metastatic carcinoma, melanoma or synovial sarcoma, or, more significantly, as a peculiar histiocytic or granulomatous response (Enzinger 1970). In only three of our seven cases was the correct diagnosis

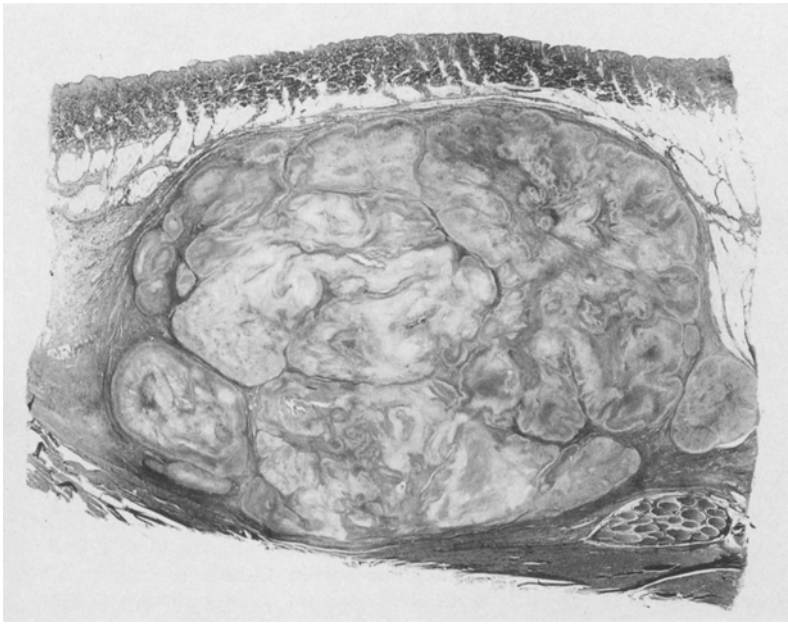

Fig. 8. Case 1. Macrosection of the recurrent tumour mass of Fig. 7, displaying a cerebroid pattern made up of many granulomatous nodules with serpiginous bands of neoplastic cells around areas of necrosis. Silver impregnation, ×2

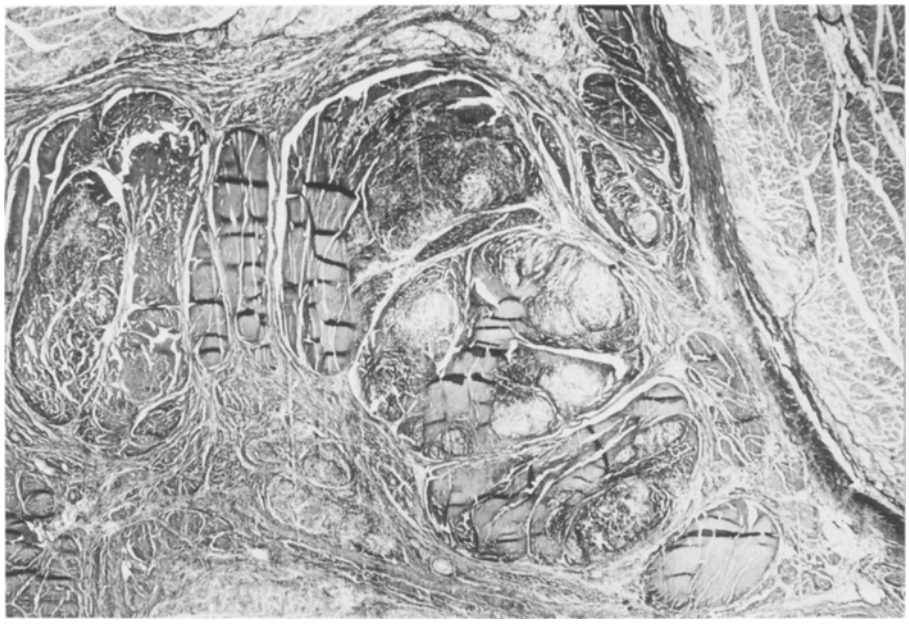

Fig. 9. Case 1. Miliary seeding of groups and nodules of tumour cells was widespread along and within tendons and fascias of the forearm. van Gieson, ×24

made at the time of initial histological examination. A benign lesion was suspected in two patients. Twice (cases 1 and 7) the correct diagnosis was delayed 7 and 12 years after initial biopsy.

Epithelioid haemangioendothelioma resembles ES by virtue of its solid pattern and attempted lumen formation (Chase and Enzinger 1985; Mills et al. 1981; Wick and Manivel 1987), similar to what was seen focally in two of our cases. Patterns reminiscent of vessel formation have been noted in cases of ES seen at the Mayo Clinic (H.R. Reiman, personal communication). According to Enzinger, haemorrhage in ES has raised the question of angiosarcoma (Chase and Enzinger 1985). In our patient, the cavernous vascular pattern of wide blood-filled channels lined by layers of neoplastic cells displaying a hobnail appearance and erythrophagocytosis closely mimicked a cavernous type of angiosarcoma. The case had been included in a TNM field study reviewed by pathologists specialized in soft tissue tumours and had been seen in addition at the Memorial Sloan-Kettering Cancer Center, New York. The diagnosis of angiosarcoma was never questioned. For these reasons we consider the angiomatoid pattern a morphological variant that warrants attention.

The differential diagnosis can be settled by the immunohistochemical response pattern. In keeping with the findings reported in the literature (Daimaru et al. 1987; Fisher 1988; Manivel et al. 1987; Persson et al. 1988;

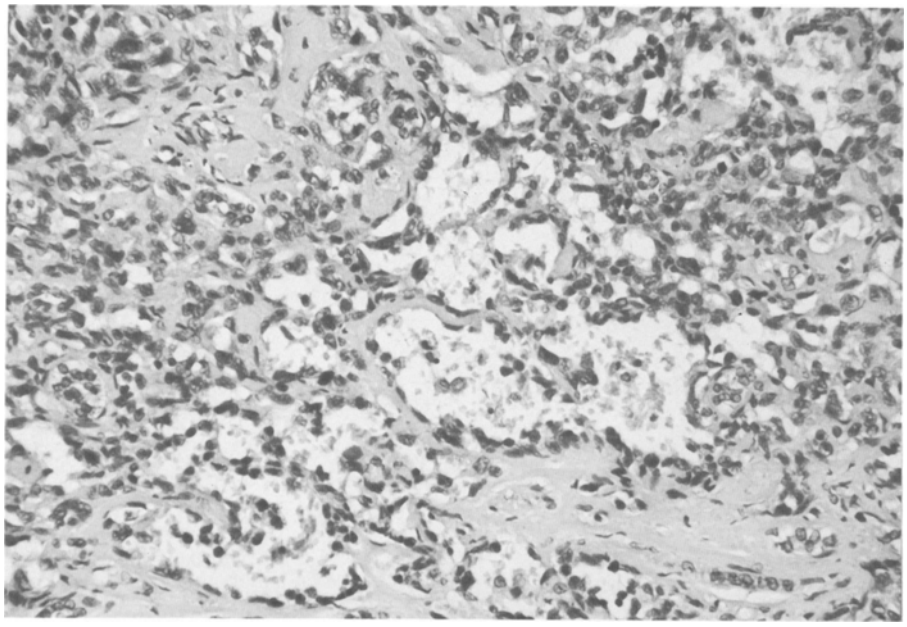

Fig. 10. Case 1. Perirenal metastasis at post-mortem, displaying a similar angiomatoid pattern noted previously. ×160

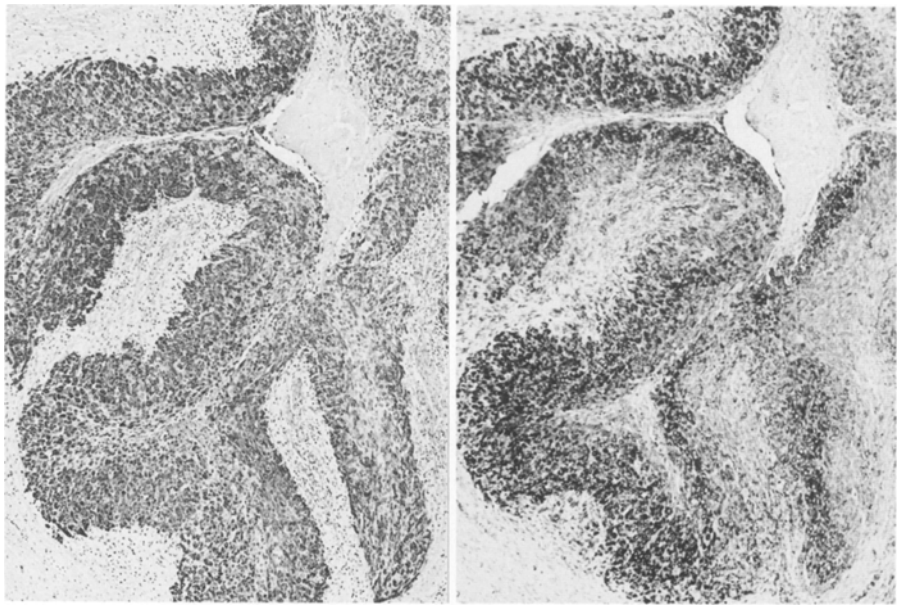

Fig. 11. Case 7. Typical focus of epithelioid sarcoma displaying a serpiginous granuloma pattern. Positive immunohistochemical reaction with (*left*) a pan-cytokeratin marker (lu-5) and (*right*) vimentin. ×40

Table 3. Immunoreactivity in seven cases of epithelioid sarcoma

		Mesenchymal and others	
Epithelial			
LU-5	5/5	Vimentin	7/7
EMA	6/6	CIV-22	3/3
CK	4/4	Desmin	2/5
CAM 5.2	3/3	AT	2/5
		ACT	5/6
		FIII-RAG	0/4
		UEA-1	0/3
Neurogenic			
S-100	0/6		
NSE	3/5		

Reeves et al. 1987; Wick and Manivel 1987), our ES were consistently reactive for cytokeratins and EMA, as well as to vimentin (Mills et al. 1981). Epithelioid haemangioendothelioma does not express cytokeratins but reacts with F VIII-RAG and UEA-1. Positive reactions with markers such as ACT, NSE and desmin have been noted elsewhere (Mukai et al. 1985; Schmidt and Harms 1987) and are not conclusive findings. The bivalent epithelial/vimentin immunoreactivity of a lesion histologically compatible with ES strongly suggests that diagnosis and allowed the identification of the initial lesion in our patient as an ES rather than an angiosarcoma.

Epithelioid and/or granulomatous lesions in the extremity of children and young adults should raise the

suspicion of ES, even when angiomatoid or haemorrhagic. Appropriate immunohistochemical screening will reduce considerably the risk of failing to recognize ES in its early and potentially curable stage.

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References

Bos GD, Pritchard DJ, Reimann HM, Dobyns JH, Ilstrup DM, Landon GC (1988) Epithelioid Sarcoma. An analysis of fifty-one cases. J Bone Joint Surg [Am] 70:862–870

Bryan RS, Soule EH, Dobyns JH, Pritchard DJ, Linscheid RL (1974) Primary epithelioid sarcoma of the hand and forearm: a review of thirteen cases. J Bone Joint Surg [Am] 56:458–465

Chase DR, Enzinger FM (1985) Epithelioid sarcoma. Diagnosis, prognostic indicators, and treatment. Am J Surg Pathol 9:241–263

Daimaru Y, Hashimoto H, Tsuneyoshi M, Enjoji M (1987) Epithelial profile of epithelioid sarcoma. An immunohistochemical analysis of eight cases. Cancer 59:134–141

Enzinger FM (1970) Epithelioid sarcoma. A sarcoma simulating a granuloma or a carcinoma. Cancer 26:1029–1041

Fisher C (1988) Epithelioid sarcoma: the spectrum of ultrastructural differentiation in seven immunohistochemically defined cases. Hum Pathol 19:265–275

Guesdon JL, Ternyck T, Aurameas S (1979) The use of avidin-biotin interaction in immunoenzymatic techniques. J Histochem Cytochem 27:1131–1139

Lang AB, Odermatt BF, Rüttner JR (1986) Monoclonal antibodies to human cytokeratins: application to various epithelial and mesothelial cells. Exp Cell Biol 54:61–72

Manivel JC, Wick MR, Dehner LP, Sibley RK (1987) Epithelioid sarcoma. An immunohistochemical study. Am J Clin Pathol 87:319–326

Mills SE, Bruns ME, Fechner RE, O'Hara MF, Bruns DE (1981) Intermediate filaments in eosinophilic cells of epithelioid sarcoma. Am J Surg Pathol 5:195–202

Mukai M, Torikata C, Iri H, Hanaoka H, Kawai T, Yakumaru K, Shimoda T, Mikata A, Kageyama K (1985) Cellular differentiation of epithelioid sarcoma. An electron-microscopic, enzyme-histochemical, and immunohistochemical study. Am J Pathol 119:44–56

Odermatt BF, Lang AB, Rüttner JR, Winterhalter KH, Trüeb B (1984) Monoclonal antibodies to human type IV collagen: useful reagents to demonstrate the heterotrimeric nature of the molecule. Proc Natl Acad Sci USA 81:7343–7347

Persson S, Kindblom L-G, Angervall L (1988) Epithelioid sarcoma. An electron-microscopic and immunohistochemical study. Appl Pathol 6:1–16

Prat J, Woodruff JM, Marcove RC (1978) Epithelioid sarcoma: an analysis of 22 cases indicating the prognostic significance of vascular invasion and regional lymph node metastasis. Cancer 41:1472–1487

Reeves BR, Fisher C, Smith S, Courtenay VD, Robertson D (1987) Ultrastructural, immunocytochemical, and cytogenetic characterization of a human epithelioid sarcoma cell line (RM-HS1). J Natl Cancer Inst 78:7–18

Santiago H, Feinerman LK, Lattes R (1972) Epithelioid sarcoma. A clinical and pathologic study of nine cases. Hum Pathol 3:133–147

Schmidt D, Harms D (1987) Epithelioid sarcoma in children and adolescents. An immunohistochemical study. Virchows Arch [A] 410:423–431

Wick MR, Manivel JC (1987) Epithelioid sarcoma and epithelioid hemangioendothelioma: an immunocytochemical and lectin-histochemical comparison. Virchows Arch [A] 410:309–316