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Case report

Morphological and cytogenetic studies of angiosarcoma in Stewart-Treves syndrome

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Summary. A morphological and cytogenetic analysis of a multifocal angiosarcoma in a typical case of Stewart-Treves syndrome is reported. The morphological analysis indicated differentiation along both blood and lymph vessel endothelium lines. By light and electron microscopy there were areas with well-developed erythrocyte-containing, capillary-like vessels and poorly differentiated areas with abortive vascular formations. In these the endothelium revealed immunoreactivity to factor VIII RAg, binding of *Ulex europaeus* I and *Psophocarpus tetragonolobus* agglutinin lectins, Weibel-Palade bodies ultrastructurally and presented a continuous enclosing external lamina and immunoreactivity for laminin and collagen IV, all features of blood-vessel differentiation. There were also lymphangioma-like areas as well as poorly differentiated areas where the immunohistochemical, lectin-binding and ultrastructural features were compatible with a lymph vessel differentiation. Cytogenetic analysis of cultured tumour cells revealed chromosome counts in the diploid region. About 40% of the cells analysed had a normal diploid karyotype. The remaining cells showed a multitude of mainly nonclonal structural alterations; 17 unique marker types resulting from different translocations and deletions were observed. There were also a few cells with clonal numerical deviations showing monosomy 22, monosomy X and trisomy 2 respectively. It is of interest that the losses of chromosome 22 and the X chromosome also have been observed in Kaposi's sarcoma and that the PD-ECGF gene, a novel angiogenetic factor, has been mapped to chromosome 22.

Key words: Angiosarcoma – Cell culture – Cytogenetics – Lectins – Stewart-Treves syndrome

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Introduction

Angiosarcomas of the skin develop almost exclusively in the following clinical settings: (1) the lymphoedematous extremity, secondary to prior mastectomy in most cases; (2) the face and skull, usually in elderly individuals; and (3) skin that has been previously irradiated (Cooper 1987). The angiosarcomas which occur in association with mastectomy lymphoedema are often referred to as Stewart-Treves syndrome after Stewart and Treves' report of six such cases in 1948. In the case of this group of angiosarcomas, the term lymphangiosarcoma has often been used to underline the belief that they arise from proliferating lymphatic endothelium. The general term angiosarcoma, which is used to describe both haemangiosarcoma and lymphangiosarcoma, may be preferable since there are no light-microscopic characteristics which can clearly divide them into two entities.

Recent cytogenetic analyses of several different types of soft tissue tumour have demonstrated that these tumours, like leukaemias and lymphomas, show specific, neoplasia-associated chromosome abnormalities (Sandberg 1990). However, partly as a result of technical difficulties in analysing solid tumours, our knowledge of the chromosomal patterns in soft tissue tumours is still limited. When it comes to angiosarcomas, data are only available from two published cases (Molina et al. 1989; Mandahl et al. 1990), neither of which was associated with Stewart-Treves syndrome.

In this paper we describe a case of Stewart-Treves syndrome in which a multifocal angiosarcoma was studied light- and electron-microscopically, immunohistochemically and with lectin histochemistry to elucidate development and probable cell differentiation. Short-term cultured cells of the tumour were used for a cytogenetic analysis.

Case report

A woman, who had been wheel-chair bound since childhood due to poliomyelitis, was operated on for a left-sided breast carcinoma at the age of 42 years. A mastectomy and axillary lymph node resection were performed and irradiation therapy was given postoperatively. At a follow up examination 10 years after the removal of the breast carcinoma, a bluish, elevated nodule, 3 cm in diameter, was observed on the medial aspect of her left upper arm. During the following 3 months, multiple haemorrhagic, partly ulcerated, flat lesions appeared at the medial and dorsal aspect of the upper arm and the entire arm and hand presented the features of lymphoedema. A biopsy from one of the nodules verified the diagnosis of angiosarcoma. Ten months after the first occurrence of a haemorrhagic nodule, amputation of the left arm was performed. At that time, numerous nodules appeared all around the circumference of the upper arm; the largest lesions had a diameter of 3 cm and extended into the underlying soft tissues. A month after the operation, haemorrhagic nodules appeared in the skin of the chest wall on the left side. At biopsy, they were found to be tumour nodules of similar appearance.

Materials and methods

For the light-microscopic study of the surgical specimen sections 4 μm thick were cut from paraffin blocks of the tumours. The sections were stained with haematoxylin and eosin and according to van Gieson's trichrome method. Silver impregnation according to Gordon and Sweet was performed in order to demonstrate reticulin. For electron microscopy, small pieces of tumour tissue were fixed in 3% glutaraldehyde and routinely processed. For immunohistochemical analysis the avidin-biotin complex method was applied to formaldehyde- and ethanol-fixed, paraffin-embedded tissues as preivously described (Lundgren et al. 1989). The primary antisera and lectins and their concentrations are given in Table 1. One of the lectins, *Psophocarpus tetragonolobus* agglutinin (PTA), which has been shown to have a high affinity for some *N*-acetyl galactosamine residues in a blood group independent manner (Appukuttan and Basu 1981; Kortt 1984; Goldstein and Poretz 1986) has recently been found to bind selectively to the endothelium of blood vessels (Laitinen et al. 1990).

Table 1. Antibodies and lectins used in the study, their concentrations and the results of the immunohistochemical and lectin-binding analysis

Antibody		Dilution	Staining result
Anti-vimentin, V9[a]	M	1/20	+
Anti-factor VIII RAg[a]	Po	1/500 (T)	+[g]
Anti-α-smooth-muscle specific actin, 1A4[b]	M	1/600	−[h]
Anti-collagen IV, CIV 22[a]	M	1/50 (P)	+
Anti-laminin, 2G6/A2[c]	M	1/50 (P)	+
Anti-cytokeratin, CAM 5.2[d]	M	1/4 (T)	−
Anti-cytokeratin, KL-1[e]	M	1/500	−
Anti-cytokeratin, AE1/AE3[f]	M	1/300 (T)	−
Anti-epithelial membrane antigen, E29[a]	M	1/100	−
Lectin UEA-I, biotinylated[b]		5 μg/ml	+[g]
Lectin PTA, biotinylated[b]		10 μg/ml (T)	+[g]

M, Monoclonal; Po, polyclonal; P, pretreated with pepsin; T, pretreated with trypsin; UEA-I, *Ulex europaeus* I agglutinin; PTA, *Psophocarpus tetragonolobus* agglutinin

[a] Dakopatts, Copenhagen, Denmark
[b] Sigma, St. Louis, Mo.
[c] Sera-Lab, Crawley Down, UK
[d] Becton-Dickinson, Mountain View, Calif.
[e] Immunotech, Marseille, France
[f] Boehringer Mannheim Biochemica, Mannheim, FRG
[g] Many of the spindle-shaped and epithelioid tumour cells in solid areas were negative
[h] Positivity in cells enclosing well-developed vascular structures and around some vascular slits in the solid tumour areas

For cytogenetic studies fresh tumour tissue was minced into small pieces 1–2 mm in diameter and enzymatically digested in a buffered collagenase solution (1000 units collagenase/ml) for 2 h at room temperature. The digested material was washed twice in fresh culture medium and thereafter resuspended in Eagle's alpha MEM supplemented with 20% fetal calf serum, 5 μg streptomycin/ml, 200 units benzylpenicillin-K/ml, 200 mM L-glutamine, and explanted in 25 cm^2 tissue culture flasks. The cells were grown at 37° C in a water-saturated atmospere containing 5% carbon dioxide in air. Chromosome preparations were made from cells growing exponentially. Colchicine was added 16 h before harvest, to a final concentration of 0.01 μg/ml. The methods for chromosome preparation and G-banding were essentially the same as those described previously (Stenman and Mark 1983). Magnified photographs were used for the karyotype analysis. The nomenclature follows that of ISCN (1985).

Results

The numerous tumour nodules in the right upper arm, involving the dermis and subcutaneous tissue, varied in size from minute lesions, only detectable by light microscopy, to 3-cm large nodules. The covering epidermis was partly hyperplastic and acanthotic but was mostly thinned and in areas ulcerated. The nodules were characteristically poorly delineated and long, branching extensions of proliferating, atypical vascular structures were often seen extending far away from the nodules into the deep subcutaneous fat tissue.

The nodules revealed a wide morphological spectrum in terms of vascular differentiation, cellularity and atypia. Generally, the smallest nodules presented the highest degree of vascular differentiation. Some of them had the appearance of an haemangioma or lymphangioma composed of open vascular spaces lined by a single row of endothelial cells with no or very discrete atypia (Fig. 1 A). Some of these vessels appeared to be empty or contained a lymph-like material, while others were filled with erythrocytes. Such well-differentiated angiomatous areas also occurred in the periphery of many of the larger tumour nodules (Fig. 1 B). The larger nodules were generally highly cellular and presented a severe degree of cellular and nuclear polymorphism and high mitotic activity. Some areas of these cellular nodules had a predominantly solid growth pattern with either epithelioid, tightly packed cells or spindle-shaped cells in areas, with a tendency to form a fascicular pattern. Also in the highly cellular, predominantly solid nodules, there were numerous vascular formations, often slit-like and angulated, with polymorphic large, endothelium-like cells protruding into the lumen. In areas, there were prominent papillary structures between which irregular sinusoid vascular spaces were formed. Some of the vascular spaces appeared to be empty while others were

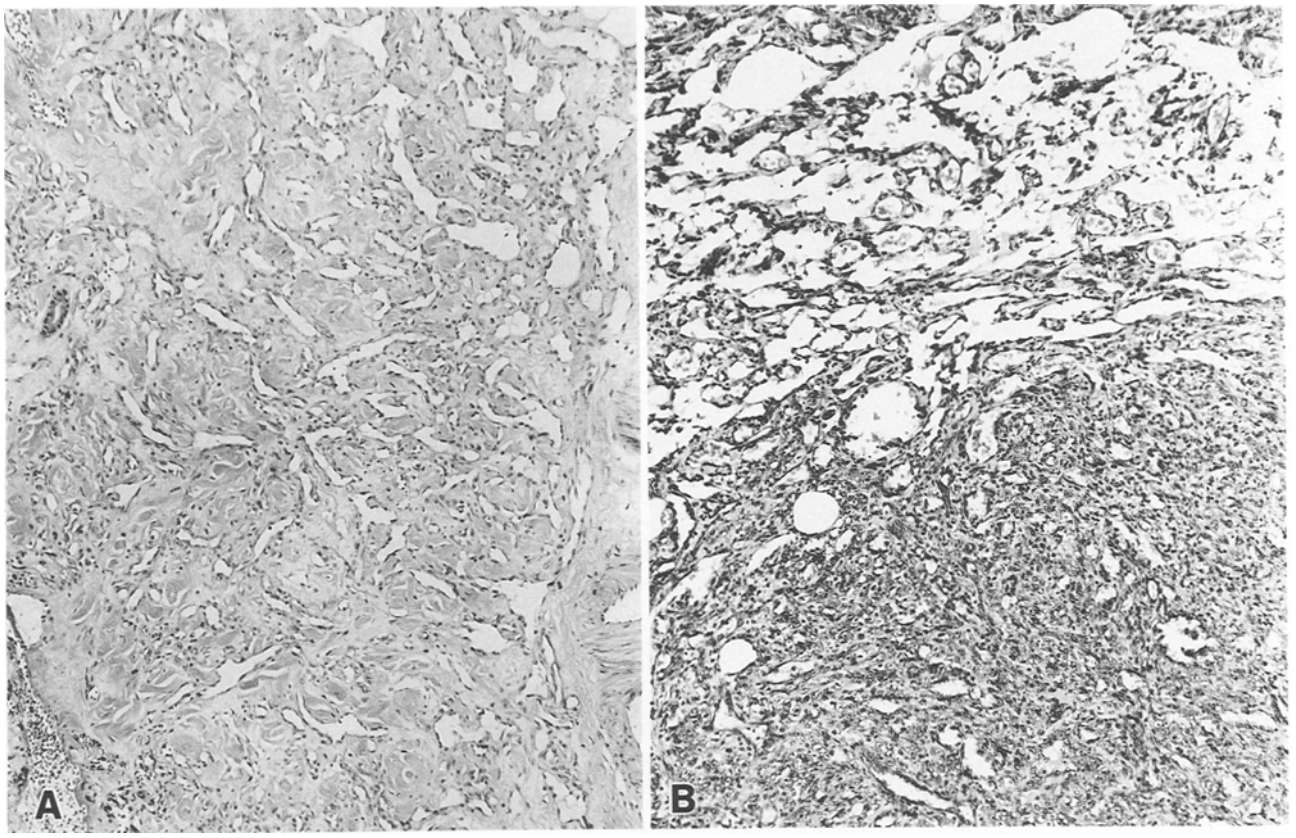

Fig. 1. **A** Well-differentiated area with irregular, branching, mostly empty vascular structures mingling with a fibrous stroma. **B** Tumour area with well-developed, anastomosing vascular slits with protruding papillary projections at the top and with a few narrow, vascular slits in the mainly solid area at the bottom. H&E; **A** ×45, **B** ×90

filled with erythrocytes. The tumour cells of the cellular areas were characterized by a large, vesicular, rounded or oval nucleus with one or more distinct nucleoli. There were some areas of bleeding and necrosis.

Silver impregnation demonstrating reticulin enhanced the vascular structures and also helped to reveal abortive vascular formations within the highly cellular, solid parts of the tumours. There was binding of the lectins *Ulex europaeus I* (UEA-I) and PTA to the endothelium cells of many but not all of the well-formed vascular structures. Also in the solid, cellular areas there were some slit-like spaces with lectin binding in the lining cells, while the majority of the tumour cells in the solid parts did not bind these lectins.

The results of the immunohistochemical analysis are presented in Table 1. All the tumour cells in every part of the nodules were strongly positive for vimentin (Fig. 2A). The tumour cells lining most of the well-differentiated vascular spaces were strongly positive for factor VIII RAg (Fig. 2C). The majority of the cells within the highly cellular, solid areas were negative for factor VIII RAg, although in these areas there were some positive cells which appeared in groups or were arranged around abortive, compressed vascular spaces, otherwise difficult to recognize in routinely stained, light-microscopic sections (Fig. 2D). In all parts the tumour cells were negative for α-smooth-muscle-specific actin. A distinct rim of cells positive for α-smooth-muscle-specific actin, corresponding to pericytes, was, however, seen enclosing the well-differentiated vascular structures (Fig. 2F). Also in the highly cellular, solid, spindle cell parts there was a positivity for α-smooth-muscle-specific actin in some cells enclosing narrow, vascular slits (Fig. 2E). Positivity for laminin and collagen IV helped to identify external laminae around most of the well-differentiated, vascular spaces. A positivity was also seen occasionally around individual cells or groups of cells in the highly cellular, solid areas (Fig. 2B). There was no positivity for cytokeratins or epithelial membrane antigen (EMA).

The ultrastructural appearance varied depending on the degree of vascular differentiation seen in the various tumour nodules examined. In the well-differentiated, angioma-like areas, the tumour cells lining the vascular spaces revealed features of normal endothelium, such as tight junctions between the cells, numerous pinocytic vesicles, an abundance of intermediate cytofilaments and prominent external laminae investing the vascular formations. In such areas, Weibel-Palade bodies could be detected in the endothelium. There were also well-developed vascular formations where the endothelium lacked Weibel-Palade bodies. Such vessels also lacked distinct external laminae and surrounding pericytes, thus presenting features of lymph vessels. In poorly differentiated and cellular, solid areas, in which no vascular differentiation could be detected light microscopically, the

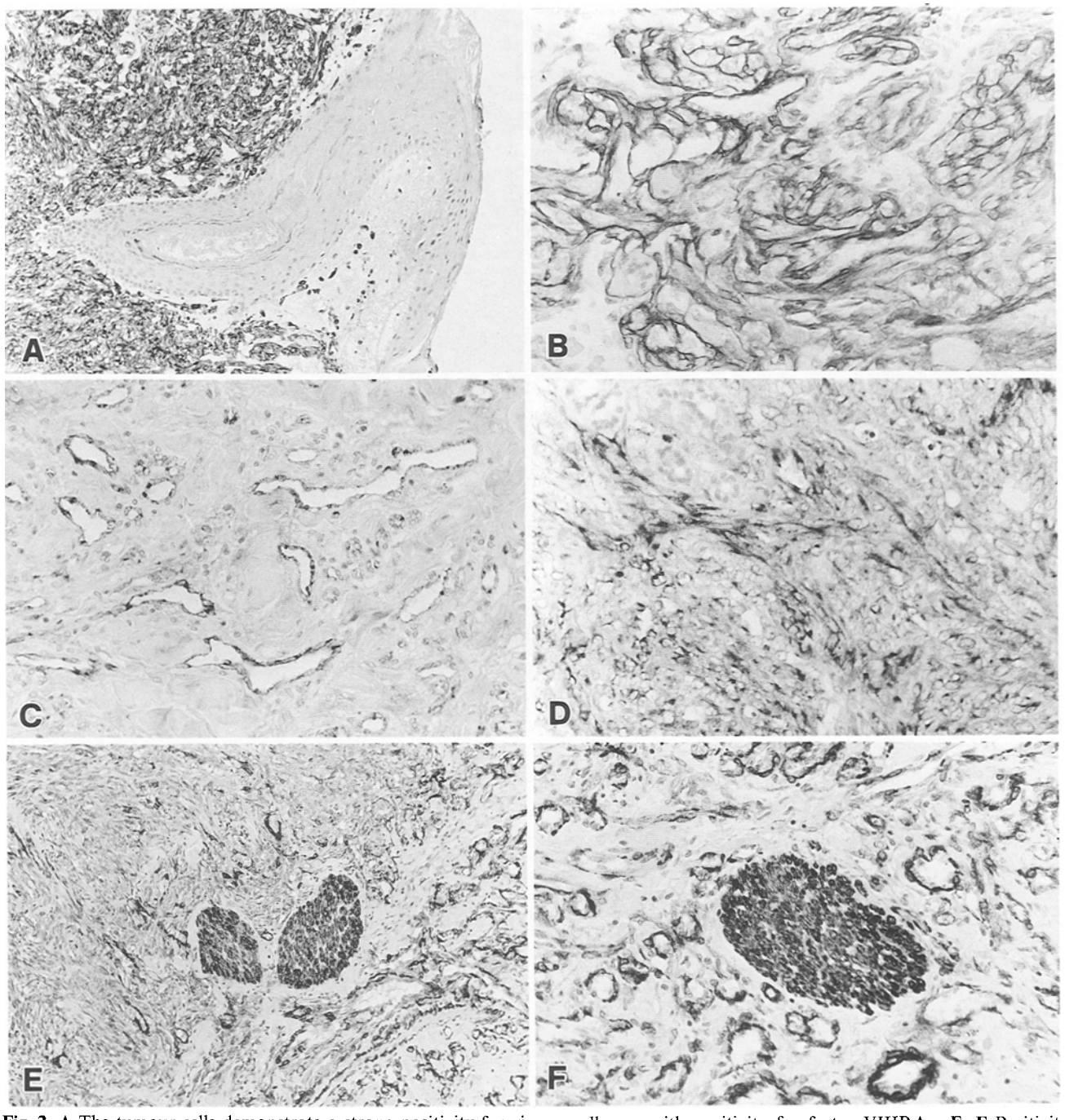

Fig. 2. **A** The tumour cells demonstrate a strong positivity for vimentin. The squamous epithelium of the skin and a hair-follicle serves as a negative control. **B** A positive staining for collagen IV, giving prominence to external lamina material around cell groups and narrow vascular slits within a solid area of the tumour. **C** Well-differentiated area with positivity for factor VIIIRAg in the endothelium of the vascular formations. **D** Solid, partly spindle-cell area with positivity for factor VIIIRAg. **E, F** Positivity for smooth-muscle-specific actin in pericytes surrounding well-differentiated, vascular structures (bottom right in **E** and in **F**). The strongly positively stained cell groups are piloerectorum muscle. There are also some positive cells enclosing narrow vascular slits in the solid parts of the tumour (top left in **E**). ABC method

electron-microscopic examination helped to disclose abortive vascular slits (Fig. 3A). Sometimes the tumour cells in these areas also revealed intracytoplasmic lumen formations. In such poorly differentiated cellular areas, Weibel-Palade bodies (Fig. 3B) were usually not identified. The tumour cells in these areas often had a tendency to form nests, sometimes enclosed by incomplete segments of external lamina. There were very narrow, abortive vascular slits containing compressed erythrocytes and sometimes leucocytes. In the cellular, solid areas the tumour cells varied in shape from polygonal, epithelium-like to spindle-shaped. The nuclei revealed prominent nucleoli and irregularly distributed heterochromatin clumps. In the highly cellular areas without obvious

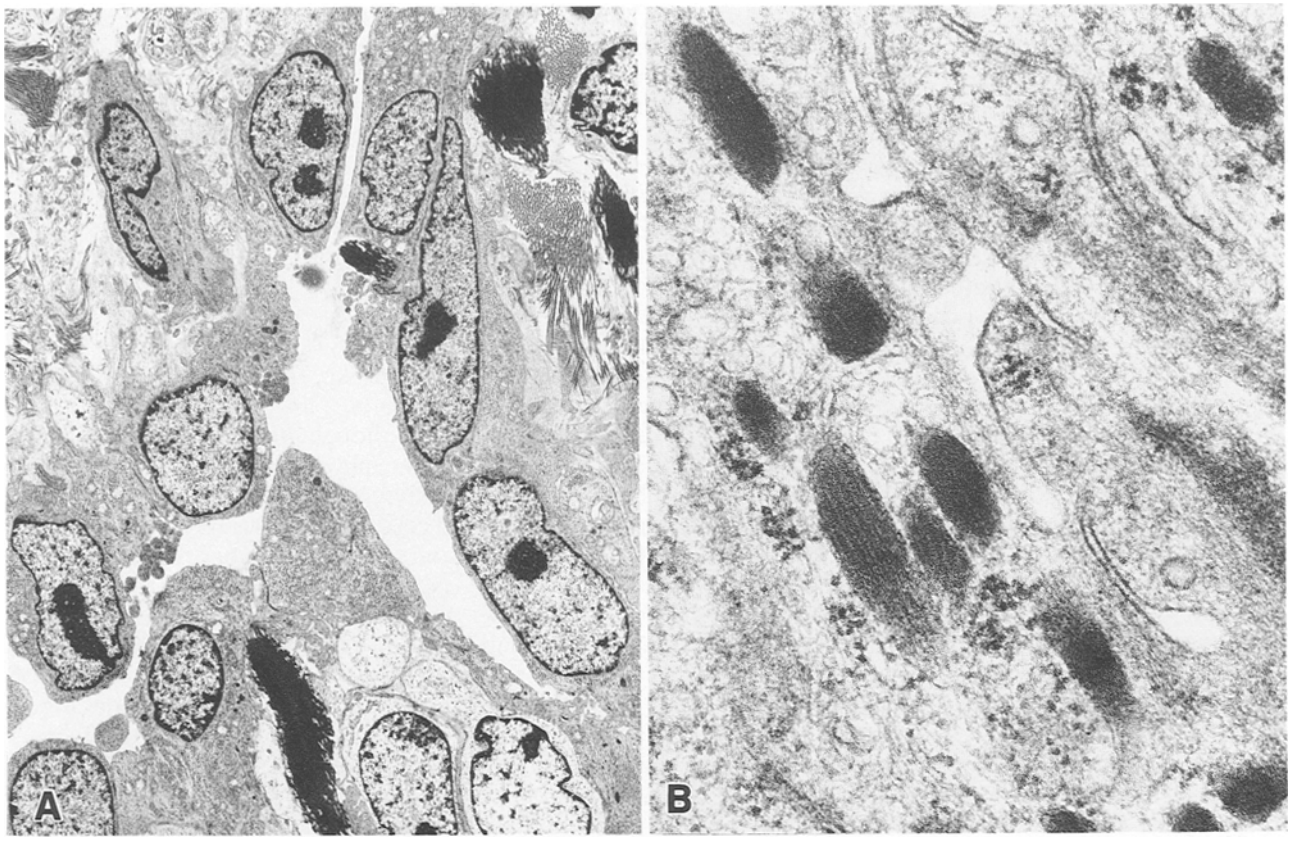

Fig. 3. **A** Poorly differentiated, highly cellular tumour area with a narrow vascular slit. **B** Very few tumour cells, enclosing the vascular slits in poorly differentiated parts, contain some Weibel-Palade bodies. **A** ×3000; **B** ×60000

vascular formations the tumour cells were connected by prominent tight junctions.

Cells were harvested for chromosome analysis after 11 days in vitro. The chromosomal findings in the 32 karyotyped cells are presented in Table 2. All the cells had chromosome counts in the diploid region. Of the 32 cells analysed in detail, 13 had a normal karyotype and a further 6 cells showed random losses of single chromosomes. The remaining 13 cells showed a multitude of nonclonal structural alterations as well as a few clonal numerical changes. No fewer than 17 unique marker types, resulting from different translocations and deletions, were observed. None of the markers was recurrent. There were also a few clonal numerical deviations including three cells with monosomy 22, three cells with monosomy X, and two cells with trisomy 2. In addition, some of these cells contained other numerical and/or structural changes. There were also two hyperdiploid cells, one of which showed trisomy 3 and the other trisomy 2 and trisomy 7.

Table 2. Karyotypic characteristics of the 32 cells analysed

Karyotype	No. of cells
41, XX, −3, −6, −6, +der(7)t(6;7)(p21.1;p22) −17, −17, −20	1
45, XX, −1, +2, −22	1
45, XX, −6	1
45, XX, −10	1
45, XX, −13	1
45, XX, −14	1
45, XX, −16	1
45, XX, −20	1
45, XX, −22	2
45, X, −X	1
46, XX	13
46, X, +del(1)(q21),t(6;8)(q22–23;q24), −X	1
46, XX, t(1;12)(p34.1–34.3;q13)	1
46, XX, t(5;?)(p13;?)	1
46, X, t(5;19)(q21–22;p13.3), −X, +mar	1
46, XX, t(10;17)(q11.2;p11.2)	1
47, XX, t(3;21)(p21;p13), del(7)(q21), +19	1
47, XX, +3, t(X;10)(q28;q11.2)	1
48, XX, +2, +7	1

Discussion

The present case of a multifocal angiosarcoma developing in an arm with chronic lymphoedema, caused by mastectomy and axillary lymph node resection, represents a typical example of Stewart-Treves syndrome. The results of the light- and electron-microscopic examinations and immunohistochemical and lectin histochemical analyses illustrate the difficulties involved in deciding whether such angiosarcomas differentiate in the direction of blood or lymph vessels or both. Thus, light microscopically there were some very well differentiated, haemangioma-like as well as lymphangioma-like areas.

Moreover, in solid, poorly differentiated areas a positivity for factor VIII RAg and the binding of the lectins (UEA-I) and PTA also occurred and a complete external lamina surrounding vascular formations was identified by electron microscopy and immunoreactivity for collagen IV and laminin. Furthermore, Weibel-Palade bodies were found in the haemangioma-like areas as well as in a few cells of the cellular, poorly differentiated parts. All these features indicate blood vessel endothelium origin. However, the well-differentiated angiomatous areas also contained endothelial cells which lacked Weibel-Palade bodies and revealed no positivity for factor VIII RAg, lectin binding or complete external laminae, all features compatible with lymph-vessel origin. Considering the clinical and morphological similarities between multifocal angiosarcoma in Stewart-Treves syndrome and multiple Kaposi's sarcoma, it is of interest that roentgenographic and morphological studies of Kaposi's sarcoma have indicated that the occurrence of lymphaticovenous shunts may be an early event in the development of Kaposi's sarcoma and that in the fully developed Kaposi's sarcoma the tumour cells share properties of blood and lymphatic endothelium (Palmer 1972; Dictor 1986; Dictor and Andersson 1988; Dictor et al. 1991 a).

The term pseudo-Stewart-Treves syndrome has been suggested (Sigal et al. 1987) for a clinical picture resembling that of Stewart-Treves syndrome caused by cutaneous and lymphatic metastases of a carcinoma. In the present case, the well-differentiated, haemangioma- and lymphangioma-like areas clearly indicated the vascular nature of the tumour. In cases where well-differentiated vascular areas are lacking, however, ultrastructural and immunohistochemical analysis may be needed. It is of interest that the highly cellular, solid areas without any light-microscopic features of vascular differentiation were also found to contain abortive vascular formations on ultrastructural examination and that some tumour cells in such areas stained positively for factor VIII RAg and bound the UEA-I and PTA lectins. The lack of positivity for cytokeratins and EMA as well as the ultrastructural absence of epithelial features also helped to rule out the possibility of a metastatic carcinoma. It should be noted, however, that the expected expression of cytokeratins has been reported in angiosarcomas. Brooks, for example, found that 4 of 14 angiosarcomas expressed cytokeratins in tumour cells scattered throughout the tumours (J.S.J. Brooks, unpublished work, 1989). Cytokeratins may occasionally also be expressed in proliferating endothelial cells in reactive lesions and have been reported in a few instances in benign endothelial tumours such as haemangiomas and epithelioid haemangioendothelioma (van Haelst et al. 1989).

The most prominent cytogenetic feature of the present angiosarcoma was the karyotypic heterogeneity observed among the aberrant cells. Apart from two cells with monosomy X, none of the other cells had the same karyotype. Nevertheless, a few cells with certain numerical deviations in common were found. Thus, there were three small clones which, in addition to other abnormalities, also showed trisomy 2, monosomy 22 and monosomy X respectively. All the 17 different marker types which were recorded were unique, that is to say were found in only one cell. Since this is the first cytogenetic investigation of angiosarcoma in Stewart-Treves syndrome, it remains uncertain whether any of the clonal numerical changes which were found represent non-random aberrations in this tumour type. There are only two previous reports of angiosarcomas in the literature. Both these cases occurred without any association with Stewart-Treves syndrome. One of the cases, an angiosarcoma of the scalp, showed a complex hypotetraploid karyotype with a variety of numerical and structural alterations (Molina et al. 1989). Consistent structural abnormalities involving 1p, 2q, 3p, 8p, and 13p were observed. In the other tumour, an unusual case of a haemangioma which was thought to have developed into an angiosarcoma of the left buccal mucosa and maxilla, about half of the analysed cells had a normal karyotype and the remaining cells showed trisomy 5 and/or loss of the Y chromosome as the sole abnormalities (Mandahl et al. 1990). No common cytogenetic abnormality has therefore been found in these three cases of angiosarcoma. The only similarity that could be found was the presence of a relatively large fraction of cells with normal karyotype in our case (41%) and in the case described by Mandahl et al. (1990) (52%). Whether these cells represent normal cells or tumour cells with a normal karytype is at present unclear.

Our findings of the loss of chromosome 22 and the X chromosome are of interest in relation to previous findings in certain other blood vessel tumours. Thus, sporadic Kaposi sarcomas frequently show monosomy 22 and deletions of 22q as well as monosomy X (Scappaticci et al. 1986). Moreover, a t(13;22)(q22;q11) has been reported in haemangiopericytoma (Limon et al. 1986). The involvement of chromosome 22 in several types of blood vessel tumours is of particular interest since the human platelet-derived endothelial cell growth factor (PD-ECGF) gene have recently been mapped to chromosome 22 (Hagiwara et al. 1991). PD-ECGF is a novel angiogenic factor which stimulates endothelial cell growth in vitro and promotes angiogenesis in vivo. It will be of interest to study whether any of these blood and lymph vessel tumours reveal aberrant expression of PD-ECGF.

The present tumour revealed a wide spectrum in terms of vascular differentiation from haemangioma/lymphangioma-like areas to highly cellular, solid, spindle-cell areas. Using corresponding light-microscopic examination, we were able to show that the tumour pieces used for the cultures were from the cellular, poorly differentiated parts of the tumour. In one of the two previously described angiosarcomas studied cytogenetically there were also benign-looking, haemangioma-like areas (Mandahl et al. 1990). If only such well-differentiated parts of the tumour were cultured, this could possibly explain the discrete karyotypic changes observed in that case. It should be noted that benign haemangiomas in repeated cytogenetical analysis have shown normal karyotypes (N. Mandahl, personal communication).

The rapid progressive course after the first occurrence of angiosarcoma in the present case agrees well with

previous reports of Stewart-Treves syndrome. A mean survival time of 19 months after the development of angiosarcoma has been observed (Woodward et al. 1972). Considering the reports in the literature suggesting the value of quantitative DNA analysis in order to distinguish between malignant and benign soft-tissue tumours (Bauer and Kreicbergs 1989), it may be noted that all the karyotyped tumour cells had chromosome numbers in the diploid-near-diploid region and that a cytophotometric DNA measurement of paraffin sections performed in this case also revealed a diploid pattern. In a recent study of the DNA content of angiosarcomas using the flow cytometric technique, diploid, peridiploid, tetraploid as well as aneuploid patterns were observed and a variable pattern was seen in different tumour nodules in one and the same patient (Dictor et al. 1991b). It is not surprising with a knowledge of the sensitivity of such quantitative DNA methods that the numerous chromosomal abnormalities seen in the present case could not be recognized in quantitative terms. We have also observed other examples of soft-tissue sarcomas with a poor prognosis which at quantitative DNA measurements demonstrate a diploid pattern, thereby indicating that such methods should be used with great caution if they are used to predict the prognosis (Persson et al. 1988; Stenman et al. 1990).

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