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Original Articles

Vascular Tumors of the Mammary Gland

A Histochemical and Ultrastructural Study

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Summary. A total of five haemangiosarcomata and two benign haemangiomas arising in the mammary gland have been studied electron microscopically and by histochemical techniques. Malignant tumors were mainly composed of endothelial cells reactive to alkaline phosphatase and adenosine triphosphatase, and of pericytes and undifferentiated mesenchymal elements. A juvenile haemangioma showed a more structured wall with an increase of endoplasmic reticulum and filaments, and a diminution of membrane modulations and rod-like tubular bodies. A cavernous haemangioma showed an ultrastructure very similar to normal vessels.

The ultrastructural and histochemical data suggest a blood vessel origin of mammary angiosarcomas and show that vascular neoplasms of the breast, benign or malignant, are composed of a combined proliferation of the different cell types present in the vessel wall, as described in other organs.

Key words: Blood vessel neoplasms – Electron microscopy – Histochemistry – Angiosarcoma – Breast neoplasms.

Introduction

Primary vascular tumors of the breast are usually considered uncommon neoplasms. Among them, mammary haemangiosarcoma is the most frequently found type, benign haemangioma having been observed only in exceptional cases, (Hamperl 1973; Lapertosa et al. 1980). The published reports have provided accurate knowledge of the biological and histopathological characteristics of the tumors (Bässler 1978), as well as their response to therapy (Steingaszner et al. 1965; Chen et al. 1980), but no previous reference has been found to their ultrastructural characteristics.

The present report concerns the electron microscopical features of two benign haemangiomas, one of the cavernous type and the other of the juvenile variant, and of five haemangiosarcomas.

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Table 1

Case	Age	Sex	Breast	Size cms	Histological diagnosis	Duration clinical history	Follow up
1	11 months	Female	Right	2,5 × 2	Juvenile hemangioma	3 months	alive 1 year
2	35 years	Female	Right	3 × 3	Benign cavernous hemangioma	2 years	alive 2 years
3	13 years	Female	Left	9 × 8	Well differentiated hemangiosarcoma	6 months	died 3 years, after multiple local recurrences
4	45 years	Female	Left	10 × 9	Well differentiated hemangiosarcoma	2 years	lost for follow up
5	18 years	Female	Right	12 × 12	Poorly differentiated hemangiosarcoma	4 months	died 1 year multiple metastasis
6	60 years	Female	Left	?	Poorly differentiated hemangiosarcoma	?	local recurrences in left arm six months after mastectomy
7	35 years	Female	Right	8 × 8	Moderately differentiated hemangiosarcoma	2 years	alive without tumor

Materials and Methods

Among a total of 788 primary malignant mammary tumors, collected during the period 1976 from 1980, two benign haemangiomas and five haemangiosarcomas have been found. They account for about 0.9% of the total. The clinical findings and follow up data of the neoplasms are summarized in Table 1.

Fragments of tissue for routine histology were fixed in 10% formalin and Bouin's fixative, embedded in paraffin and the sections stained with H.E. Van Gieson's and Masson's trichrome and Laidlaw's impregnation.

Fresh material was available from cases 2 to 7 and it was cut into 1 mm^3 immediately after surgery. These pieces of tissue were fixed in cold 2.5% glutaraldehyde in phosphate Milloning buffer, postfixed in osmium tetroxyde, dehydrated in graded alcohols and embedded in Epon. Thin sections were stained with alkaline toluidine blue, after which suitable thin sections were prepared, mounted on copper grids and examined in an electron microscope.

Formalin fixed material from case 1 was washed in buffer postfixed in glutaraldehyde and osmium and treated in the way described above.

Fresh material from cases 2, 3, 4, 5, 6, and 7 was quickly frozen in liquid nitrogen and was stained to demonstrate ATPase (Dubowitz and Brooke 1973), and alkaline phosphatase activity (Lillie 1965).

Findings

The clinical data and follow-up data of the cases are summarized in Table 1.

Light Microscopy

a) Benign Tumors. The cavernous haemangioma was composed of a mass of large vascular lumina, lined by a row of attenuated endothelium without atypia, mitotic activity or papillary projections. Beneath the cells a wide band of collagen could be seen.

The juvenile angioma showed a histological picture similar to that found in the skin and salivary glands. It was composed of small vessels with a different degree of permeability. The endothelium was plump with oval nuclei and was surrounded by one to three rows of spindle elements. No normal breast tissue was found in the interstitium of either tumor (Fig. 1).

b) Malignant Tumors. The tumors showed a structure similar to previously reported cases. The more differentiated neoplasms showed numerous, freely anastomosing capillary lumena lined by tumor cells. They had an attenuated cytoplasm and large hyperchromatic nuclei with some mitotic figures. In other areas some spongy vascular spaces with numerous papillary projections could be seen. The papillae were surrounded by endothelium and in their axis were located some rounded elements, occasionally with a clear cytoplasm, as well as remnants of the collagen framework of the gland. Finally, in other places, solid buds of cells were seen projecting into the lumen of the vessels.

The less differentiated tumors were mainly composed of spindle cells associated in fascicles interspersed with collagen and reticulin fibers. Inside the mass of spindle elements some capillary-like lumena were seen. In the peripheral part of these neoplasms some differentiated areas were also identified (Fig. 2).

The morphology of the tumor was reproduced in the recurrences and in lymph node metastasis, with a progressive loss of maturity in successive local recurrences of the tumor.

Histochemistry

a) Malignant Tumors. The techniques to demonstrate alkaline phosphatase and adenosintriphosphatase were positive in the neoplastic cells which bordered the mature vessels and in some of the papillary areas. The areas of solid growth and the spindle cells were constantly negative to alkaline phosphatase, but in places slight positivity to ATP-ase could be seen. In all the cases the reactivity of the neoplastic endothelium was always of a lesser degree than that of normal vessels.

b) Benign Cavernous Haemangioma. This also showed a positive reaction, both for adenosine triphosphatase and alkaline phosphatase, in the endothelial lining.

Electron Microscopy

a) Benign Tumors. The vessels of the *juvenile haemangioma* showed a very thick wall. The endothelial cells were very prominent and protuded into the lumen which was reduced to a narrow slit. They had a low electron density

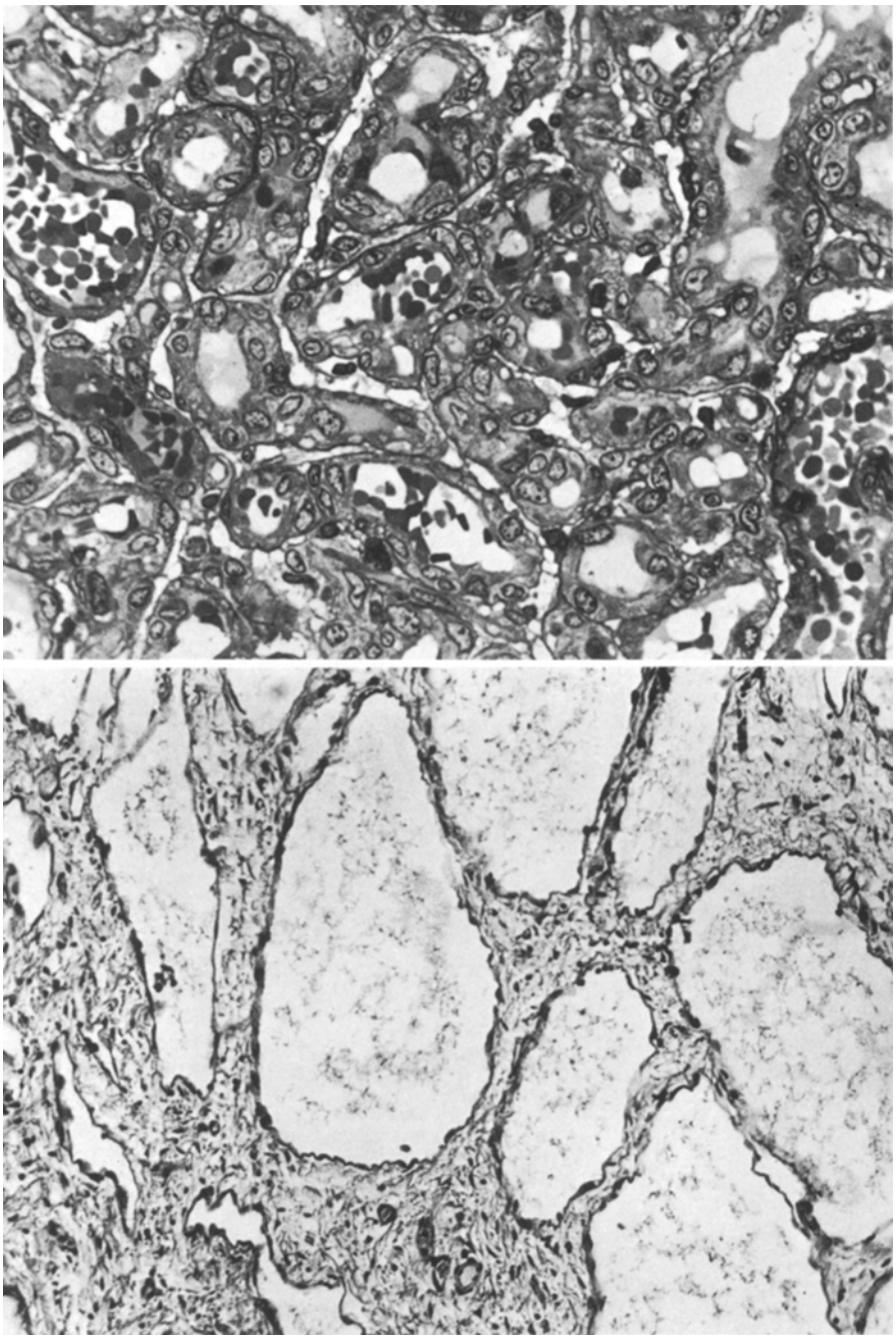

Fig. 1. (*Left*) Cavernous haemangioma. The tumor is composed by wide vessels with a collagenous wall covered by attenuated endothelium. H.E. 160×. (*Right*) Juvenile angioma. The tumor vessels are of small caliber and with a different degree of permeabilization. Semithin section. Toluidine blue 250×

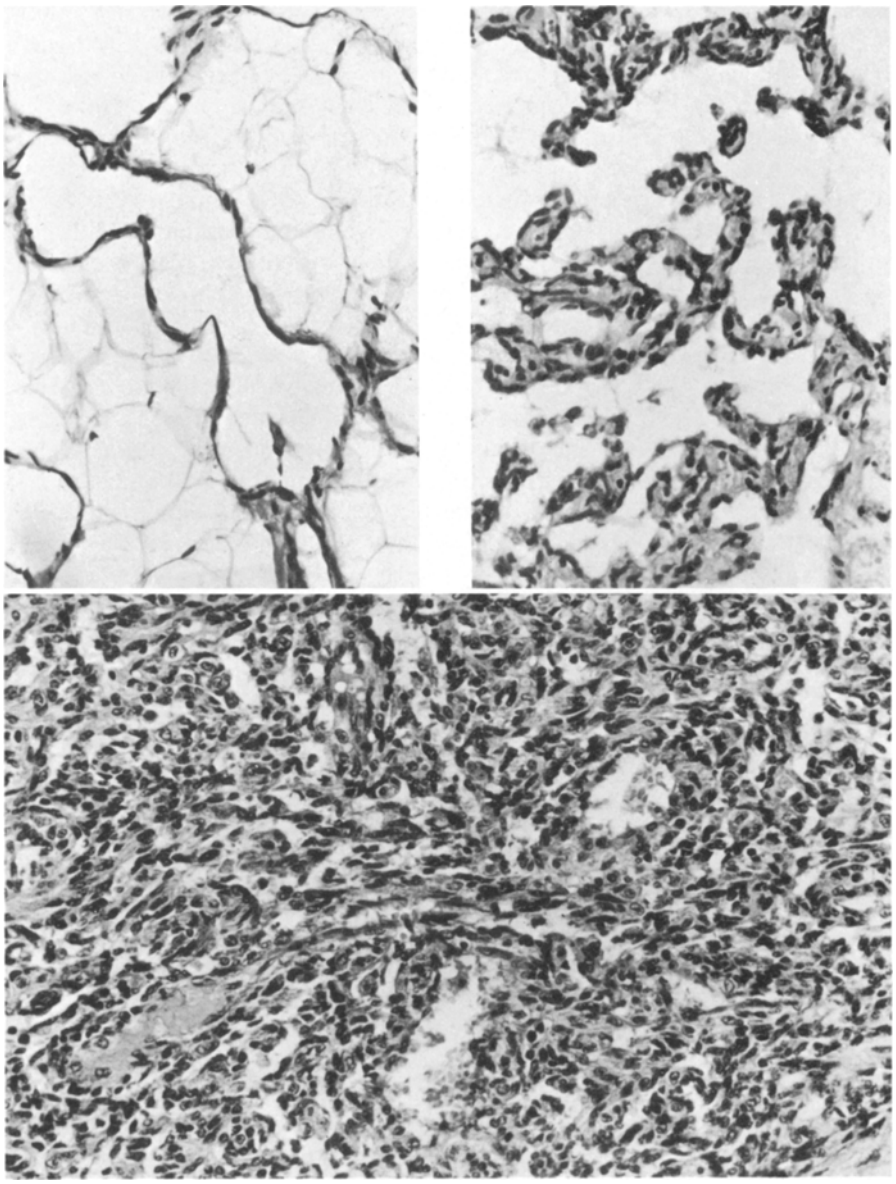

Fig. 2. (*Top left*) Well differentiated area of haemangiosarcoma. The picture resembles benign angioma. However the capillary vessels are covered by hyperchromatic cells with irregularly distributed nuclei. H.E. 160×. (*Top right*) Moderately differentiated area of haemangiosarcoma. The tumor shows a marked tendency to constitute intraluminal papillae. H.E. 160× (*Bottom*) Undifferentiated area of haemangiosarcoma. The tumor is composed by a mass of spindle elements with some vascular lumens. H.E. 160×

cytoplasm, with scanty surface modulations. The projections were usually short and blunt and present on the luminal aspect of the cells only. There were abundant bundles of filaments, free ribosomes and profiles of rough endoplasmic reticulum which showed masses of electron dense material in places. Pinocytotic vesicles were very scarce. Isolated Weibel-Palade bodies were found. The endothelial cells were joined by union complexes and were surrounded by one to three layers of spindle cells. These elements also showed abundant filaments, some with focal densities, some pinocytotic vesicles and rough endoplasmic reticulum. All these organelles were most evident in the outer layers of cells. These elements were surrounded by basal membrane and also show desmosomial unions, and were interpreted as pericytes (Fig. 3).

The *cavernous haemangioma* showed a very attenuated wall composed of two layers of cells. The inner layer was composed of endothelial elements. The cells were elongated in cross section. Near the nucleus, there was a widening of the cytoplasm, where centrioli could be found as well as RER and RER cysternae, Weibel-Palade bodies, free ribosomes and some residual bodies. Some pinocytotic vesicles and bundles of filaments were also found. Membrane modulations were irregular in distribution, being scarce and short in places and very long and numerous in other places. The external layer of cells was composed by a discontinuous sheet of flattened pericytes surrounded by basal lamina which showed very elongated cytoplasmic expansions and some pinocytotic vesicles (Fig. 4).

b) Malignant Tumors. Four different types of cells have been identified: endothelium, pericytes, undifferentiated cells and fibroblasts.

Endothelial Cells

The cells showed a very thin cytoplasm, with bundles of filaments measuring 10 nm in width. They showed small elongated mitochondria and numerous pinocytotic vesicles aligned with both surfaces of the cell. The nuclei were prominent, plump and with coarse cromatin, and lay in an expansion of the cytoplasm. Near the nuclei there were some Golgi cysternae, centrioli, mitochondria and pinocytotic vesicles. Some membrane-bound tubulated dense bodies, interpreted as Weibel-Palade bodies measuring 100–150 nm were seen in all the cases. Frequently the cells showed spherical projections filled with multiple small vesicular structures which joined the cytoplasm by a narrow "neck", and projected into the lumen of the vessel (Fig. 5). The plasma membrane formed expansions which projected on both sides of it. In the basal part of the cells, the interdigitating expansions constituted small cavities between the neoplastic cells showed abundant junctions, but frequently the vessel showed discontinuity in the endothelial covering. The cells were surrounded by a discontinuous electron-dense basal lamina. No fenestrations or anchoring filaments were found.

Undifferentiated Cells

In the well differentiated areas these were of smaller size than endothelial cells or pericytes, and were roundish with a smaller amount of cytoplasm. This

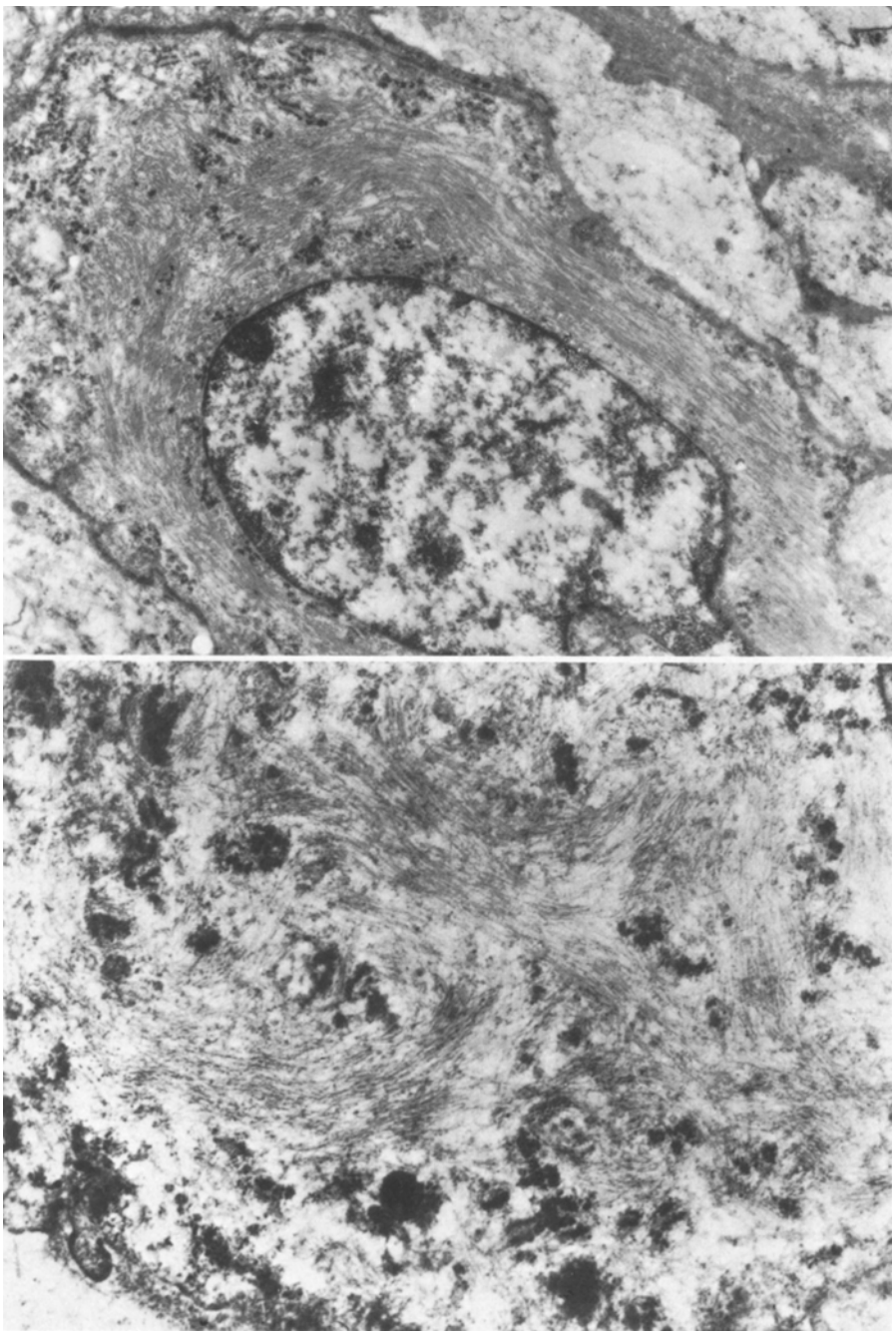

Fig. 3. (*Left*) Juvenile angioma. The cytoplasm of the endothelium shows abundant filaments, and rough endoplasmic reticulum. The apical surface of the cell (*left upper corner*) shows some short expansions projecting into the lumen. Double stained. 8,000×. (*Right*) Juvenile angioma. Pericytic cell surrounded by basal lamina and showing intercellular junctions and bundles of intracytoplasmic filaments. Double stained. 4,000×

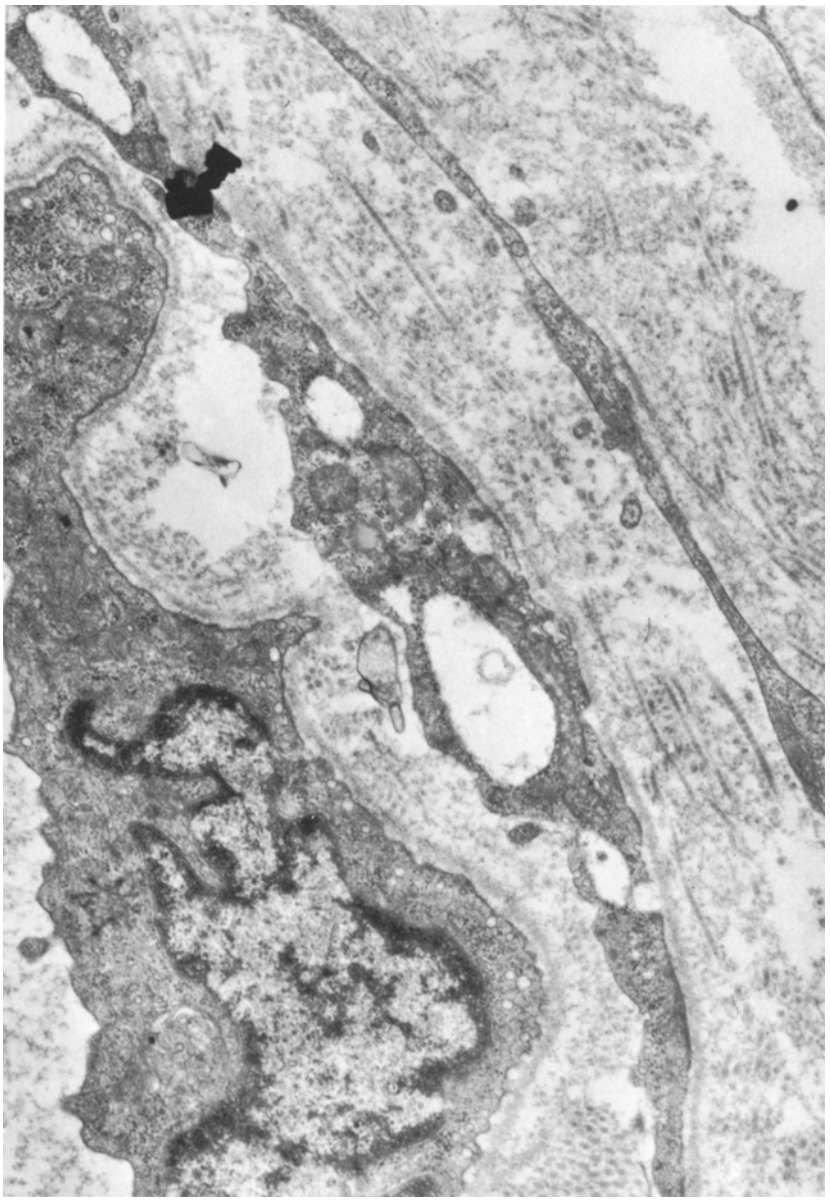

Fig. 4. Cavernous haemangioma. The wall appear composed by a layer of endothelium with a well developed basal lamina. These cells are surrounded by pericytic cells also surrounded by basal lamina. Externally it can be seen the cytoplasmic expansions of a fibroblast. Double stained. 8,000×

showed abundant ribosomes and scanty organelles with very few mitochondria, profiles of rough endoplasmic reticulum and short expansions all around the contour of the cell. Undifferentiated cells were situated in the papillary areas in the axis of the papillae and in the most differentiated vessels in the perivascular connective tissue. In the immature tumors they usually showed a spindle shape, with a smooth plasma membrane, and an oval nucleus. The cytoplasm was

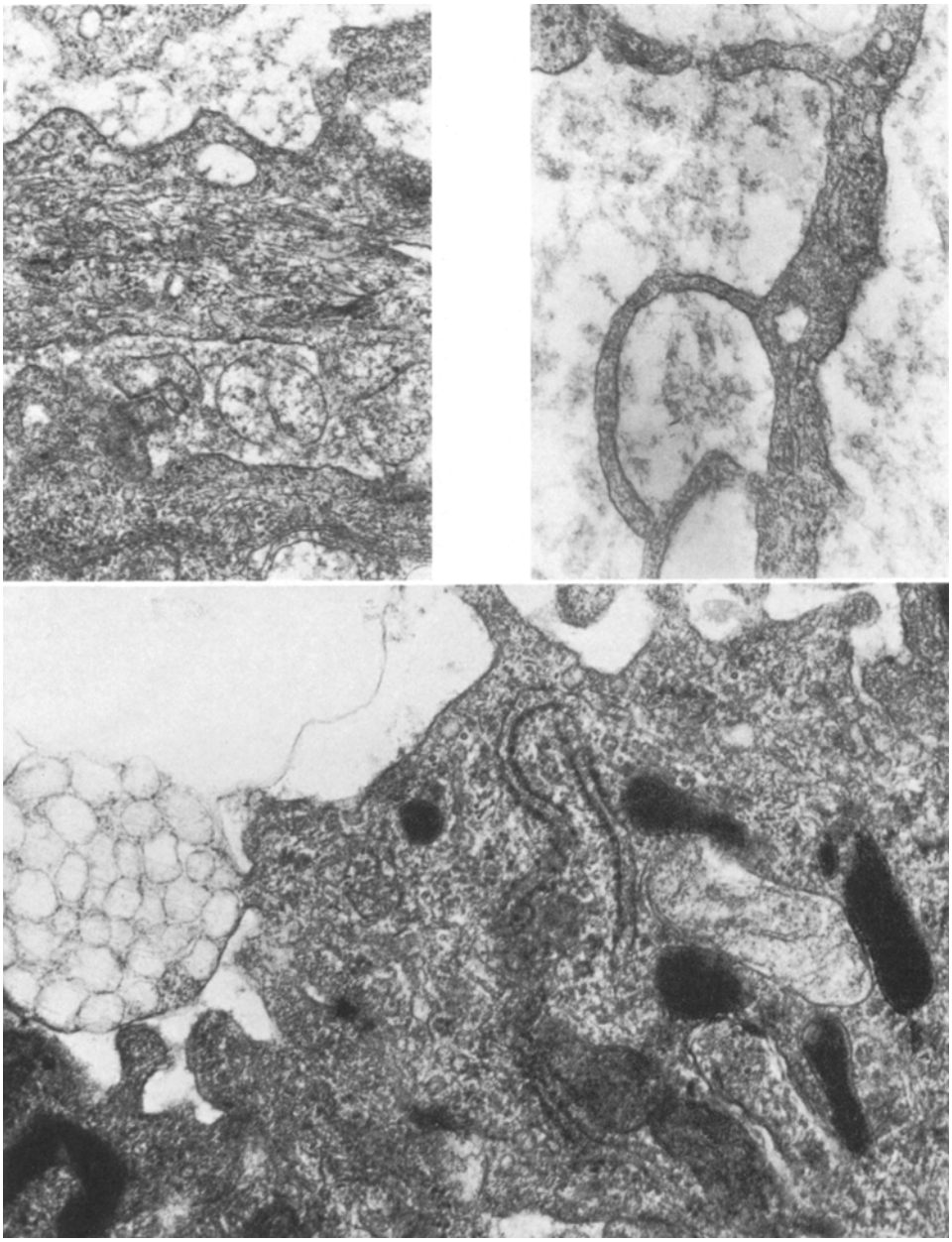

Fig. 5. (*Top left*) Cytoplasm of endothelial cell in well differentiated haemangiosarcoma showing some pinocytotic vesicles and abundant filaments. Double stained. 25,000×. (*Top right*) Well differentiated hemangiosarcoma. Membrane nodulations projecting into the lumen. Double stained. 40,000×. (*Bottom*) Well differentiated haemangiosarcoma. Dense bodies interpreted as Weibel-Palade and an spherical aggregate or vesicles in the free surface of the cell. Double stained. 20,000×

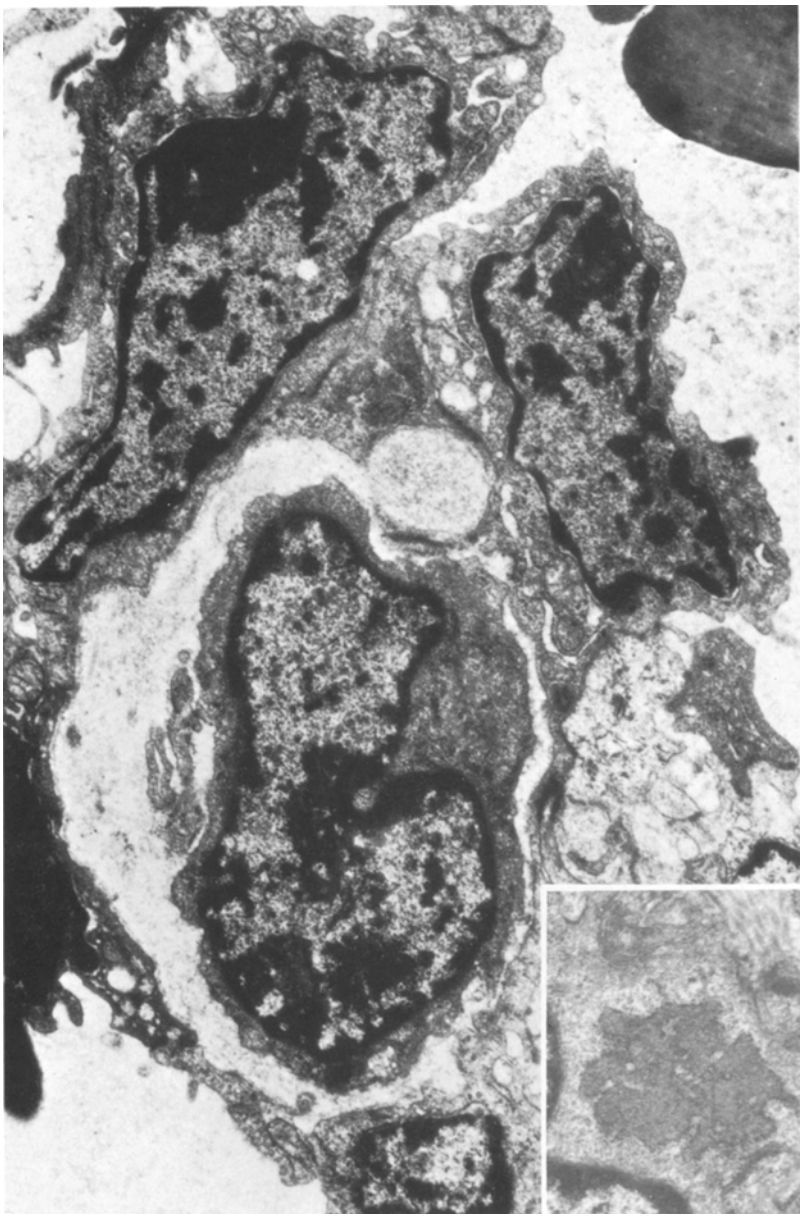

Fig. 6. Low power electron micrograph of a papillae. The axis or the stalk is occupied by undifferentiated cells very similar *in morphology to that bordering the surface of the papillae. Double stained.* 3,000× (*Insert*) *Some cells in the axis of the* papillae show prominent endoplasmic reticulum with deposits of electron dense material. Double stained. 8,000×

of low electron density, with scanty organelles and abundant ribosomes. Sometimes electron-dense material was seen inside the rough endoplasmic reticulum.

Pericytes

Outside the endothelial covering, another type of cell was identified. These showed a strong similarity to the endothelium as far as the nuclear shape

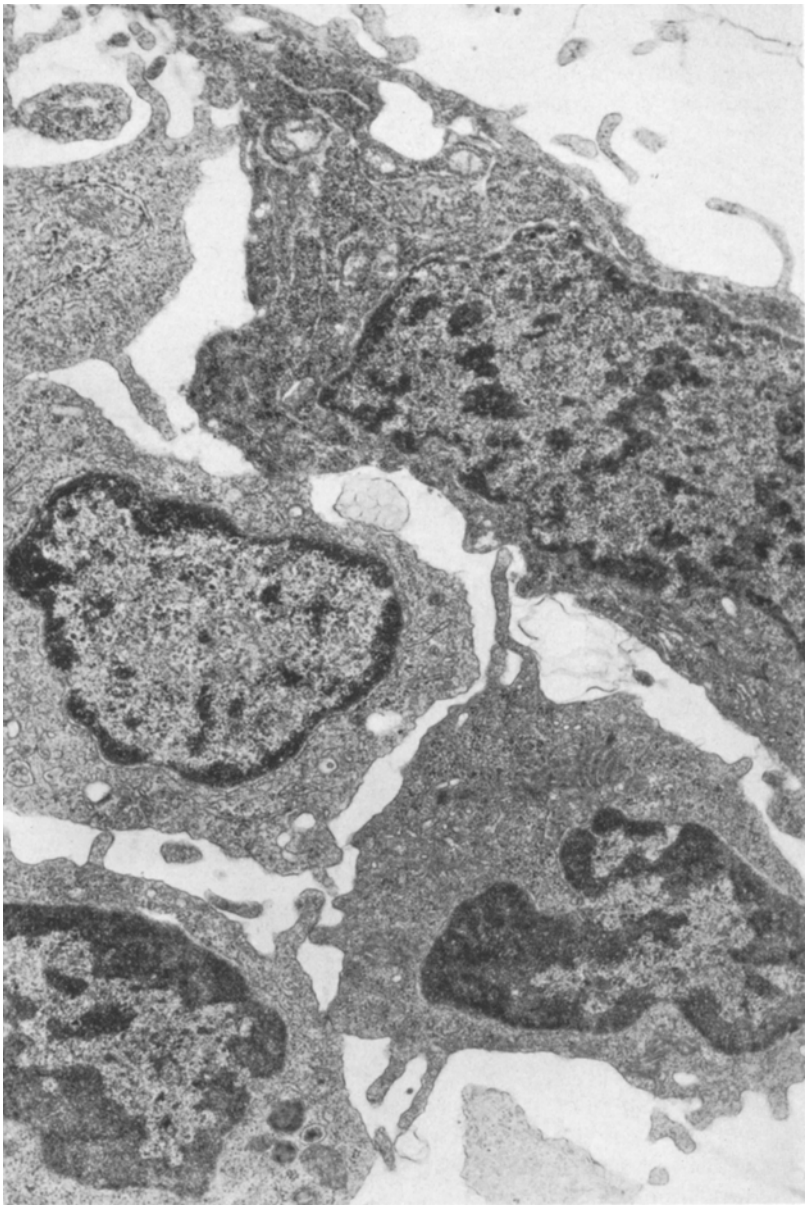

Fig. 7. Undifferentiated area of haemangiosarcoma. The cells are poligonal and retain some microvilli in the surface as well as aggregates of small vesicles. Double stained 5,000×

and cytoplasmic organelles were concerned. They were partially surrounded by basement membrane material and showed short expansions which came into close contact to the basal expansions of endothelium. In these areas no interposition of basement membrane or union complexes were seen. They also showed fibrils, pinocytotic vesicles and abundant RRE profiles a well developed Golgi apparatus and some cilia. The cells showed more numerous and elongated expansions, and formed a discontinuous sheet under the endothelium. In these

areas of the tumors, they lay at a larger distance from the endothelial cells and showed a complete disappearance of the basal membrane covering.

Other extravascular elements include fibroblasts, histiocytes and leucocytes.

The arrangement of the neoplastic vessel in haemangiosarcoma was also different from that of the benign tumors. The endothelial elements showed gaps between adjacent cells which permit free communication between the lumen of the vessel and the interstitium. In other places the endothelium showed focal proliferations budding into the lumen (Fig. 7). In these places the cells maintained most of the characteristics found in the flattened elements which border the vessels. Some intracytoplasmic lumena were also seen as well as collapsed slit-like channels compressed by the tumor.

Discussion

Mammary angiosarcoma is an uncommon breast neoplasm which has been reported in 87 cases until now (Chen et al. 1980). The tumors appear in middle aged females but with a wide range of age and is usually of large size in the moment of diagnosis. The prognosis is very poor and most patients die as result of local recurrences or metastatic disease. The biological behaviour of our cases conforms in general with the pattern outlined above but some points merit special comment. Axillary metastasis in the moment of the mastectomy are reported as a rare event. However in our case 5 an undifferentiated tumor, positive lymph nodes were found in the initial resection, so the necessity of radical mastectomy must be emphasized at least for the most agressive variants. On the other hand it must be pointed out that the histological appearance of the neoplasm could not be a safe guide to anticipate the evolution of the tumor as some undifferentiated neoplasm as our case 5 can follow an accelerated course with early dissemination, and others as our case 7, can persist for larger periods of time without metastasize.

The main contribution of electron microscopy to the knowledge of vasoproliferative lesions and vascular tumors has been the description of the fine structural characteristics of cells which constitute the reactive or neoplastic proliferation, allowing a better understanding of their histogenesis. While in some tumors only one cell type has been identified as in glomangioma (Toker 1969; Vekatachalan 1969; Murad et al. 1968; Kuhn and Rosai 1969; Fabich and Hafez 1980), or in some haemangiopericytomas (Ramsey 1966; Silverberg et al. 1971; Popoff et al. 1974), a combined proliferation of several cell types normally present in the vessel wall has been found in other cases. So cells with transitional features to endothelium (Battifora 1973), and to smooth muscle elements (Hahn et al. 1973; Wilbanks et al. 1975; Eimoto 1977), have been demonstrated in haemangiopericytoma and a double population of endothelium and pericytes in benign haemangioma (Balazs et al. 1978; Taxi and Gray 1979) some reactive proliferations, for example intravascular papillary hyperplasia (Kreutner et al. 1978) or intravenous pyogenic granuloma (Ulbright and Santa-Cruz 1980). In malignant forms while some cases of lymphangiosarcoma (Merrick et al. 1971) and haemangiosarcomas have shown a pure proliferation of endothelium (Williams et al. 1979), others contained both pericytes and smooth muscle (Silverberg

et al. 1971, Friederici and Roberts 1967). Haemangiosarcoma has been found to be composed of neoplastic endothelium and pericytes in the salivary gland (Tomec et al. 1979), brain (Mena and Garcia 1978), and heart (Talens et al. 1977), and by these two cell types with transitional forms to smooth muscle in bone (Steiner and Dorfman 1972) and skin (Rosai et al. 1976). This complex composition of the neoplastic proliferation is also maintained in the most aggressive small cell variants of the soft tissues (Bednar 1980) and in related neoplasms such as Kaposi's sarcoma (Pepler and Theron 1962; Hashimoto and Lever 1964; Mottaz and Zelickson 1966; Gomez-Orbaneja et al. 1971; Harrison and Kahn 1978).

Our results in mammary tumors are in agreement with this. Most of the proliferating elements are found bordering the neoplastic vessels in the most mature tumors, and show cytoplasmic characteristcs and a histochemical reactivity consistent with those found in non-tumor endothelium and in the neoplastic endothelium of experimental angiosarcomas (Warner et al. 1971; Toth and Wilson 1971; Toth 1973; Toth and Malick 1976). These features suggest a high functional activity. No previous reference has been found to the presence of cytoplasmic blebs in the endothelium of haemangiosarcoma. Similar structures filled with small spherical vesicles have been described in arterial endothelium in experimental ischaemia and in rabbits, treated with adrenaline and cholesterol (Shimamoto and Sunaga 1973; Nelson et al. 1976). They have been interpreted as a consequence of an exaggerated permeability, and their morphogenesis attributed either to the progressive dilatation of the Golgi cysternae or to a focal accumulation of pinocytotic vesicles. They have been a constant finding in our angiosarcomas, so it seems unlikely that they represent an artifact. Taking into account the experimental data it can be hypothesized that the blebs represent the expression of an alteration of fluid transport across the cell, due to ischaemic phenomena inside the tumor. Pericytes, which also proliferate in experimental angiogenesis (Cavallo et al. 1973) are another component of mammary angiosarcoma and have been seen only in the better structured vessels. In the undifferentiated areas more primitive cells appear, which may predominate in the final picture of the tumor. These cells, either located in the axis of the papillae or forming part of the spindle cell masses, show a lower number of organelles, abundant ribosomes and a lack of ultrastructural markers of endothelium, mainly Weibel-Palade bodies. They do not show histochemical reactivity to alkaline phosphatase and ATP-ase. The possible role of these cells as a source of new endothelial or extravascular cells remains to be solved. Finally, we have not been able to demonstrate smooth muscle fibers, their absence being attributed to sampling error, or to the fact that they might not be a constant component of the tumor.

The ultrastructural composition and the histochemical reactivity of the neoplastic vessel are a relevant point, as some authors have suggested a lymph vessel origin for angiosarcomas of other territories such as the skin (Rosai et al. 1976; Reed et al. 1966). Rosai et al. in an analysis of five cases, admitted a blood vessel origin for only one of his cases which showed cytoplasmic fenestration, leaving the other four open to reclassification because of the absence of ultrastructural markers of endothelium and negativity to alkaline phosphatase.

In our series the three differentiated tumors have shown Weibel Palade bodies in the cytoplasm of the endothelial cells, coinciding with abundant filaments, pinocytotic vesicles, discontinuous basal lamina and intercellular unions. All these cases also showed a positive reaction to alkaline phosphatase and adenosine triphosphatase and a lack of the anchoring filaments, characteristic of lymph vessels (Fine and Horn 1969; Rojo-Ortega et al. 1973). In the most undifferentiated tumors with a predominance of the spindle cell component, these cells show nearly a complete lack of ultrastructural markers and histochemical reactivity for both enzymes. However the elements which border a few mature differentiated vessels also showed fibrils, pinocytotic activity and Weibel Palade bodies as well as a positive reaction to alkaline phosphatase and adenosine triphosphatase. These features and the presence of pericytes allow us to advocate a blood vessel origin confidently for all our cases.

The general structure of the vessels in mammary angiosarcoma seems to be that of "continuous" vessels without fenestrations, like the vessels of the normal mammary gland (Ozello 1971). However, discontinuities of the wall can be seen, mainly at the growing edge. These can be explained as a consequence of the rapid growth of the channels (Schoefl 1964; Andersen et al. 1975). The intracellular lumena found in cutaneous angiosarcomas (Rosai et al. 1976) have been related to the mechanism of angiogenesis inside the tumor, which may progress by the development of intracellular lumena in a different way from that which usually occurs in embryogenesis and in granulation tissue. In our cases some intracellular lumina have been found but it seems unlikely that the bulk of the proliferating vessels vould be permeabilized by this mechanism and probably most lumena appear by the development of extracellular spaces between adjacent endothelial cells.

Except for the so-called "perilobular haemangioma" (Rosen and Ridolfi 1977), benign vascular tumors are rarely recorded in the breast (Hamperl 1973; Lapertosa et al. 1980; McDivitt et al. 1967). On the other hand there are also very few reports concerning the ultrastructural characteristics of this variety of tumors (Balazs et al. 1978; Taxi and Gray 1979). While in the cellular angiomas of infancy (Taxi and Gray 1979) the endothelial cells showed a morphology very similar to that of normal adult endothelium, with abundant surface modulations, Weibel-Palade bodies and micropinocytotic vesicles, in the benign hepatic haemangioblastoma (Balazs et al. 1978), the cells showed a different morphology with scanty membrane projections, pinocytotic vesicles and abundant cytoplasmic organelles. Our case 2 shows a morphology consistent with this. The cells were plump with predominance of the cytoplasmic filaments and rough endoplasmic reticulum over the luminal projections, rod-like tubular bodies and pinocytotic activity. These appearances are in contrast to those of normal fetal vessels (Roy et al. 1974), and their significance must remain as a subject for debate. Ryan et al. (1971) have suggested that surface modulations have a functional significance, producing an increase of the surface of the cell and a modification of the blood flow along it. Fujimoto et al. (1975) and Burri and Weibel (1968), have hypothesized that the rod-like tubular bodies could have a relationship with the thrombegenic capacity of the endothelium. Both facts, plus the well known role of pinocytosis in the transport of substances across the endothelium, suggest a low functional activity of the endothelium in juvenile haemangioma, possibly coincidental with an increased protein synthesis, as shown by the presence of dilated cisternae of rough endoplasmic reticulum.

It can therefore be concluded that mammary haemangiosarcoma is a neoplasm mainly composed of neoplastic endothelial cells which show transitional forms to pericytes and undifferentiated mesenchymal cells. Their ultrastructural characteristics are very similar to those of similar neoplasms in other locations. The histochemical reactivity and electron microscopical features of the neoplastic endothelial cells suggest a high functional activity and a high rate of transport of substances across the cell cytoplasm. In contrast, the undifferentiated cells present a lack of histochemical and ultrastructural features of endothelium. The general structure of the neoplastic vessel is imperfect with deficient differentiation of the constituents of the wall and the presence of gaps.

Juvenile haemangioma and cavernous haemangioma show a more complex structure in their walls with stratification of the different types of cells and a continuous wall. The features of endothelium in juvenile haemangioma suggest a low functional activity rather than morphological de-differentiation.

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