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CLINICAL FEATURES OF MALIGNANT HAEMANGIOPERICYTOMAS AND HAEMANGIOENDOTHELIOSARCOMAS

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Abstract

The clinical features of 23 patients with malignant vascular tumours, referred for treatment in the period 1968–85, are described. The tumours consisted of 15 haemangioendotheliosarcomas (angiosarcomas) and 8 malignant haemangiopericytomas. Ten haemangioendotheliosarcomas were located in skin or mucous membranes and 5 in viscera and deep soft tissues. None of the 8 haemangiopericytomas were superficially located. One cutaneous haemangioendotheliosarcoma arose in a lymphoedematous leg, while 4 others occurred in previously irradiated areas. There was one case of a Thorotrast-induced hepatic haemangioendotheliosarcoma. No predisposing factors could be demonstrated in the cases of malignant haemangiopericytoma. Median survival was 11 months for the haemangioendotheliosarcomas and 19 months for the haemangiopericytomas. Patients who were operable at the time of admission had a longer median survival (37 months) than those who presented with advanced disease (5 months). Local control was obtained by surgery in 3 cases and by radiation therapy in 2. No complete responses were seen on chemotherapeutic regimens.

Key words.: Soft tissue, neoplasms; malignant haemangiopericytomas, haemangioendotheliosarcomas, clinical features, treatment, prognosis.

Malignant tumours of vascular origin are rare, comprising less than 10% of all soft tissue sarcomas (5, 7, 12). Since their histological picture is quite varied, they often create considerable differential diagnostic problems. However, the introduction of modern immunohistochemical methods has made it possible to identify these tumours with greater reliability (18).

The following is a presentation of the clinical data on 23 patients with both histologically and immunohistochemically confirmed haemangiotheliosarcomas and malignant haemangiopericytomas.

Material and Methods

A search of the clinical files of the Finsen Institute revealed 40 patients who were referred for treatment in the period 1968–85 with a diagnosis of either angiosarcoma or malignant haemangiopericytoma. Ten patients were excluded as no histological material was available. Patients with borderline lesions (e.g. epithelioid haemangiomas) or with Kaposi's sarcoma were not included in the study and there were no cases of malignant epithelioid haemangiomas.

The histopathological review of the remaining 30 cases confirmed the diagnosis of haemangioendotheliosarcoma in 15 cases and of malignant haemangiopericytoma in 8 cases. Seven tumours were found to be of non-vascular origin. Apart from fulfilling standard diagnostic criteria (7), the haemangioendotheliosarcomas expressed positivity for laminin as well as the endothelial markers factor VIII-related antigen and/or the lectin of Ulex Europaeus I. They also contained the intermediate filament actin. The haemangiopericytomas likewise showed immunoreactivity for actin. The immunohistochemical findings are discussed in detail elsewhere (10).

Survival was recorded from the date of admission.

Results

Patient Characteristics

Haemangioendotheliosarcomas. The patients—10 females and 5 males—had a median age of 61 years (range 20–88) (Table 1). The anatomical location of the primaries is shown in Table 2; the most common site was the skin. Presenting symptoms were non-specific and generally reflected the location of the primary lesion. In the skin, the disease started either as a slight but progressive discolouration or as small reddish-blue nodules with a propensity to ulcerate, often accompanied by pain. In a few cases the first symptoms (general malaise, fever, pain) were caused by metastatic disease. There were no cases with symptoms of disseminated intravascular coagulation. Symptom

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duration before referral ranged from 3 to 30 months, with a median of 10 months. On admission, 6 patients had locally advanced disease while 3 had distant metastases.

Predisposing factors could be identified in 6 patients (40%); their case stories also serve to illustrate the varied clinical manifestations of the tumours:

Case No. 2: A 73-year-old woman underwent explorative laparotomy for non-characteristic abdominal complaints of about one year's duration accompanied by increasing pain in the right hypochondriac region. The liver showed diffuse infiltration by haemangioendotheliosarcoma and metastases were found in the intraabdominal lymph nodes. The patient had received Thorotrast in connection with an x-ray investigation for gallstones 30 years previously (1947). No treatment could be offered, and the patient died one month later with lung metastases.

Case No. 13: A 34-year-old man who 13 years earlier received radiation treatment (Coutard's technique, 36 Gy) for a haemangioma of borderline malignancy located in the upper part of the mouth. Although there were serious problems with recurrent fistulas and sequestrations of bone, recurrence of malignancy was not verified histologically until one year after the referral to the Finsen Institute. Even then, the histological picture was initially interpreted as a poorly differentiated carcinoma. Repeated attempts at surgical excision were not successful and the patient died 38 months later from extensive loco-regional disease.

Case No. 22: A 68-year-old woman who 25 years prior to admission had received radiation treatment for warts on the dorsum of her right hand. In the course of a year, she developed a tumour of 4×4 cm in the same area. Biopsy showed haemangioendotheliosarcoma, and a limited resection was performed, with amputation of three fingers. Three and a half years later, subcutaneous metastases occurred on the remaining part of the hand and the forearm, necessitating a humero-scapular amputation. The patient was still alive and well five years later.

Case No. 35: A 56-year-old man with Hodgkin's disease, successfully treated with MOPP and radiation therapy: inverted Y, 6 MV lin. acc., 37 Gy/29 f. Six years later the patient developed an induration and discolouration of the skin in the pubic area. A skin biopsy showed only non-specific reactive changes, interpreted as lichen sclerosus, but the lesion progressed with ulceration and a new biopsy was now diagnostic of haemangioendotheliosarcoma. The patient received six seried of doxorubicin (75 mg/m^2 every third week, cumulated dose 670 mg); a partial regression of 6 week's duration was induced, but the treatment was discontinued when the tumour started to grow again. He died 7 months after the diagnostic biopsy, from profusely bleeding local disease; there were no distant metastases.

Case No. 39: A 63-year-old woman suffering since childhood from a very severe and therapy-resistent psoriasis. In the 1940's she was treated with Thorium-paintings as well as Bucky-irradiation for lesions in the scalp. Later she received PUVA and low-dose methotrexate. Since 1971 she had recurrent basal cell carcinomas of the scalp and an haemangioendotheliosarcoma was detected incidentially by curettage in 1985. An excision was performed, but microscopy showed invasion of the underlying bone. Surgery was therefore supplemented by radiation therapy (60 kV, 48 Gy/16 f), but the tumour recurred almost instantaneously just outside the radiation field. The patient died 11 months later with advanced loco-regional disease.

Case No. 40: A 37-year-old woman who for unknown reasons had a moderate lymphoedema of her right leg; it had been present for 8 years, when within 3 months she developed multiple (20–25) cutaneous, ulcerating and bleeding tumours on the right femur. Biopsy confirmed the diagnosis of haemangioendotheliosarcoma. An exarticulation of the hip was performed but the operation was irradical and the malignancy recurred locally in the cicatrice. She therefore started treatment with ifosfamid and doxorubicin (5 g and 50 mg per m^2 respectively every 3 weeks). The disease was stable on this treatment for 6 1/2 months; then renewed progression occurred. Currently a phase II treatment is contemplated.

Table 1

Age and sex distribution

Age (years)	Haemangio-endotheliosarcomas		Malignant haemangiopericytomas	
	F	M	F	M
0–19	–	–	1	–
20–39	2	2	2	1
40–59	2	1	2	–
60–	6	2	1	1
Total	10	5	6	2

Table 2

Location of primary tumors

	Haemangio-endothelio-sarcomas	Malignant haemangiopericytomas
Soft tissues	1	6
Skin	8	–
Mucous membranes (oral cavity, vagina)	2	–
Viscera	4	1
Liver	2	–
Lung	–	1
Ovary	1	–
Breast	1	–
Unknown	–	1
Total	15	8

Malignant haemangiopericytomas. Seven adult patients, 5 women and 2 men, with a median age of 58 years (range 21–73) were presented (Table 1). The tumours were generally located in the deep soft tissues (Table 2). In one case the primary lesion was located in the lung; in another the site of primary could not be ascertained. Symptoms were caused by local invasion, often affecting nerves. Delay ranged from 1 to 24 months; however, one patient with a tumour in the thigh claimed that it had been present for more than ten years. Apart from this, no predisposing factors could be identified. Two patients had locally advanced disease at presentation while 2 others had distant metastases.

There was one case of an infantile haemangiopericytoma:

Case No. 7: A girl, who already at birth had a subcutaneous tumour on her right lower leg. At 6 weeks, it measured 5×4×2.5 cm. In consideration of the patient's age it was decided to observe the tumour without biopsy. However, after 17 months the tumour had increased in size to 9×6×5 cm. A biopsy was performed, followed by amputation in the knee joint. The patient was alive and well 14 years later.

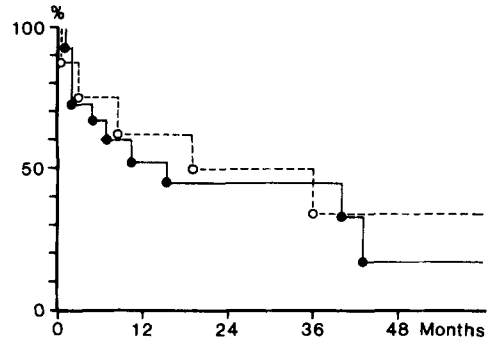

Fig. 1. Survival (Kaplan-Meier method) of 15 haemangioendotheliosarcomas (●—●) and 8 malignant haemangiopericytomas (O---O) calculated from the time of admission.

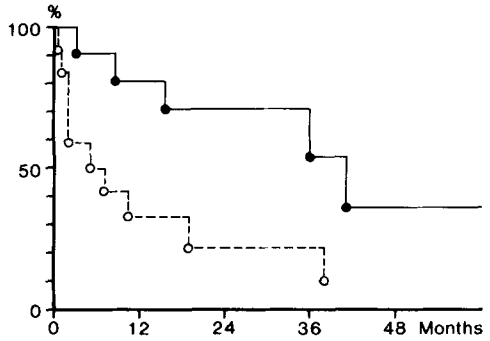

Fig. 2. Survival (Kaplan-Meier method) as a function of operability at the time of admission; haemangioendotheliosarcomas and malignant haemangiopericytomas combined. Eleven operable patients (●—●) and 12 patients with advanced disease (O---O).

Table 3

Results of intended curative treatment of primary, non-disseminated lesions. (Four patients with distant metastases are not included)

	No. of patients	No. of local failures
Surgery	9	6
Surgery + radiation therapy	1	1
Radiaton therapy	5	3
Radiation therapy + chemotherapy	1	1
Chemotherapy	3	3
Total	19	14

Table 4

Chemotherapeutic regimens used in the treatment of advanced haemangioendotheliosarcomas and haemangiopericytomas

Regimen	EORTC protocol No.	PD	Responses
Cyvadic	62761	2	–
Doxorubicin	62801	2	1 PR for 6 weeks
4-epi-doxorubicin	62801	2	1 PR for 4 months
Mitomycin-C	62812	1	–
Cisplatin	62781	1	–
Cyclofosfamid	62821	2	–
Ifosfamid	62821	–	1 NC for 6 months
Ifosfamid + Doxorubicin	62842	–	1 PR for 10 months 1 NC for 6 1/2 months

PD = progressive disease (including early deaths), NC = no change, PR = partiel remission.

Therapy

The treatment of the localized haemangioendotheliosarcomas and haemangiopericytomas followed the general guidelines for management of soft tissue sarcomas (5, 12). Surgery was preferred whenever possible. In one case, radiation treatment was preferred for cosmetic reasons (a cutaneous haemangioendotheliosarcoma in the face). The lesion recurred 9 months later. Otherwise, radiation therapy was used palliatively, when the tumours were technically inoperable, or added if the surgical procedure turned out to be non-radical. With the exception of case No. 39 mentioned above and palliative case, radiation treatment was delivered with supervoltage equipment (lin. acc., 4 or 6 MV); tumour doses varied between 30 and 60 Gy. Chemotherapy was added or used alone in cases of very large and ill-defined tumours where radiation therapy would have been insufficient or impossible. The chemotherapy for locally advanced or metastatic disease was given in accordance with EORTC's protocols for treatment of advanced soft tissue sarcomas.

Treatment Results and Survival

The local failure rate was 72%. Local control was obtained by surgery alone in 3 cases and by radiation therapy alone in 2 (Table 3). One of the latter was a cutaneous haemangioendotheliosarcoma that responded to a dose of 50 Gy (6 MV, 25 f, 5 f/week); however, cutaneous metastases occurred outside the radiation field 8 months later. In the other patient, who had a haemangiopericytoma in the axilla, lung metastases were discovered after a disease-free interval of only one month. Otherwise, local recurrence always preceded the development of metastatic disease.

The median survival (Fig. 1) for patients with haemangioendotheliosarcomas was 11 months (range, 1–101); 4 patients are currently alive, 2 of these with no evidence of disease. For malignant haemangiopericytomas the median survival was 19 months (range 1 week–175 months). Two of these patients are currently disease-free, and one has a local recurrence.

Patients who at admission had operable tumours had a better survival than those with locally advanced or metastatic disease, median 37 vs. 5 months (Fig. 2). However, the small numbers do not allow any statistical evaluation.

The responses to chemotherapy are listed in Table 4. No complete remissions were seen.

Discussion

Malignant vascular tumours are of mesenchymal origin and show differentiation towards either endothelial cells or pericytes. In the former case, the term angiosarcoma, or haemangioendotheliosarcoma, is generally applied. Lymphangiosarcomas are included in this group, since they are histologically similar (7, 14, 19). Kaposi's sarcoma, although showing some features of endothelial differentiation, remains a separate clinico-pathological entity (7). The most common term for malignant tumours with pericytic differentiation is malignant haemangiopericytomas (7). Since the clinical behaviour of the 2 groups generally resembles that of other soft tissue sarcomas, they are included in therapeutic recommendations and clinical trials concerning this group. However, as this study shows, they exhibit some characteristics of their own.

Haemangioendotheliosarcomas are rare in parenchymatous organs; they are often located in the skin and subcutaneous tissues (7, 14). This does not, however, facilitate diagnosis and treatment. Frequently a biopsy is not performed until the lesion has been present for a considerable time. Surgery and radiation therapy are often unsuccessful since the tumour is more extensive than expected clinically (15, 19). This aggressive behaviour justifies their automatic high-grade designation in histological grading systems (3, 16). The superficially located tumours often cause ulceration and bleeding, which may eventually be fatal. Another complication of large lesions is disseminated intravascular coagulation (1). There were no examples of this in the present material.

Haemangioendotheliosarcomas belong to the group of sarcomas that may be induced by irradiation. Hepatic haemangioendotheliosarcomas are a well-known sequel to exposure to the radioactive contrast-agent Thorotrast (5, 7). Following therapeutical irradiation, however, they occur only rarely (2, 14). The most common soft tissue sarcomas to arise after radiation treatment are pleomorphic fibrosarcomas and malignant fibrous histiocytomas (7, 11). It is noteworthy that 4 of our 15 haemangioendotheliosarcomas had received therapeutical irradiation for benign or borderline lesions in the relevant areas. The median latent period for postirradiation sarcomas is generally considered to be 10–15 years (11, 13), but in individual cases it may be considerably longer, as our data show. It has been suggested that the combination of radio- and chemotherapy may increase the risk of inducing a secondary malignancy (9), and interestingly, 2 of the above mentioned patients had also at some time received cytostatic agents (see case 35 and 39). Another wellknown predisposing factor is the presence of a longstanding lymphoedema (cf. case No. 40). The clinico-pathological entity of an angiosarcoma arising in a chronically oedematous arm after mastectomy is generally known as Stewart-Treves' syndrome or postmastectomy lymphangiosarcoma; its histological picture does not differ significantly from other angiosarcomas (7, 14, 19). In this context it may be noted that a rare, malignant version of epithelioid haemangioendothelioma (commonly considered a borderline lesion (7)), has been recorded as occurring in the liver of young women receiving oral contraceptives (4).

With regard to haemangiopericytomas, no predisposing factors are known. A subcutaneous variety occurring in early childhood (congenital or infantile haemangiopericytoma) is reported to have a benign clinical course (6, 7). Haemangiopericytomas in adults are often deep-seated tumours with a propensity for location in the lower extremities and the retroperitoneum. They may consequently be present for a long time and attain a considerable size before they give rise to symptoms and are diagnosed. They are rare in parenchymatous organs. Large tumours may be associated with paraneoplastical syndromes, such as hypoglycaemia (6, 7). However, in none of our patients such syndromes were observed.

Haemangioendotheliosarcomas and malignant haemangiopericytomas should probably be treated like other soft tissue sarcomas. The primary treatment of choice is radical surgery. However, as our data show, this modality is possible in less than half of the cases at the time of diagnosis. Moreover, even cutaneous haemangioendotheliosarcomas recur in the majority of the cases in spite of wide excision of the primary tumour: only 1 out of our 8 patients 1 out of 9 in the material of Maddox & Evans (14) and 3 out of 10 patients reported by Rosai et al. (19) were cured in this way. Multiple biopsies may be recommended, in order to map out the extent of these ill-defined and often multifocal tumours.

The exact value of adjuvant radiation therapy and chemotherapy is difficult to assess, mainly due to the rarity of these tumours. Aggressive treatment with high-dose megavoltage radiation therapy and multi-drug chemotherapy seems to have the best chances of success (5, 8, 17). In the advanced state of the diseases, responses are few but do occur (15). Proper evaluation of the different treatment modalities can only be assessed in prospective trials sufficiently large to allow for stratification with regard to wellknown prognostical factors, among these histological subtype.

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