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Vascular Tumors in the Region of the Breast

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Summary. Three vascular tumors in the breast region with different degrees of differentiation are presented. The first neoplasm is a haemangiosarcoma (of the vascular neoplasms, these tumors are the type which occur most frequently in the breast). Haemangiosarcomas show an infiltrative growth of atypical blood capillaries, frequently with formation of highly cellular and solid capillary sprouts. Ultrastructurally, the tumor cells are characterized as endothelial, also in the region of the capillary sprouts. The second tumor (an angiosarcoma in Stewart-Treves-syndrome, STS) is characterized by an intensive endothelial proliferation. Solid spindle-celled regions are also found in which the tumor cells correspond to undifferentiated mesenchymal cells, but other cells possessing properties of smooth muscle cells and pericytes may be found.

The third tumor corresponds light and electron microscopically to a haemangiopericytoma of the soft tissue. The pericytic character of the tumor cells is most clearly seen in the immediate vicinity of the vessels. With increasing distance from the capillaries, the tumor cells take on the characteristics of fibroblasts. The tumors reflect the diversity of the angioplastic differentiation potential of the mesenchyme.

Key words: Breast – Haemangiosarcoma – Stewart-Treves-syndrome – Haemangiopericytoma.

Introduction

Compared to the numerous publications on brest cancer, there are only a few communications on non-epithelial tumors in the literature. According to Bässler (1978), sarcomas account for about 1% of all malignant tumors with this localization, including cystosarcoma phylloides. Vascular neoplasms in the region

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of the breast are rare. Intramammary haemangiomas and lymphangiomas are found as benign tumors.

Vascular sarcomas occur in various forms. Haemangiosarcomas of the mammary gland have been described in 66 cases to date (York, 1972; Jautzke, 1973; Watanabe and Nakano, 1973; Breitfellner, 1975).

"Lymphangiosarcomas" after prior mastectomy for carcinoma in the context of Stewart-Treves-syndrome (STS) appear mainly in the region of the upper and lower arm on the operated side. Out of the 200 published cases (Kuhn, 1977), only two were localized in the thoracic wall in the region of mastectomy scar (Woodward et al., 1972; Schmitt and Littmann, 1977). Their lymphangiosarcomatous or haemangiosarcomatous nature is disputed.

The third variant form, haemangiopericytoma of the mammary gland has been recorded in the literature in three cases (Kauffman and Stout, 1960; Torino, 1972).

Because of the rarity of vascular tumors in the breast, the difficulties of differential diagnosis and as a contribution to clarifying questions of formal pathogenesis concerning the differentiation of the multipotent matrix, three of our own cases will be reported.

The characteristics of haemangiosarcoma, angiosarcoma in STS and haemangiopericytoma will be compared with reference to light and electron microscopic findings.

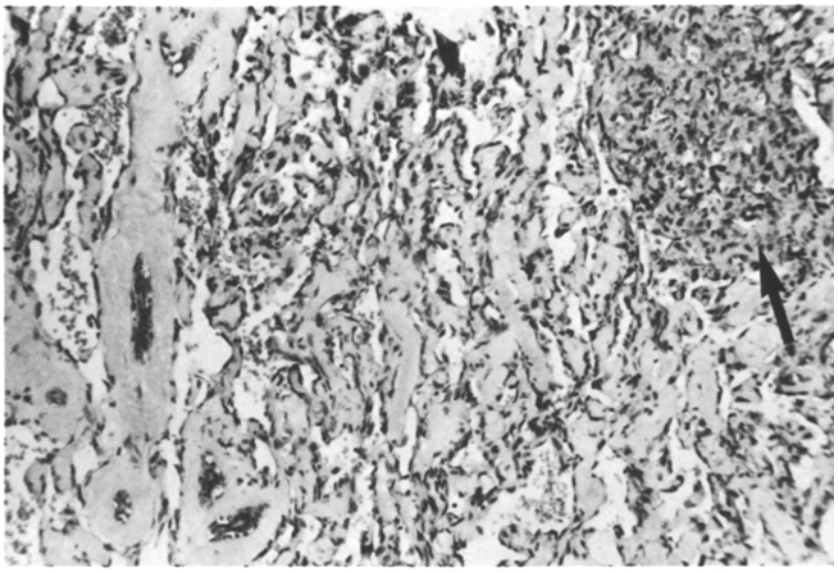
Case Reports

Case 1

Clinical History. A 27-year-old woman had two births (1972 and 1976). She had not taken oral contraceptives. In March 1977, an exploratory excision from the left breast revealed an angiomatous tumor in fibrocystic mastopathy. In November 1977, an intramammary tumor was removed from the left breast and a tumor situated above the areola from the right breast. Seven days later, there was a single bilateral breast amputation without followup irradiation. A sterilization was carried out by laparotomy. Since then, there has been no clinical indication (up to April 1979) for a tumor recurrence or metastases.

Gross Pathology. The measurements of the excised tumor of the left breast were $5 \times 4 \times 3{,}5$ cm and of the tumor of the right breast $3 \times 3 \times 2{,}5$ cm. On the cut surfaces, a red-greyish, soft, ill-defined tumor was seen.

Microscopic Pathology. The tumor consists of capillaries and capillary sprouts mostly with a narrow lumen, frequently filled with erythrocytes. The endothelial cells are elongated, the nuclei are longish or oval, and occasionly bizarre. The frequency of mitosis is moderately high. The cytoplasm of the endothelium is scanty and slightly eosinophilic. The endothelial layer is partly flat, and in places small endothelial pads are found projecting in the direction of the lumen. The tumor cells show pericapillary proliferation in the form of small buds and capillary sprouts and are enmeshed by a fine silver-staining network of fibers. Apart from areas rich in stroma, frequently with sinusoidal vessels, the tumor forms intensely proliferating structures focally, which largely consist



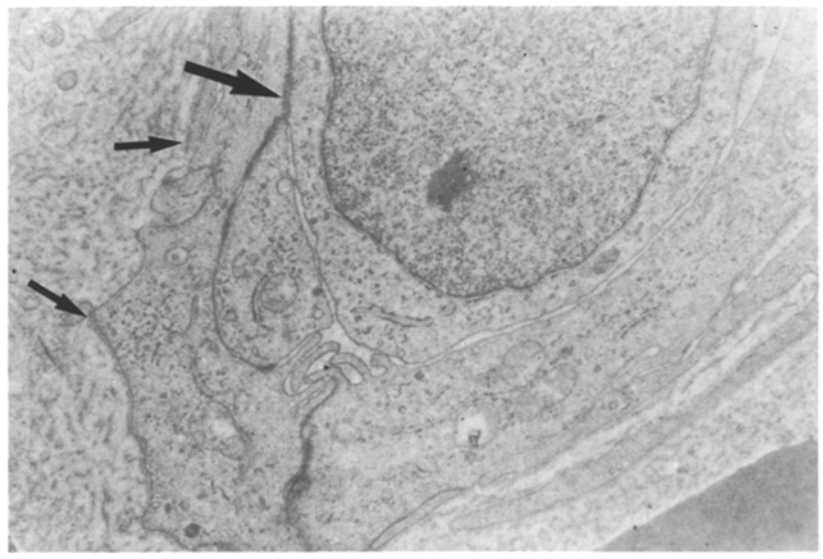


Fig. 1. Case 1, Haemangiosarcoma. Labyrinth of anastomosing blood capillaries in a hyalinized stroma. Endothelial cells flattened or budded into vessels lumina. A cellular area with numerous capillary sprouts (*arrow*). HE, ×32

Fig. 2. Case 1, Haemangiosarcoma. Capillary with cleft like lumen. Cytoplasm of endothelial cells filled with coarse cytofilaments, few dense bodies and micropinicytotic vesicles. Discontunity of basement membrane (*arrows*) and extended zonulae occludentes (*big arrow*). Thin section, ×8,000

of capillary sprouts or almost solid cell nests. The neoplasm grows infiltratively into the adipose and mammary gland tissue.

Assessment. Haemangiosarcoma.

Electron Microscopy. The endothelium of the tumor capillaries possess a generally copious cytoplasm with oval mitochondria of crista type, scanty RER, moderate glycogen and large single or multiple Golgi bodies arranged perinuclearly. On the cell membranes facing the lumen and the interstitium numerous pinocytotic vesicles are found. The cytoplasm of many cells contains roundish or irregular osmophilic inclusions delimited by membranes which reveal closely packed microtubular structures. The cells show filaments, which are mostly irregularly arranged and distributed throughout the entire cytoplasm (diameter 8 to 12 nm), occasionly they are densely packed near to the cell membrane. The nuclei of the tumor cells are roundish or irregularly invaginated. The nuclear chromatin is moderately dense and concentrated near to the nuclear membrane. The nucleoli show a coarse-fibrous skeleton. The endothelium of the capillary sprouts are linked together by extensive zonulae occludentes. Externally, the capillaries are surrounded by a thin basement membrane which is interrupted at many places by basal protrusions of the endothelia. The periendothelial cells frequently form short sprouts with tiny clefts in the center into which the cells send short pseudopodia. The clefts are sealed off from the interstitium by extensive zonulae occludentes.

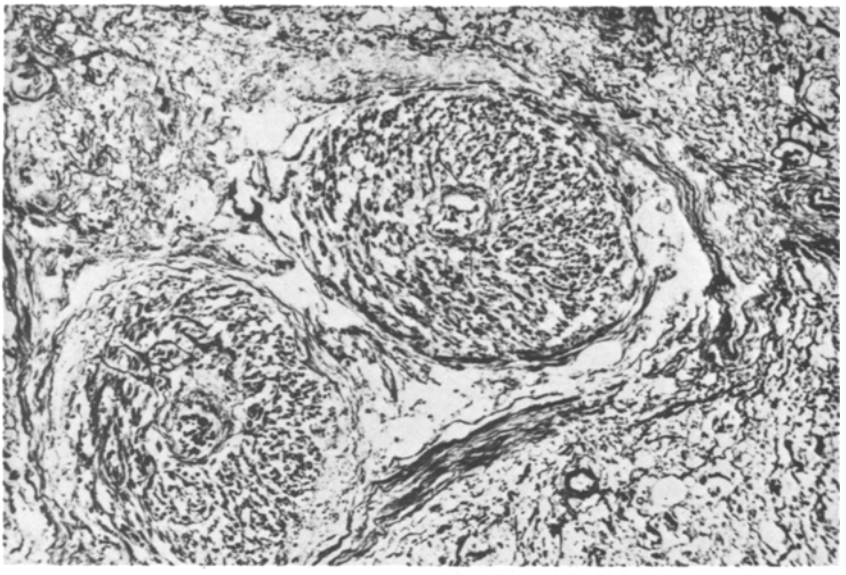
Case 2

Clinical History. In February 1967, a subcutaneous mastectomy of the left breast was carried out in a 55-year-old woman because of an extensive solid ductal carcinoma. Excicion of concomitant axillary lymph node metastases was also performed and followed by telecobalt irradiation with 5000 rads. In October 1977, a large ulcerative tumor developed on the left anterior chest wall. Apart from a medium-grade chronic lymphatic oedema, the left arm did not show any tumorous changes.

Gross Pathology. The measurements of the excised neoplasm were $8 \times 6 \times 5$ cm. On the cut surface, a hemorrhagic, highly necrotic grey-redish tumor tissue infiltrating the adjacent fat tissue was shown.

Radiologically, there were signs of lymphangiosis carcinomatosa of the left lung and suspicion of bone metastases. The woman died in January 1978. An autopsy was not performed.

Microscopic Pathology. The tumor tissue contains numerous unstructured large capillary vessels which are seen in certain regions as networks in a reticular plexus of fusiform tumor cells and which are partly filled with erythrocytes. The vascular clefts are bordered by highly atypical endothelium-like tumor cells, which frequently proliferate in small nodes and which protrude into the lumen. In other places, the tumor cells are formed into large solid or fascicular associations or are arranged radially around the lumina of larger vessels. They display elongated oval polymorphic nuclei with coarse clumpy karyoplasm and generally large nucleoli. In silver-stained preparations, only scanty and fragmen-



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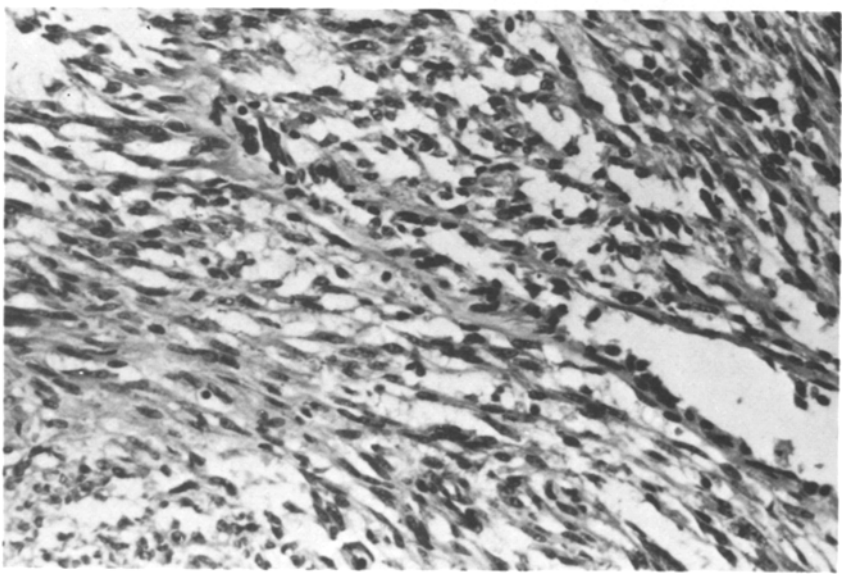

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Fig. 3. Case 2, STS. Nodular arrangement of pericytic tumor cells around central vessels. Sparse argyrophilic fibers in the interstitial space. Gomori, ×32

Fig. 4. Case 2, STS. Honey-comb like system of capillaries, lumina invested by a monolayer of endothelial cells with highly atypical nuclei. HE, ×80

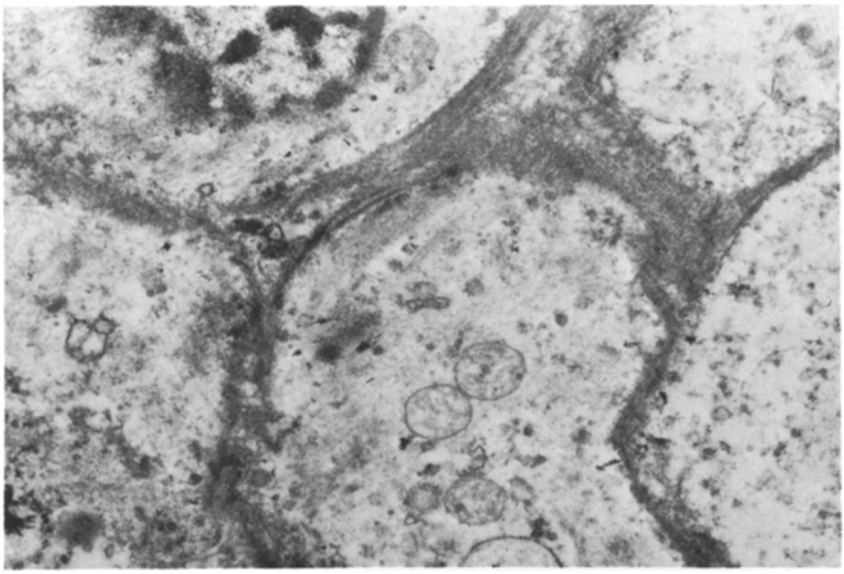

Fig. 5. Case 2, STS. Tumor-pericytes with clear cytoplasm, displaying only few organelles but numerous filaments. Cells surrounded by reticular fibers. Thin section, ×9,000

tary reticulin fibers are found. The tumor is rich in atypical mitoses, extensive necroses and hemorrhages.

Assessment. Angiosarcoma with endotheliomatous and pericytic differentiation in the left wall of the thorax, following surgery and irradiation of a mammary carcinoma.

Electron Microscopy. The endothelial tumor cells possessed roundish or longish cell nuclei with large, frequently multiple nucleoli. The nuclear membrane is sometimes deeply invaginated. In the cytoplasm, scanty mitochondria, unstructured filaments and RER are found. The endothelial cells are linked together by zonulae occludentes. They are located on a basement membrane which in some cases shows nodular widening and envelops occasional pericytic cells. In some cases, the tumor cells in the solid regions resemble smooth muscle cells, and in other cases they have a very low content of organelles. Scanty reticulin and collagen fibers are enclosed between the densely arranged tumor cells.

Case 3

Clinical History. A 33-year-old woman had noticed a slowly growing nodule in the left breast six years before coming for examination in July 1977. Mammography did not give any indication for malignancy. A sharply delimited tumor 2 cm in diameter and situated deeply in the tissue of the mammary gland was excised from the upper outer quadrant.

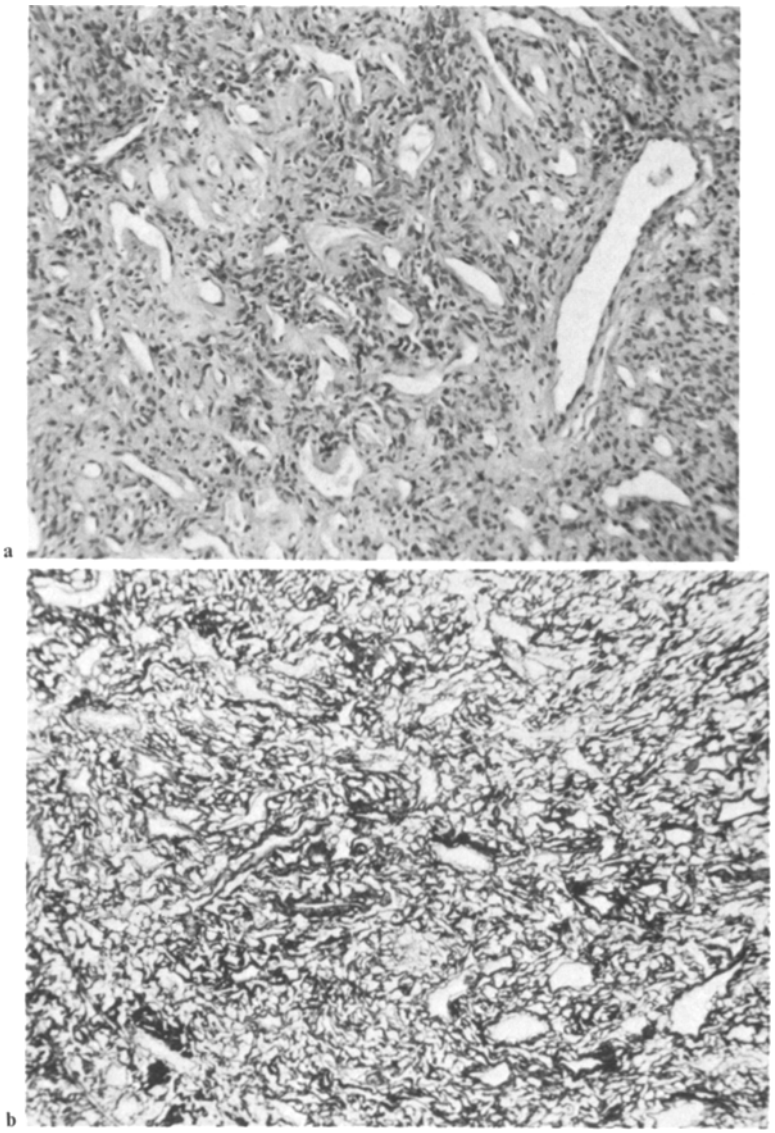

Fig. 6a and b. Case 3, Haemangiopericytoma. Mostly capillary tumor vessels with lumina of varying width. Vessel walls partly hyalinized. No special arrangement of tumor cells, no organoid architecture. HE ×33 (**a**). Tumor cells embedded in a delicate network of reticular fibers. Gomori ×33 (**b**)

Gross Pathology. The tumor is firm and elastic, and homogeneously whitish-grey on the cut surfaces. A narrow border of mammary gland tissue adheres to the outside.

Microscopic Pathology. The tumor consists of numerous evenly distributed mainly capillary blood vessels. The vessel wall shows band like hyalinization in places. Elongated to oval cells with an irregular, occasionly mantlelike ar-

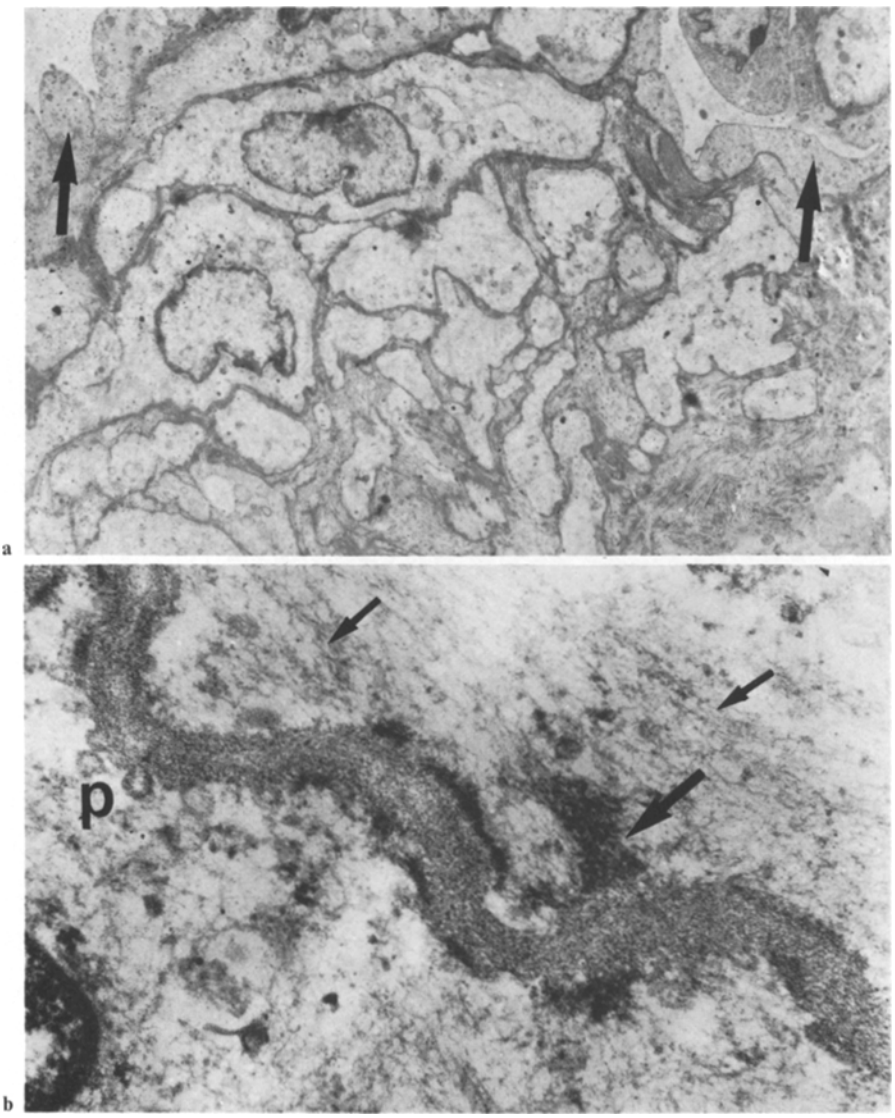

Fig. 7a and b. Case 3, Haemangiopericytoma. Tumor vessels lined by a monolayer of endothelial cells (*arrows*). Around a thin basement membrane, densely packed pericytes very similar to smooth muscle cells. Thin section, ×2,400 (**a**). Cell membranes of neighboured tumor-pericytes with attachment plates (*big arrow*), pinocytotic vesicles (*p*) and quite numerous myofilaments (*small arrows*). Thin section, ×4,000 (**b**)

rangement are found perivascularly. The cell nuclei have moderate chromatin density and are oval or longish. The tumor pericytes are separated from the vessels by a basal membrane and sorrounded by a cuff of reticulum fibers. The endothelial cells of the capillaries are monomorphic and mostly flattened. Polynuclear giant cells may be seen in the lumen. These are sometimes rich in cytoplasm and located like an endothelium on the basement membrane.

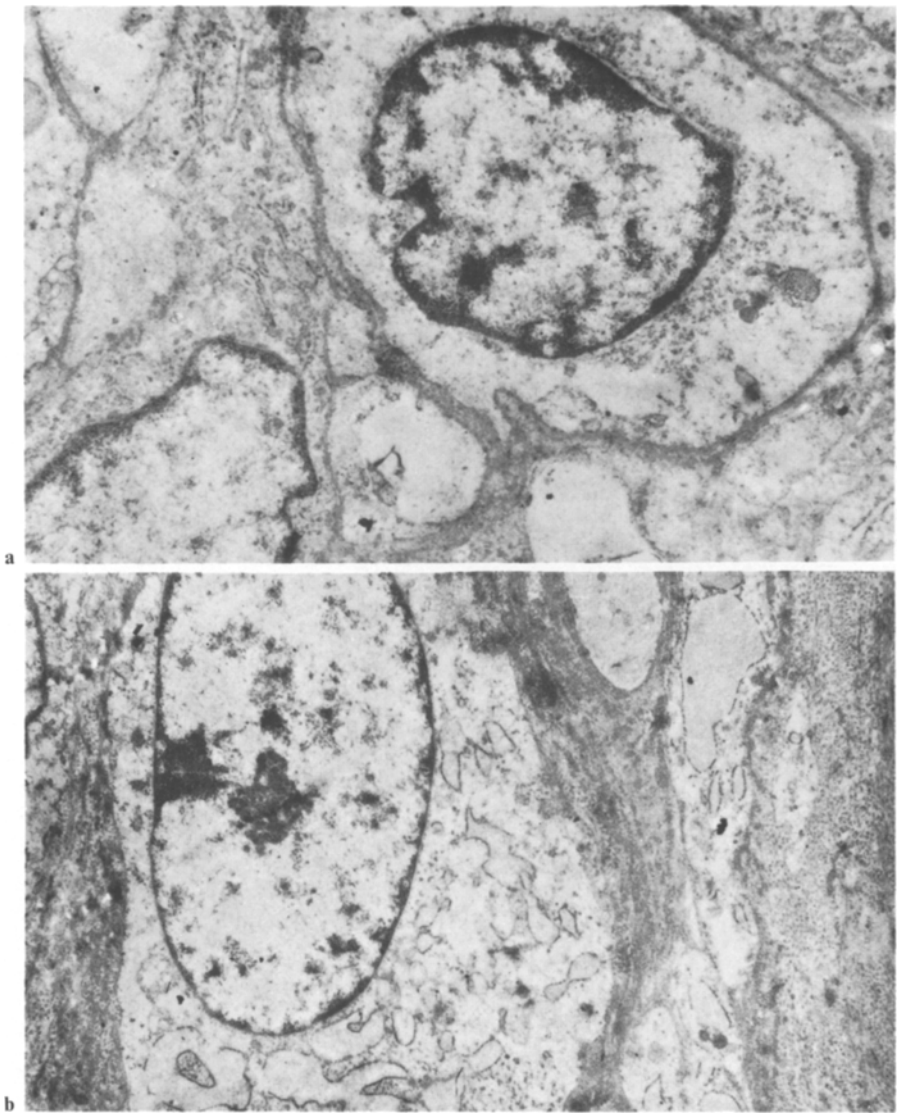

Fig. 8a and b. Case 3, Haemangiopericytoma. Tumor cells with different distances to a tumor vessel. Closed up to the vessel a pericyt with sparse organelles but rather conspicious filaments in cytoplasm. Thin section, ×8,000 (**a**). More distant to the vessel fibroblastic tumor cells with abundant, dilated rough endoplasmatic reticulum. Thin section, × 10,000 (**b**)

Very occasionally, mitoses are found. There are a few mast cells around capillaries. There are no indications of fat or hemosiderin storage, and neural elements are lacking.

Assessment. Haemangiopericytoma.

Electron Microscopy. The endothelium of the tumor vessels is monostratified. The cells are linked together by zonulae occludentes. The cytoplasm is clear

and poor in organelles. Besides small mitochondria, it contains a little, sometimes intensely dilated RER, little glycogen, occasional dense bodies and sparse filaments 8–12 nm thick. The basement membrane is thick and consists of reticulin and embedded collagenous elementary fibrils. Ultrastructurally, the tumor pericytes show a different differentiation which depends on the distance from a blood vessel. In the immediate vicinity of vessels, the pericytes frequently still resemble smooth muscle cells: The cell body is roundish to oval, and shows a moderate number of thin and also blunt processes. Numerous pinocytotic vesicles are found on the cell membrane. The rest of the cytoplasm shows numerous loosely and irregularly arranged filaments, fusiform densities and attachment-plates.

With increase in the distance from the vessel, the tumor cells assume more fibroblastic character: the cell nucleus becomes longish, the surface differentiation decreases. The number of attachment-plates is reduced, the filaments become sparser and the extent of the pinocytosis becomes less. The amount of fibers between the cells increase. The giant cells in the vascular lumina are very rich in cytoplasm. Their cytoplasm contains numerous ribisomes, and otherwise only scanty organelles such as short tubes of RER and small roundish dense bodies.

Discussion

Common to all three breast tumors is a marked angioplastic potency, but they illustrate the diversity of this kind of neoplasms.

The first neoplasm showed an almost exclusively endothelial proliferation. Ultrastructurally, the capillary endothelium of the tumor has some similarity with normal vascular endothelium. In the intensely proliferating tumor which is rich in mitoses, there is a characteristic cell structure pointing to its endothelial nature despite the low degree of cellular differentiation. The malignant character of the cells is evident from the large, frequently deeply invaginated cell nuclei which contain euchromatin predominantly and also show nucleoli of coarse structure.

The histological structure of the tumor we have discribed corresponds to most of the tumors designated as haemangiosarcomas of the breast in the literature (Patrick et al., 1957; Shore, 1957; Batchelor, 1958; Mackenzie, 1961; Steingaszner et al., 1965; Gulesserian and Lawton, 1969; Kessler and Kozenitzky, 1971; York, 1972; Watanabe and Nakano, 1973; Jautzke, 1973; Breitfellner, 1975).

The differential diagnosis of haemangiosarcoma from benign haemangioma can present difficulties, especially when well differentiated tissue with monomorphic endothelium lining the capillaries predominates in the primary tumor (Mackenzie, 1961; Steingaszner et al., 1965; Gulesserian and Lawton, 1969; Kessler and Kozenitzky, 1971). Diagnosis of a malignant tumor becomes possible only after a careful study of numerous sections and after demonstration of hyperchromatic and atypical cell nuclei.

As Hamperl (1973) showed when discussing intramammary haemangiomas

("lobular angioma"), the capillary-rich loose coating tissue of the glandular lobes is the probable site of origin of a haemangiosarcoma.

In the second neoplasm (an angiosarcoma in STS), a proliferation of perithelial cells is found besides the angioplastic components. Common to both is a high-grade anaplasia of the cellular and tissue structure. The dense mat of reticulin fibers around the pericytic cells seen in haemangiopericytoma is lacking.

The characteristics of myocytes can only be occasionally demonstrated. The combination of malignant endothelial cells and cells with pericapillary proliferation in this tumor corresponds to the angiosarcoma described in STS (Stewart and Treves, 1948; Sternby et al., 1961; Taswell et al., 1962; Siverberg et al., 1971; Kermarec and Varim, 1975; Winkler, 1975; Kuhn 1977).

STS (Stewart-Treves-syndrome) involves an angiosarcoma which has arisen on the basis of a chronic lymphatic oedema following a mastectomy because of mammary carcinoma and developing in congenital, post-traumatic and lymphangitic oedema (Scott et al., 1960; Francis and Lindquist, 1960; Woodward et al., 1972; Dubin et al., 1974). Vascular tumors of the same size have not been observed following elephantiasis after infection with filaria, the most frequent cause of chronic lymphatic oedema (Scott et al., 1960).

It has not yet been possible to clarify with electron optic investigations as to wether this neoplasm is a lymphangiosarcoma or haemangiosarcoma (Silverberg et al., 1971; Dubin et al., 1974; Kermarec and Varim, 1975; Winkler, 1975). The tumor we investigated showed pericytic-like tumor cells and a basement membrane in the vicinity of the tumor capillaries. These structures indicate the presence of a *haemangiosarcoma,* since according to Leak (1972) normal capillary lymph vessels do not display any pericytes and also show no continuous basement membrane.

Like Silverberg et al. (1971), Dubin et al. (1974) and Kermarec and Varim (1975), we were unable to find any electron microscopic markers of epithelial structures such as desmosomes, microvilli, secretory granules etc.

The third mammary tumor described here was a haemaniogericytoma (Stout and Murray, 1942) characterized by numerous evenly distributed capillaries in a dense assemblage of unstructured, light microscopically monomorphic pericytes embedded in a network of silver-staining fibers. The pericytes in the immediate vicinity of the vessels are frequently similar to smooth muscle cells. With increasing distance from the capillary lumina, they are differentiated as fibroblasts.

The tumor we described was classified as *benign* because of the absence of necrosis, haemorrhages and nuclear polymorphism with very occasional mitosis as well as a well-developed pericellular cuff of reticulin fibers. According to Kauffman and Stout (1960), the loss of or scanty development of a pericellular fiber ring is an important sign of malignancy in haemangiopericytoma. Basically, the transitions are fluid, and the establishment of the pathological status therefore uncertain (McMaster et al., 1975; Enzinger and Smith, 1976).

The occurence of transitional forms between pericytes and smooth muscle cells was described in a few haemangiopericytomas of the soft tissue (Stout, 1949; Hahn et al., 1973; Kuhn, 1977).

Our observation of a transformation of the tumor pericytes far away from

Table 1. Reeported vascular tumors of the breast

Tumor	Number	Authors
"Lobular" haemangioma	25	Giozetti and Vio, 1963; Hamperl, 1973
Lymphangioma	5	Bässler, 1978
Haemangiosarcoma	67	York, 1972; Jautzke, 1973; Watanabe and Nakamo, 1973; Breitfellner, 1975; Volmer et al., 1979
Angiosarcoma in STS	3	Woodward et al., 1972; Schmitt and Littmann, 1977; Volmer et al., 1979
Haemangiopericytoma	4	Kauffman and Stout, 1960; Torino, 1972; Volmer et al., 1979

Table 2. Clinical and pathological-anatomical property of vascular breast tumors

	Haemangiosarcoma	Angiosarcoma in STS	Haemangio-pericytoma
Age at which disease appeared	youth and middle age, average 34 years	morbidity peak in the 7th decade of life average 10 years after mastectomy	any age
Localization	preferentially affects right breast and upper outer quadrant	mainly upper arm, very rarely in the wall of the thorax	number of cases for the breast too small
Size of the tumor	1.5–8 cm, average 4.5 cm	multicentric	0.8–22 cm average 6.5 cm
Local behavior	exceedingly infiltrative, rapidly growing	multicentric, infiltrative	slow suppression of growth
Texture	soft, rich in blood, spongy	in some cases firm nodular, mainly hemorrhagic tissue	soft to firm, light grey to brownish, in some cases with hemorrhages
Pathological status	highly malignant	highly malignant	50% malignant
Tendeny to recurrence	extremely high	high	high
Metastases	frequent, lungs, skin, liver, ovary, skeleton	frequent, lungs, skeleton	15–50%, lungs, skeleton
Survival time	average 25 months	average 19 months	varies

capillaries into fibroblastic-like cells is in agreement with the findings of Enzinger and Smith (1976), who were able to demonstrate characteristics of a fibrous histiocytoma in addition to the typical features in a few haemangiopericytomas. The occasional polynuclear giant cells are free in the vessel lumina in some cases, in others they are situated like an endothelium on the basement membrane. Electron microscopically, they do not show any specific characteristics, so that their interpretation as proliferation of endothelium is uncertain.

In its cellular differentiation, the haemangiopericytoma resembles capillary wall structures and pre- and post-capillary vessels of the normal tissue: Depending on their localization in terminal vascular system, the perivasal cells can display differentiation characteristics of pericytes, via "primitive" muscle cells (intermediate cell type) to mature smooth muscle cells (Rhodin, 1968).

Vascular tumors of the breast are rare. Data on the frequency relation are found in the literature for haemangiosarcoma only: 0.03% of all mammary gland tumors (Enticknap, 1946), one haemangiosarcoma to about 1700 mammary carcinomas (Mackenzie, 1961/1962). Table 1 shows the number of published cases of vascular tumors of the breast.

The clinical behavior of the vascular mammary tumors varies, giving pointers for differential diagnostic discrimination.

In Table 2 the clinical and pathological information on haemangiosarcoma of the breast is mainly derived from the review study by Jautzke (1973). The data on angiosarcoma in STS are mostly related to tumors which have arisen in the upper limb of the operated side because localization in the thorax region is rare (Stewart and Treves, 1948; Sternby et al., 1961; Taswell et al., 1962; Woodward et al., 1972). The haemangiopericytoma of the breast is also so rare that the following information is based mainly on tumors of the human soft tissue of the limbs and of the trunk, in which they occur more frequently (McMaster et al., 1975; Enzinger and Smith, 1976).

When the breasts are affected by haemangiosarcoma on both sides as in our case, the usual cause is contralateral metastasis (Jautzke, 1973; Bässler, 1978).

Our cases of vascular tumors show a non-homogeneous behavior clinically and in terms of pathological anatomy and can be distinguished from each other by light and electron microscopy, despite occasional common characteristics.

The range of variation of the angioplastic potency is shown in haemangiosarcoma as an almost pure endotheliomatous proliferation, in angiosarcoma in the context of STS in an unstructured development from proliferated endotheliomatous and non-proliferated spindle-cell components, and in haemangiopericytoma as a predominantly uniform proliferation of pericytes.

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