Virchows Arch [Pathol Anat] (1981) 391:107–115

Virchows Archiv A

Case Reports

Fine Structure of a Malignant Hemangioendothelioma of the Esophagus

A. Llombart-Bosch[1], A. Peydro-Olaya[2], and F. Paris-Romeu[3]

[1] Head Department of Pathology, Hospital Clinico Universitario. Medical School of Valencia, Spain
[2] Professor of Histology, Department of Pathology, Hospital Clinico Universitario, Medical School of Valencia, Spain
[3] Head Department of Torathic Surgery, Ciudad Sanitaria de la Seguridad Social "Le Fe", Valencia, Spain

Summary. The histology and electron-microscopy of a malignant hemangioendothelioma of the esophagus wall appearing in a 42 year old male is presented.

By light microscopy the tumor is composed of vessels and capillary-like structures of an anastomosing nature covered by atypical endothelial cells. These cells infiltrate the intersticial spaces growing into the posterior mediastinal area.

Electron microscopy confirms the endothelial nature of the neoplastic cells, showing characteristics of the cell type, as is the presence of Weibel-Palade bodies, filaments and active pinocytosis.

Hemangioendothelioma should be differentiated from other vascular tumors (angiosarcoma) as are hemangiopericytoma or hemangioblastoma, being composed exclusively of malignantly transformed endothelial cells.

Key words: Hemangioendothelioma – Esophagus – Electron microscopy

Introduction

Malignant vascular tumors of internal organs are not common, even though they occur in many locations (Stout 1943; Lattes and Stout 1967; Ludwig and Hoffmann 1977) of the body. Vascular tumors in the esophagus wall are very rare, and are usually of a benign nature (hemangioma, lymphangioma, glomus tumors). Only exceptionally might they be part of a sistemic involvement, as in the case of Kaposi sarcoma (Si-Chun 1971). As far as we have reviewed the literature, no malignant mesenchymal sarcoma of a vascular character has been described when occurring within esophagus wall.

This paper demonstrates by electron microscopical means the endothelial nature of an angiosarcoma which developed in a 42 year old male, infiltrating the parietal wall of the esophagus.

Offprint requests to: Prof. A. Llombart-Bosch. Department of Pathology, Hospital Clinico Universitario, Av. Blasco Ibañez, 17, Valencia-10, Spain

0340-1227/81/0391/0107/$01.80

Case Report

J.M., a 42 year old male, was admitted to hospital on 22 June 1977 complaining of progressive dysphagia for the previous 6 months, with a dull ache referred to the upper sternal area. He began by swallowing solids with difficulty, and later liquids were passed more slowly. In the week prior to admittance to hospital he could hardly drink. He referred also to coughing and anorexia. The patient had a severe weight loss of 15kg, was a heavy smoker (more than 40 cigarettes a day) and had started smoking at 10. Chest X-rays showed a shadow in the posterior supraortic mediastinum. Barium swallowing suggested a tumor of the esophagus of extramural origin (Fig. 1 a).

On 23 June 1977 a right transthoracic total esophagectomy was performed. The tumor had its origin in the esophagus wall, but extension into the posterior mediastinum was shown, and mediastinal lymph nodes were involved. The resection was considered non-curative because part of the tumor could not be removed. In the same stage, left colon interposition was performed using the anterior mediastinal route, through a combined cervico-abdominal approach. The patient died on the 40th post-operative day, having suffered a cervical anastomotic leak.

Gross Pathology

The exscinded esophagus was 10 cm in length containing a tumor 5 to 7 cm, located in the middle portion of the resected esophagus. The lumina was markedly stenotic and the neoplastic growth formed multiple discrete confluent nodules on a soft hemorrhagic cut surface. No fibrous encapsulation existed and the tumor had rather infiltrated the muscular wall, extending into the mucosa and towards the serosa.

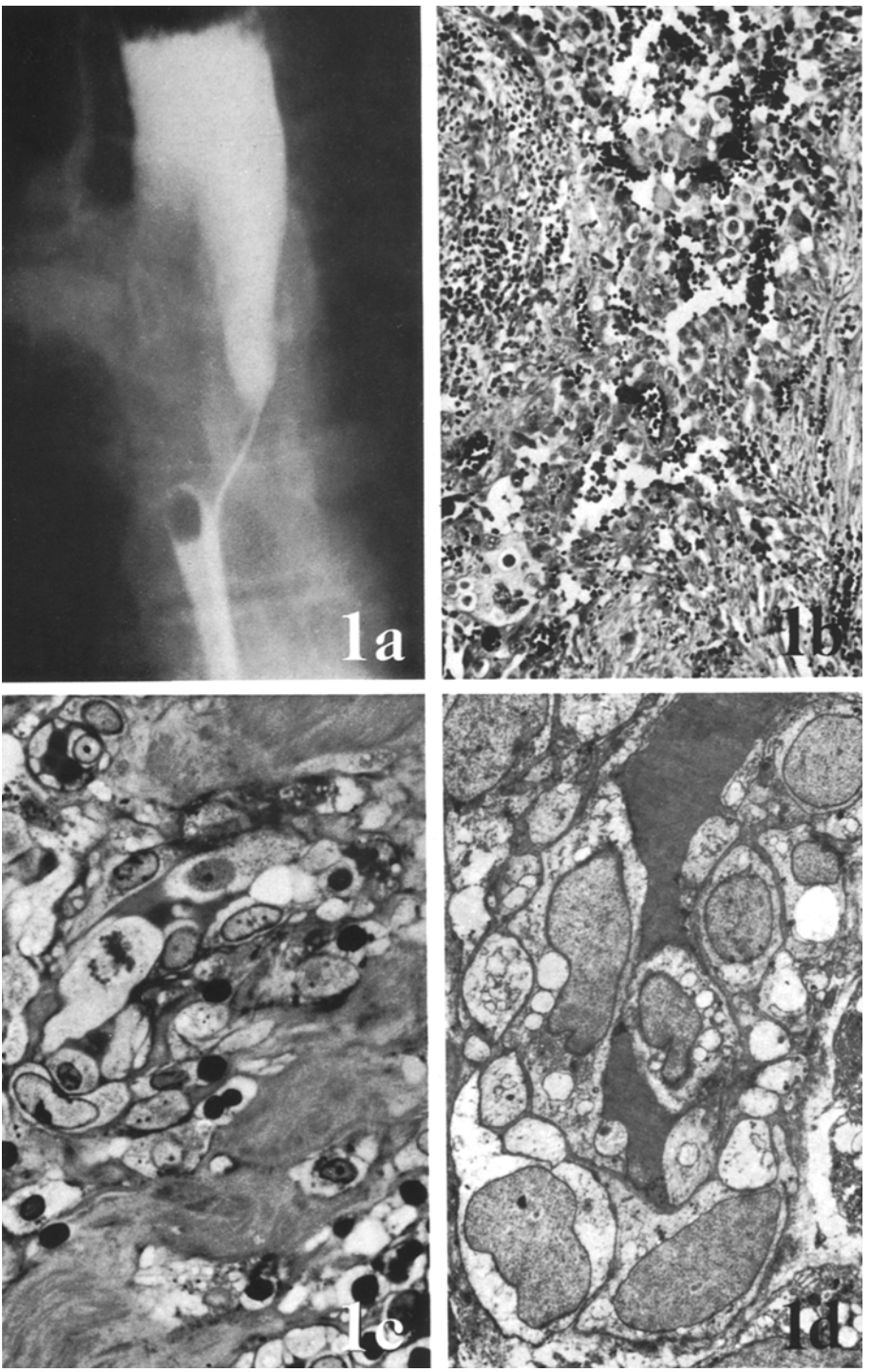
Light Microscopy

Sections from numerous paraffin-embedded blocks were stained with Hematoxilin and Eosin, Gomori reticulin, Masson's trichrome method, PAS and PTAH. The tumor revealed a massive and diffuse cellular infiltration of atypical proliferating cells, organised in solid nests, sheets, or vascular spaces, which were partially occupied by erythrocytes. There were numerous intercommunicating neoformed vasular channels, filled with swollen, clear lucent anaplastic cells, one to several layers thick. Within the vascular spaces, which were of a very irregular contour, numerous endothelial cells proliferated, adopting a lobular or papillary pattern (Fig. 1 b).

An abundant network of neoformed buds or capillary-like structures proliferated, anastomosing each other and being included within a dense interstitial matrix. Fibroblasts, isolated macrophages and blood cells participated in the stroma among the tumoral cells, all being inside a dense fibrilar and hyaline, PTAH positive material.

The degree of cell atypism varied. Some endothelial cells showed clear lucent cytoplasm and a bright round or oval nucleus with a prominent nucleolus.

Fig. 1. a The barium swallowing Roentgenogram showing a mass in the mediastinum which encircles the entire circumference of the esophagus and produces a circular narrowing, suggesting a tumor of extramucosal origin. **b** Overall picture of the neoplasm showing neoformed vascular channels with endothelial cells adopting a papillary pattern. (H.E.) ×25. **c** Semi-thin section of a vascular field with prominent endothelial cells and mitotic figures. Durcupan embedding, toluidin blue ×60. **d** Ultrastructural appearance of several endothelial cells lining vascular spaces and isolated by basal lamina. ×1,600


1a
1b
1c
1d

Giant anaplastic cells were also observed. Occasionally mitotic figures were seen (Fig. 1c).

Silver reticulin stain demonstrated how the endothelial cells were located inside a dense reticular network which connected vascular spaces with the neoformed capillary-like structures. Several fields showed extensive hemorrhagic necrosis.

Tumoral cells extended toward the muscular wall of the esophagus, infiltrating and ulcerating the epithelium. Extension of the tumor was also found in the peripheral connective tissue, proliferating into the posterior mediastinum, which was secondarily invaded.

Electron Microscopy

Several 1 mm blocks selected from different fields of the neoplasm were washed in Milloning solution after being fixed in a phosphate-buffered solution of 2% glutaraldehyde at 0–4° C for 3 min, and postfixed for 2 h in a 1% osmium tetroxide solution. They were dehydrated in a graded solution of ethanol acetone and immersed in propylene-oxide. Durcupan (Fluka AG) was used for embedding, and the sections were prepared on an LKB ultramicrotome. A double-stain was performed with uranyl acetate and lead citrate. Examinations were performed on a JEOL JEM 100 B electron microscope with an acceleration voltage of 80 and 100 KV.

The overall ultrastructural picture of the neoplasm was marked by a system of cells with round or oval homogeneous nuclei and a bright lucent cytoplasm, distributed in solid sheets or capillary profiles, and occasionally isolated by a basal lamina-like material (Fig. 1d).

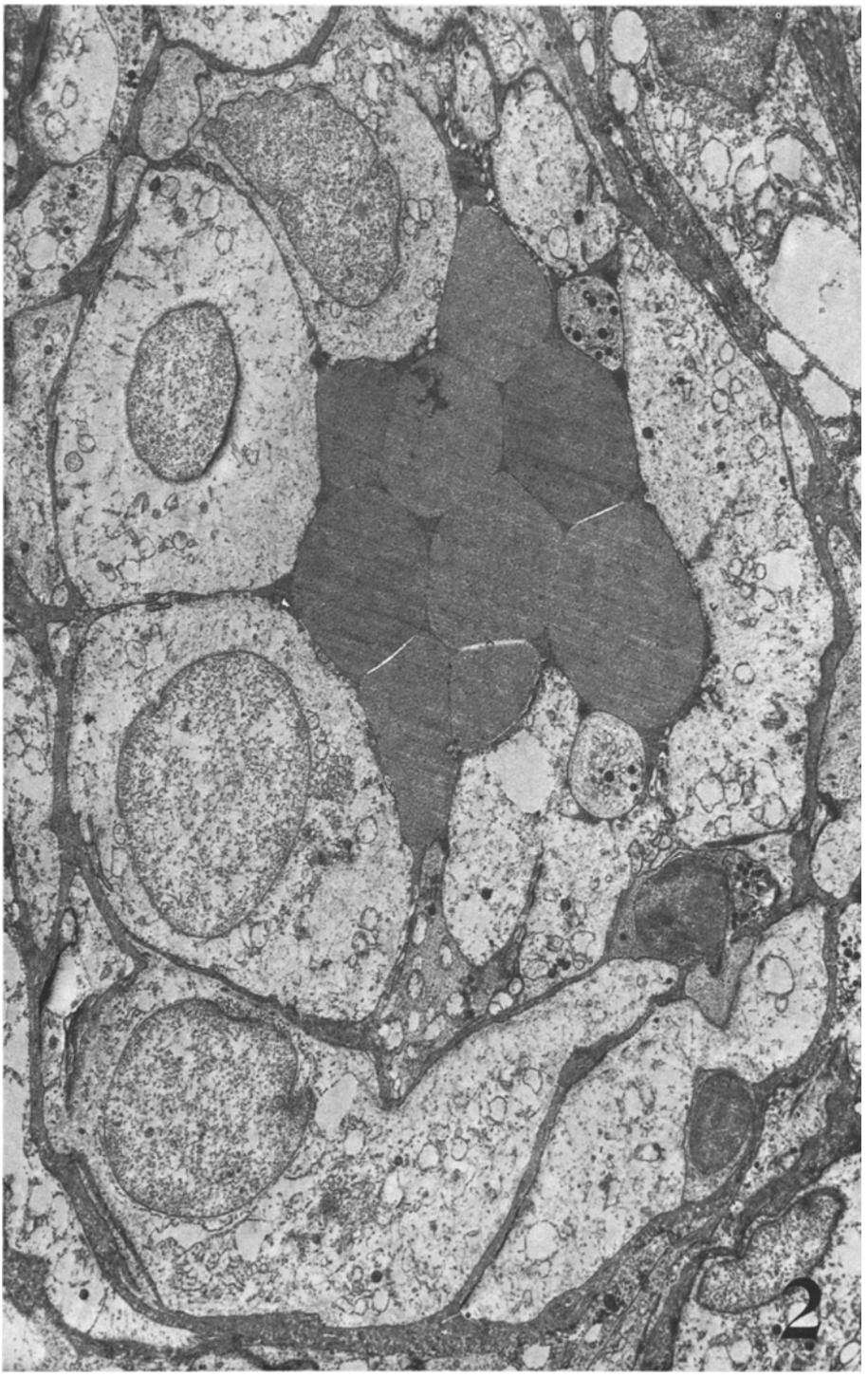
Vessels showed strikingly important variations in size and shape, and were closely related to irregularly configurated vascular channels, filled with red blood cells, neutrophyles and plasmatic cells (Fig. 2).

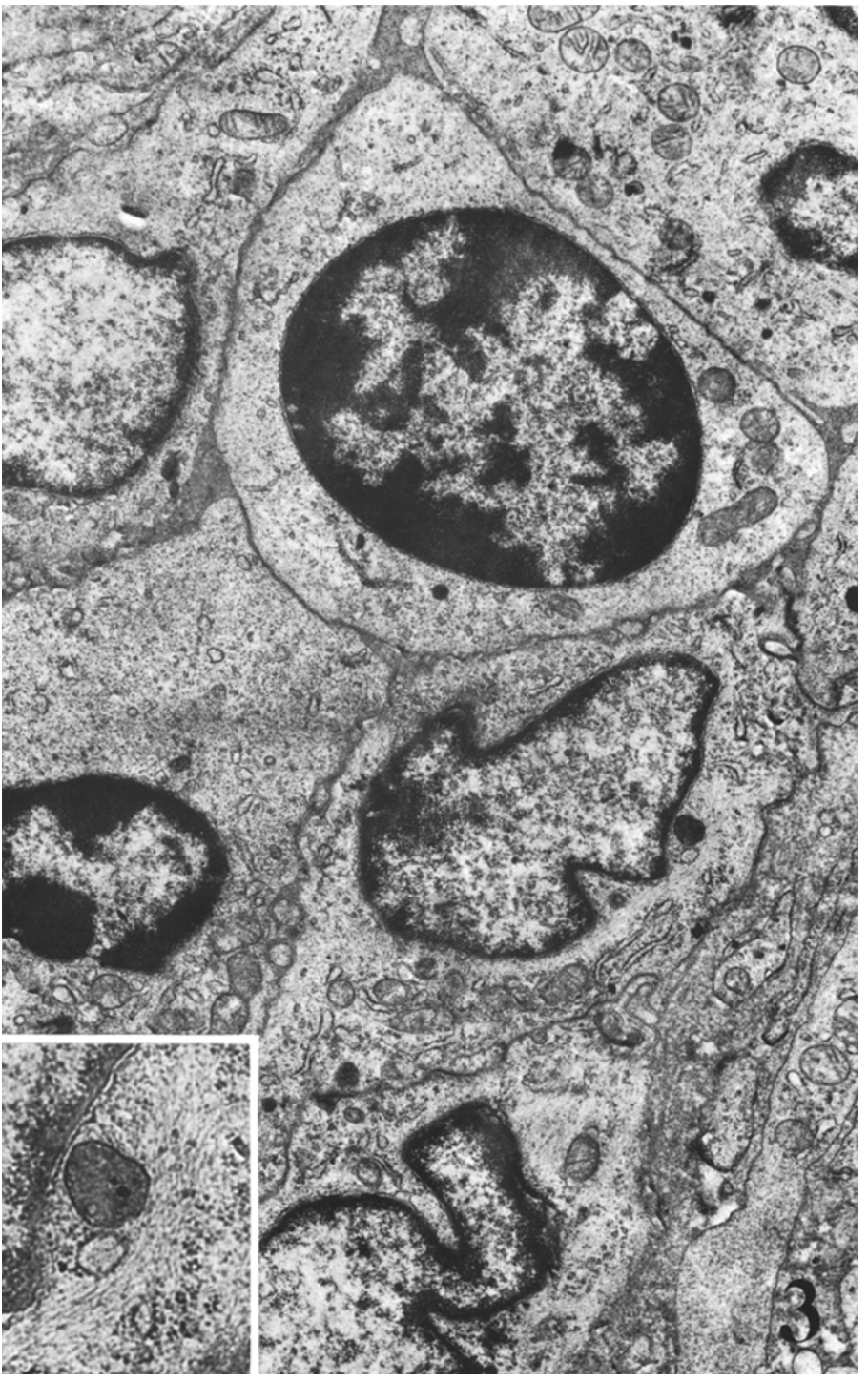
The endothelial cells were lining the vascular spaces and the small capillaries occasionally piled up several layers thick into the lumina, reducing it to a tortuous slit-like cavity filled with one or two erythrocytes. There was no evidence of those vessels differentiating into arterial or venous structures, but continuity between proliferative endothelial cells of the neoplastic tissue and the more solid fields could frequently be established. Necrosis was abundant.

In some fields there was evidence of a stromatic reactive proliferation with fibroblasts, round cells and reticular fibres or collagen bundles. Some isolated tumoral cells were distributed in sheets or capillary-like profiles. Endothelial cells were provided with an electron-lucent, vacuolated and poorly-developed cytoplasm, in which a few organelles were distributed at random.

No ultrastructural differences in morphology could be demonstrated when the proliferating endothelial cells appeared in vascular channels, nests, or dispersed in sheets infiltrating the stroma. All these cells showed a pale, watery-

Fig. 2. Neoformed capillary channels filled with red blood cells and covered by endothelial cells of the tumor. These cells are provided with large, watery-looking cytoplasm and round-oval nuclei. ×4,500


2


3

looking cytoplasm, and their most outstanding structures were as follows (Fig. 3).

- Isolated mitochondria of round or ovoid contour, poorly developed cristae, and vacuolated matrix, accumulating in groups of 4 to 5 in perinuclear areas.
- Very isolated profiles of smooth endoplasmic reticulum with dilated cysternae and electron lucent content were detected.
- Some membrane-associated vesicles and multivesicular bodies appeared near the Golgi fields. Rod-shaped structures of diverse shape and varying density content, strongly characteristic of Weibel-Palade bodies, were also observed.
- No phagocytic activity in the cytoplasm was seen.
- Cell membranes were smooth looking in projections and possessed isolated finger-like cytoplasmic invaginations. Even in the vascular surfaces the cells showed no digitation or bubbling of the membrane.
- The nucleus was round or ovoid with some occasional indentation, possessing a very finely-dispersed chromatine and a unique, prominent nucleolus, excentrically located.
- An active pinocytosis was detected in almost all tumoral cells, not only in those configurating vascular fields, but also, to a lesser extent, in those cells located in the solid areas of the neoplasm. Some cytoplasmic diluted channels were in continuity to the pinocytic vesicular system.

Endothelial cells were joined by irregular junctions of either a zonula occludens-type with large surface, or by isolated points of tight contacts. Basement membrane-like material almost regularly enveloped and surrounded the vessels. Several duplications of these basement membranes could be established.

Discussion

Diagnosis of hemangioendothelioma (HE) must be based upon optical and electron microscopical facts, demonstrating that the neoformed endothelium plays an important role in the tumoral histogenesis. Mallory (1908) and Stout (1943) confirmed that the existence of a reticular network encircling the neoformed endothelial cells is of great importance for its diagnosis at optical level. Other characteristics of these neoformed cells are the existence of a clear, watery translucent cytoplasm and a large round nucleus, which has a finely-dispersed chromatine and a bright nucleolus.

The histochemistry of HE, as has been demonstrated by several authors (Girard et al. 1970; Braun-Falco et al. 1976) shows a high enzymatic content for alkaline phosphatase, and a PAS positive material has been described in a few cases (Ramsey 1966).

Despite all these well-known data, the diagnosis of HE, when compared to other angiosarcomas, may prove laborious, owing to its very pleomorphic pattern insofar as its structures dilate from very poorly differentiated forms

Fig. 3. Tumoral cells closely packed with tight junctions, configurating a solid field of the neoplasm. Note within the cytoplasm the presence of isolated REG profiles, bundles of filaments and Weibel-Palade bodies. ×12,000. In the inset an enlargement of a vesicular-body complex (Weibel-Palade body) ×60,000

to other, better organised ones, provided with prominent neoformed vessels (Girard et al. 1970; Dorfman et al. 1971; Rosai et al. 1976).

One clue to identifying this tumor may lie in the detection of blastemic immature cells of undifferentiated mesenchymal type, but which are similar to those observed in the embryonic vascular neogenesis (Gonzalez Crussi 1970; Haar and Ackerman 1971). Also, in some tumors a relationship to blood-forming cells has been demonstrated, but this has not been the case here.

The presence of endothelial cells with a vasoformative property is the most peculiar structure in this tumor. These cells maintain a constant texture, being located within the vessels in the vascular neoformed fields, as well as in the more solid immature areas, or even when included within a dense fibrilar stroma.

At electron microscopical level, appropriate organelles endow these cells with a specific personality. The Weibel-Palade bodies and the bundles of filaments, irregularly located within the cytoplasm, are of great specificity for them (Weibel and Palade 1964; Carstens and Schrodt 1974; Rosai et al. 1976). This pinocytic activity has also been described as one of the most striking characteristics of endothelial cells (Movat and Fernando 1964; Heinrich and Metz 1976). Also specific to this cell type is the abundant electron-lucent, watery cytoplasm. However, one activity in which it may differ is its phagocytic capacity, which is remarkable in some vascular tumors, as in the case of Kaposi sarcoma (Braun-Falco et al. 1976; Heine et al. 1977; Vicente-Ortega and Llombart-Bosch 1976), but lacking in other angiosarcomas (Steiner and Dorfman 1972). In this present case no phagocytic activity was seen inside the tumor cells.

Lumen formation through the slitting off of solid buds of tumor cells is, from the architectonic point of view, a sure way to typify HE. These primitive differentiated vessels may show the presence of incomplete basals. Initiation of vascular lumen occurs within the cytoplasm of one cell through a progressive confluence of dilated vacuoles which finally extend throughout the cytoplasm. Loosening and superficial dehiscence of the membrane boundaries are also related to these lumen formations (Rosai et al. 1976; Steiner and Dorfman 1972). Primitiva lumina may be filled with erythrocytes or plasma material. A neobasal system is elaborated by these cells, each of which progressively loosens contact with its neighbor, being involved within an amorphous, laminar system of membranes.

Participation of pericytes has often been described in hemangiopericytoma (Ramsey 1966; Hahn et al. 1972; Battifora 1973) and hemangioblastoma (Cervos-Navarro 1971; Spence and Rubinstein 1975) of the Central Nervous System. No pericytes were seen in this case. Yet, it must be admitted that atypical pericytes share very close structural features, as herein described, with the endothelial cells when they have been malignantly transformed (Ramsey 1966; Mandard et al. 1978). A differentiation may be difficult between both these kinds of cells, as both share a common origin (Movat and Fernando 1964; Friederici and Roberts 1967; Murad and von Haam 1968).

The aforementioned facts lend further support to defending the individuality of HE, keeping its morphological personality within the generic group of angiosarcoma, but being distinguishable from other vasoformative tumors in which the endothelial cell is not the only one which is malignantly transformed.

References

Battifora H (1973) Hemangiopericytoma. Ultrastructural study of five cases. Cancer 31:1418–1432
Braun-Falco O, Schmoeckel C, Hübner G (1976) Zur Histogenese des Sarcoma idiopathicum multiplex haemorrhagicum (Morbus Kaposi). Virchows Arch A Path Ant Histol 396:215–227
Carstens HB, Schrodt GR (1974) Ultrastructure of sclerosing hemangioma. Am J Pathology 77:377–382
Cervos-Navarro J (1971) Elektronenmikroskopie der Hämangioblastome des ZNS und der angioblastischen Meningiomen. Acta Neuropathol (Berl) 19:184–207
Dorfman HD, Steiner GC, Jaffe HL (1971) Vascular tumors of bone. Hum Pathol 3:349–376
Friederici HHR, Roberts SS (1967) The fine structure of two postmastectomy angiosarcomas. Lab Invest 16:644–652
Girard C, Johson WC, Graham JH (1970) Cutaneous angiosarcoma. Cancer 26:868–883
Gonzalez Crussi F (1970) Vasculogenesis in the chick embryo. An ultrastructural study. Am J Anat 130:441–460
Haar JL, Ackerman A (1971) A phase and electron microscopic study of vasculogenesis and erythropoiesis in the yolk sac of the mouse. Anat Rec 170:199–224
Hahn MJ, Dawson R, Esterly JA, Joseph DJ (1972) Hemangiopericytoma. An ultrastructural study. Cancer 31:255–261
Heine H, Schaeg G, Nasemann T (1977) Licht und elektronenoptische Untersuchungen zur pathogenese des Kaposi-Sarkoms. Arch Dermatol Res 258:175–184
Heinrich D, Metz J (1976) Ultrastructure of perfusion fixed fetal capillaries in the human placenta. Cell Tissue Res 172:157–169
Lattes R, Stout AP (1967) Tumors of the soft tissues. In: Atlas of tumors pathology, second series, Fasc. 1. Armed Forces Institute of Pathology, Washington, p 145–149
Ludwig J, Hoffmann HN (1977) Hemangiosarcoma of the liver. Spectrum of morphologic changes and clinical findings. Mayo Clinic Proc 50:255–263
Mallory FB (1908) The results of application of special histological methods to the study of tumors. J Exp Med 10:575–593
Mandard AM, Herlin P, Elie H, Juret P (1978) Syndrome de Stewart-Treves. A propos d'un cas avec étude ultrastructurale. Ann Anat Path 1:63–80
Movat HZ, Fernando NVP (1964) The fine structure of the terminal vascular bed. IV. – The venules and their perivascular cells (pericytes, adventicial cells). Exp Mol Pathol 3:98–114
Murad TM, von Haam E (1968) An ultrastructural study of pericytes. Proc Elec Soc Am 26th Annual Meeting, p 66–67
Ramsey HJ (1966) Fine structure of hemangiopericytoma and hemangioendothelioma. Cancer 19:2005–2018
Rosai J, Summer HW, Kostianovsky M, Perez-Mesa C (1976) Angiosarcoma of the skin. A clinicopathologic and fine structural study. Hum Pathol 1:83–109
Si-Chun Ming (1971) Tumors of the esophagus and stomach. In: Atlas of tumor pathology, second series, Fasc.7. Armed Forces Institute of Pathology, Washington, p 65–73
Spence AM, Rubinstein LJ (1975) Cerebellar capillary hemangioblastoma: its histogenesis studied by organ culture and electron microscopy. Cancer 35:326–341
Steiner GC, Dorfman HD (1972) Ultrastructure of hemangioendothelial sarcoma of bone. Cander 29:122–135
Stout AP (1943) Hemangio-endothelioma. A tumor of biood vessels featuring vascular endothelial cells. Ann Surg 118:445–464
Vicente-Ortega V, Llombart-Bosch A (1976) Ultraestructura de la enfermedad de Kaposi. Estudio de tres casos. Oncologia 80 4:174–184
Weibel ER, Palade GE (1964) New cytoplasmic components in artherial endothelia. J Cell Biol 23:101–112

Accepted October 28, 1980