Cellular Haemangioma

Light and Electron Microscopic Studies of two Cases * **

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Summary. Light and electron microscopic studies were conducted on the immature vascular tumors of two infants, containing various stages of differentiation of the blood vessels and both benign haemangioendotheliomas and haemangiopericytomas. We were able to confirm the existance of two kinds of hyperplastic, immature cells i.e. endothelial cells and pericytes in the same tumor. Presence of crystalloid inclusions in the endothelial cells and absence of the Weibel-Palade bodies, as well as a deficiency in factor VIII-related antigen and no tissue fibrinolytic activity, suggested that the endothelial cells in these lesions were immature. Electron microscopic studies appear more decisive in the diagnosis of heterogenous cellular vascular tumors than light microscopy and if available should be used to aid in the final diagnosis. The authors propose that the term cellular haemangioma would be more appropriate in describing this vascular entity.

Key words: Electron microscopy of cellular haemangioma – Haemangioendothelioma – Haemangiopericytoma – Intracytoplasmic crystalloid inclusions – Glycogen particles – Mast cells – Factor VIII – Fibrinolytic activity

The most common vascular tumors in infants and children are capillary haemangioma and cavernous haemangioma (Iliff et al. 1962; Stark and Roth 1973). Occuring less frequently is the most immature and primitive haemangioma which has been termed hypertrophic haemangioma, hyperplastic haemangioma,

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angioblastic haemangioma, juvenile haemangioma, simple haemangioma, cellular haemangioma, agressive haemangioma, benign juvenile endothelioma and benign (infantile) haemangioendothelioma. The latter term was proposed by Stout (1943). This type of tumor is composed of primitive anaplastic endothelial cells similar to those found embryonically before the development of true vascular channels. Because of the predominance and distribution of pericytes in some of these vascular tumors, Stout and Murray (1942) suggested that the tumors be called haemangiopericytoma, and they have since been accepted as a separate entity.

However, a number of authors have reported on vascular tumors in which histological and ultrastructural features showed variable characteristics in different areas in the same tumor, such as haemangioendotheliomas and haemangiopericytomas (Brihaye et al. 1957; Eimoto 1977; Balazs et al. 1978; Gonzales-Crussi et al. 1978; Taxy and Gray 1979). There is no uniformity about the definition of this entity in the literature. Vascular tumors showing the same histological structure – excessive cellularity – have been termed both neonatal haemangioendothelioma and infantile haemangiopericytoma. Taxy and Gray (1979) thought that the heterogenous, cellular composition of these tumors suggests that separate histologic categories are unnecessary, and they proposed a new term "cellular angioma of infancy".

This paper reports on two infants with similar vascular tumors composed of both haemangioendotheliomatous and haemangiopericytomatous areas. The present study was undertaken for the following reasons:

1. To compare histopathological features obtained with light and electron microscopy with regard to their value in aiding in the diagnosis of these heterogenous cellular tumors.

2. To classify or define these tumors based on careful analysis of their histological and fine structures.

3. To clarify the confusion in the literature concerning the diagnosis of these tumors.

Materials and Methods

Clinical Data

Case 1. A two-month-old caucasian female infant had a clinically diagnosed cavernous haemangioma-like tumor involving her left upper eyelid, eyebrow and forehead. It appeared at about 3–4 days post delivery as a bluish dot on her upper lid and gradually increased until it was difficult for her to open her eye. At birth she was 5 weeks premature, a non-identical twin, and weighed 5 lbs 1 oz. The mother used Azulfidine and Bendectin during her first 3 months of pregnancy and Prednisone (60 mg, later 40 mg daily) during her last 3 months because of ulcerative colitis.

The tumor measured $3.5 \times 2.5 \times 2$ cm. The surface of the lesion was smooth and reddish with a few enlarged skin blood vessels (Fig. 1). By palpation the tumor was soft and there was no bruit or discernable pulsation of the left upper lid. The child was otherwise normal and healthy. A subtotal excision of the tumor was carried out at the age of 2 months. Physical examination at 11 months after surgery showed complete involution of the residual tumor of the upper eyelid. Movement of the eyeballs and lids was normal and symmetrical.

Fig. 1. Case 1. Two-month-old infant with soft, reddish tumor on the upper eyelid, eyebrow and forehead

Preliminary ultrastructure studies of the vascular tumor suggested that infant might have Fabry's disease. Because of this, blood samples were taken from the patient, her parents and twin to measure alfa-galactosidase activity. The results of these tests were all within normal limits.

Case 2. A seven-month-old male, product of a normal pregnancy, was noted at 3 months of age to have a subcutaneous pea-sized mass on the neck. This tumor continued to grow reaching 2 cm in diameter. It was soft and did not appear to be fixed. Skin above the tumor had a bluish cast. No other lymph nodes were palpable. Clinical diagnosis was lymphangioma. The tumor was surgically excised at 7 months of age. One year after surgery no recurrence was observed.

Morphological Techniques

For light microscopy one part of each specimen was fixed in buffered 10% formaldehyde solution. Sections were embedded in paraffin and stained with haematoxylin and eosin. Movat's pentachrome method was used for collagen fibers, Verhoeff's method for elastic fibers, Wilder's silver stain for reticulum, and periodic acid Schiff (PAS) with and without prior saliva (diastase) digestion for identification of glycogen. The Giemsa method was used for mast cells stain. They were counted in 50 10 mm² fields and averaged. Factor VIII-related antigen was measured using the immunoperoxidase technique described by Mukai et al. (1980). The second part of the specimen was frozen and stained with oil red 0 for neutral lipids, Pearse's method for phospholipids, Sudan black B for glycolipids, mercuric nitrate for phospholipid cerebroside and mercuric nitrate after ether extract for sphingomyelin. Part of the tissue was immediately frozen in liquid nitrogen to measure fibrinolytic activity, using a modification of Todd's histochemical technique (Turner and Ryan 1969).

For electron microscopy fresh tissue was cut into 1 mm³ cubes and fixed in 3% glutaraldehyde solution in 0.1 M cacodylate buffer (pH 7.4) at 4° C for 4 h, and postfixed with a 1% osmium tetroxide solution in cacodylate buffer for two hours. The tissue was then dehydrated in graded series of alcohols and propylene oxide and embedded in Epon 812. Sections measuring 1 to 2 μm in thickness were made and stained with methylene blue and basic fuchsin (Aparicio and Marsden 1969).

Ultrathin sections were cut on an LKB Huxley ultramicrotome, double-stained with uranyl acetate and lead citrate, and then examined in Siemens Elmiscop 101 electron microscope at 80 kV.
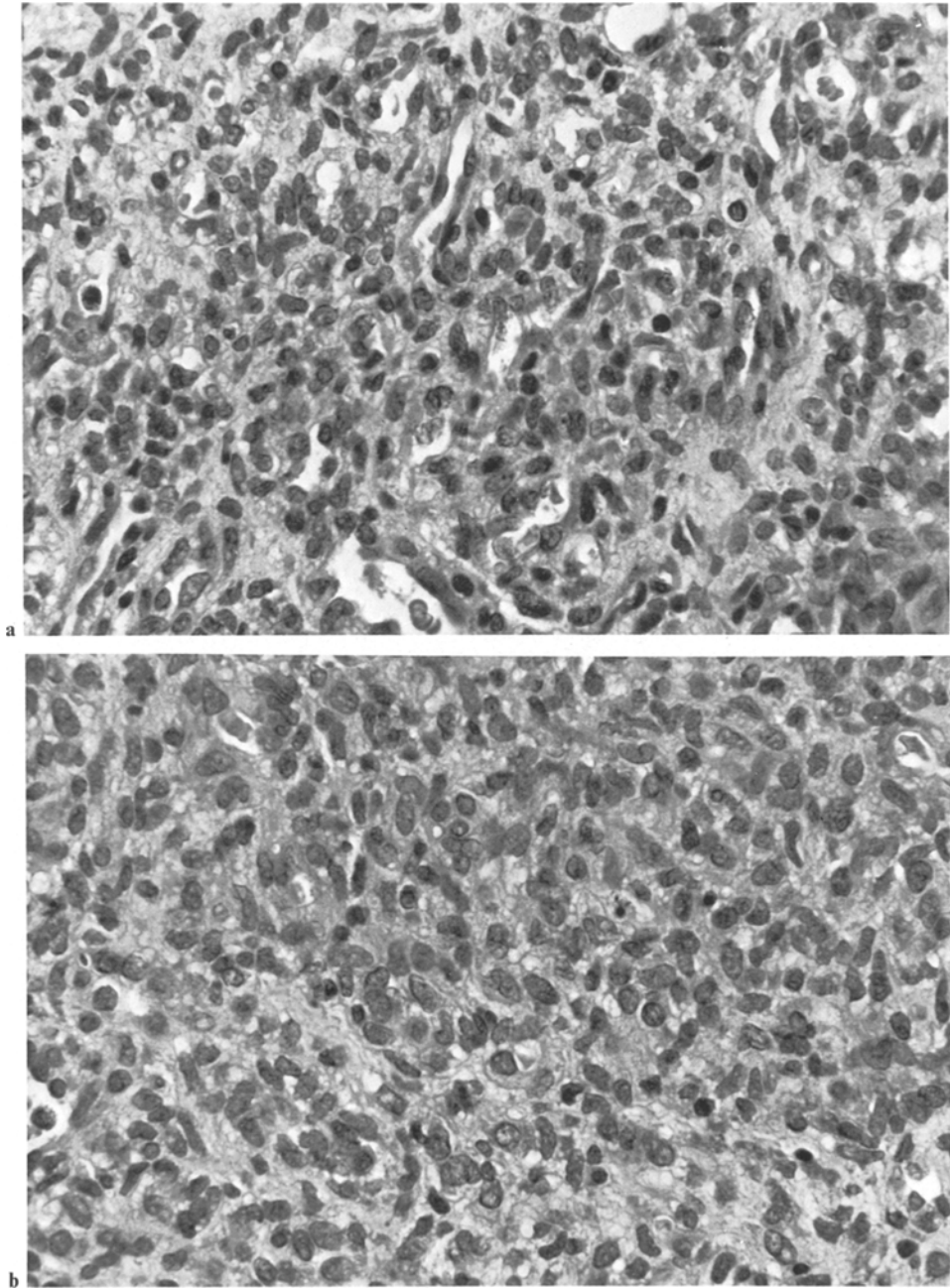
Fig. 2a. Case 1. **a** Haemangioendotheliomatous area with small vascular channels separated by an intervening fibrous stroma and surrounded by ovoid of fusiform pericytes. **b** Haemangiopericytomatous area composed of round to fusiform pericytes around slit-like vascular spaces. (H & E × 750)
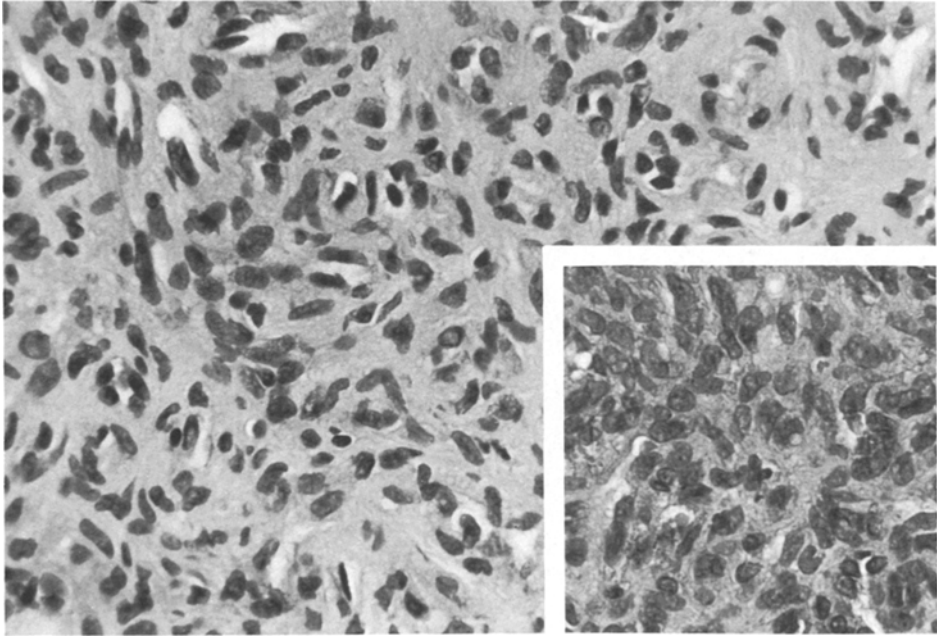
Fig. 3. Case 2. Haemangioendotheliomatous area with proliferation of endothelial cells and small lumens (H & E × 750). *Inset:* Case 2. Haemangiopericytomatous area with proliferation of the pericytes (H & E × 750)

Pathologic Findings

Light Microscopy

Case 1. There were two distinct areas of the tumor when examined with light microscopy; solid cellular parts, and areas of open vascular lumens. In the cellular portion there were proliferated endothelial cells (haemangioendotheliomatous areas) and proliferated pericytes (haemangiopericytomatous areas). The discrete or collapsed lumens were lined by plump endothelial cells and separated by ovoid to spindle shaped cells (Fig. 2a and b). The second areas consisted of blood vessels with open lumens which were lined by more flattened endothelial cells and separated by pericytes. The mitotic figures in both areas were found infrequently and were not atypical. The cellular part with proliferation of the pericytes dominated so that the histopathological diagnosis was juvenile haemangiopericytoma.

Case 2. Examination of the tumor showed a cellular neoplasm characterized by small vascular spaces partially lined by plump endothelial cells with regular vesicular nuclei and eosinophilic cytoplasm. The histopathologic diagnosis was benign haemangioendothelioma because of the predominance of this kind of tissue but there were also areas of haemangiopericytomas. In the haemangioperi-
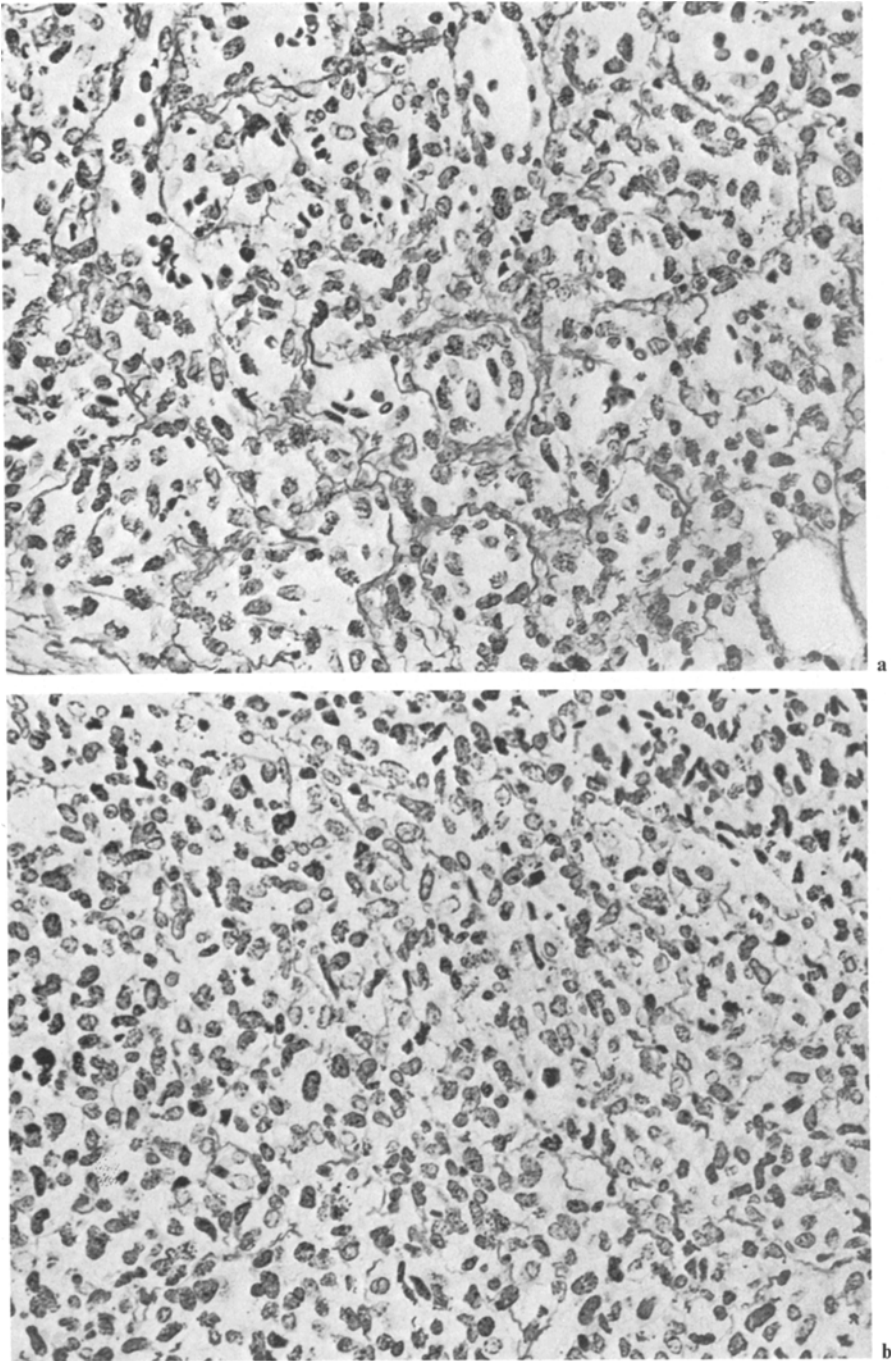
Fig. 4. Case 1. Silver impregnation. **a** Haemangioendotheliomatous area – the endothelial cells are present inside the reticulin network; **b** Haemangiopericytomatous area – irregular network of reticulin (Wilder's stain ×470)

Fig. 5. Case 1. Solid cellular part of the tumor. Small blood vessels with slitlike (*arrows*) or very narrow lumens (*L*) lined by plump endothelial cells (*E*) and surrounded by pericytes (*P*) with huge amount of the glycogen-like particles. Note electron-dense inclusions inside the cytoplasm of the endothelial cells, irregular budding and cytoplasmic processes of the endothelial cells (*head of arrows*). The basal lamina varies in thickness (*asterisk*). Collagen fibers (*C*); Erythrocyte (*R*). (×9,900)

cytomatous areas, intervascular spaces contained more ovoid and spindle shaped cells. In both areas only rare mitotic figures were noted (Fig. 3).

Reticulin stains revealed in both cases reticulin fibers around vessels in haemangioendotheliomatous areas and a few fibers around some individual cells in the haemangiopericytomatous areas (Fig. 4a and b). Collagen and elastic fibers were demonstrated in small amounts with Movat's pentachrome method and Verhoeff's technique. Periodic acid Schiff (PAS) stains before diastase digestion were positive. The Giemsa method showed a very low number of mast cells; the mean number was 1.8 in case 1 and 0.4 in case 2. (For normal skin a mean of mast cells equals 3.5). Sections stained for neutral lipid, glycolipids, phospholipids, phospholipid cerebroside, and for sphingomyelin were negative. Factor VIII-related antigen was absent in the endothelial cells and no tissue fibrinolytic activity was found in case 1.

Electron Microscopy

The ultrastructural features were similar in both cases therefore they are presented together.

1. The Solid Cellular Areas of the tumors were composed of endothelial-lined slits and pericytes which formed vascular units. These vessels were surrounded by basal lamina which was often multilayered, varied in thickness and discontinuous in some places (Figs. 5 and 6). The vascular spaces were lined by plump endothelial cells which in haemangioendotheliomatous areas showed two or three layers of these cells (Fig. 7). The endothelial cells had a pendulum-like shape, hanging into the lumen and occupying much of the vessel volume or forming bridges across the lumen. The overgrown endothelial cells possessed large, distorted, sometimes cerebriform nuclei with marginal condensation of the chromatin. One or two nucleoli and two to four amorphous nuclear bodies were seen. The endothelial cells were characterized by tight intercellular junctions. The cytoplasmic borders showed fine irregular processes, luminal microvilli, budding and basal protrusions. Micropinocytotic vesicles, abundant intracytoplasmic fine filaments, ribosomes and large mitochondria were common. Golgi zones and rough endoplasmic reticulum were well demonstrated. Intracytoplasmic electron-dense inclusions measured from 0.5 μm to 2.0 μm in diameter. Many of these inclusions showed crystalloid structures (Fig. 8). Only a few small, oval bodies suggestive of Weibel-Palade bodies, without typical rod-shaped substructures, were found in cytoplasm (Figs. 9 and 13).

Pericytes tended to encircle endothelial-lined slits. They were oval or elongated cells. Their nuclei were generally irregular in outline and in many cells were lighter than the nuclei in the endothelial cells. Sometimes one or two distinct nucleoli in pericytes were seen. The cytoplasm of the pericytes contained scattered mitochondria, extensive rough endoplasmic reticulum, moderately developed Golgi apparatus, many free ribosomes, very numerous clumps of glycogen-like particles and intracytoplasmic electron-dense inclusions which very often showed membranous features (Fig. 6, inset). The individual cells and their pro-
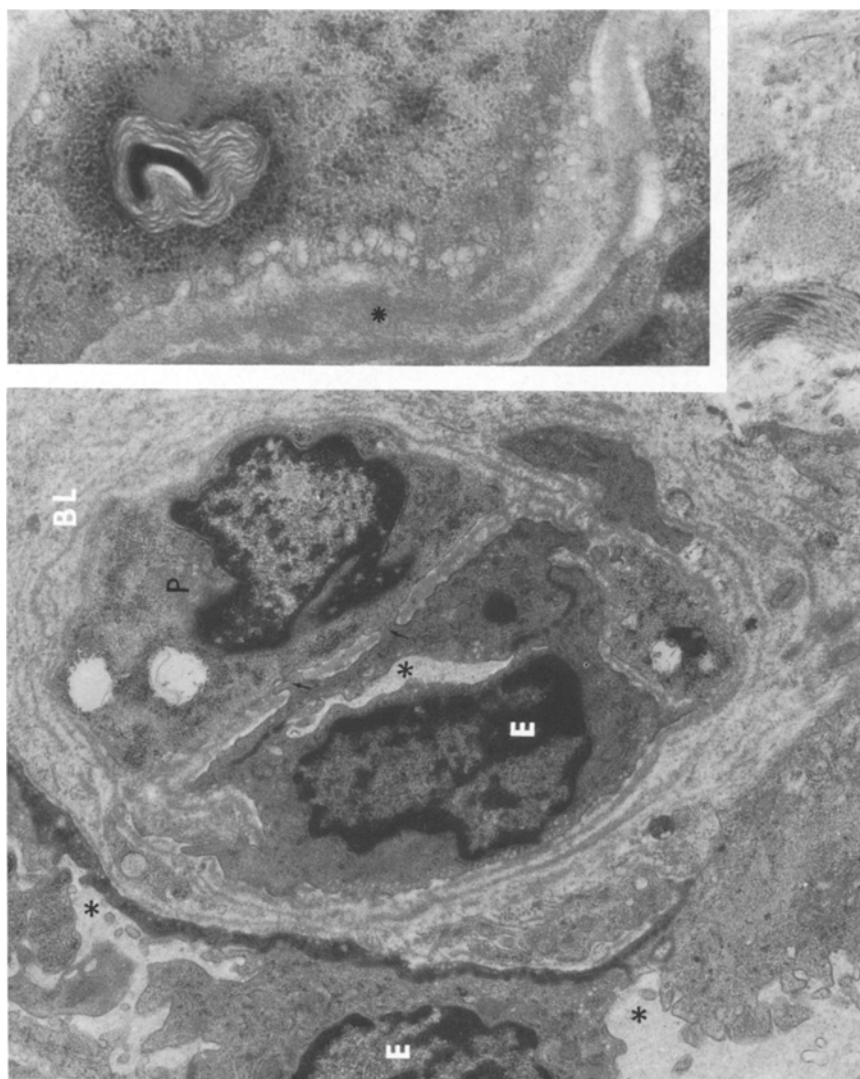
Fig. 6. Case 2. Haemangioendotheliomatous area. Small blood vessels with very narrow lumens (*asterisks*) and large endothelial cells (*E*) one of them contains dark granule. Pericytes (*P*) with clumps of glycogen-like material around empty spaces. Note connection between endothelial cell and pericyte (*arrows*), nuclear body in the pericyte and multilayered basal lamina (*BL*) (×7,200) *Inset:* Part of the pericyte with clusters of glycogen-like particles and inclusion with irregular concentric dense lamellae. Basal lamina (*asterisk*) (×31,800)

cesses were surrounded by irregular, multilayered basal lamina-like material (Fig. 10).

In the haemangiopericytomatous areas the lumen of the vessels were a little larger than those in the haemangioendotheliomatous areas and were lined with flattened endothelial cells. Pericytes were similar to those in the haemangioendotheliomatous areas and also possessed huge amounts of the glycogen-like particles. Basal lamina surrounding pericytes and their processes were regular in some parts, and multilayered and disrupted in others. The intracytoplasmic electron-dense inclusions were also observed in both endothelial cells and pericytes. The typical Weibel-Palade bodies were absent (Figs. 11 and 12).
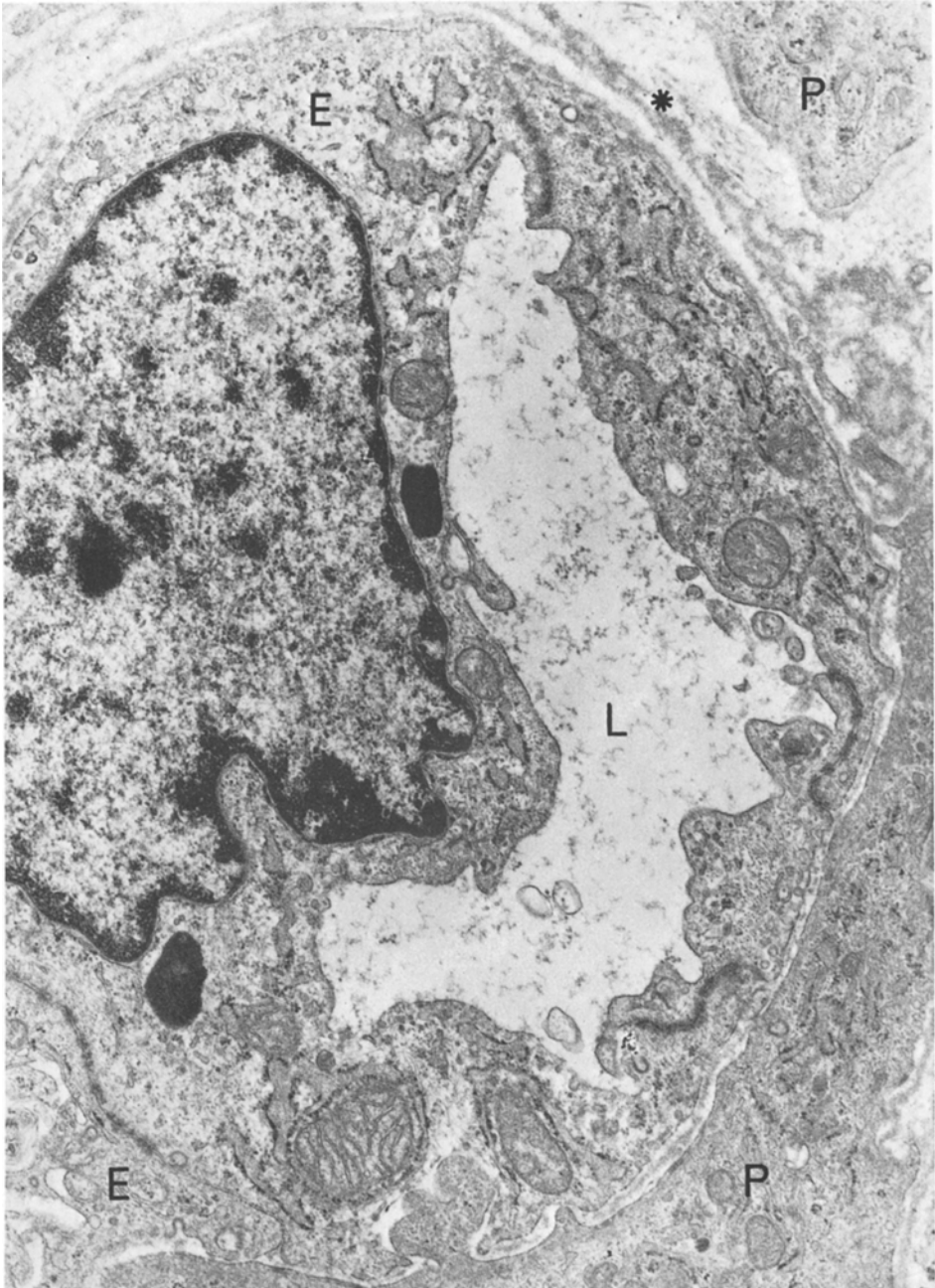
Fig. 7. Case 1. Haemangioendotheliomatous area of the tumor. Small blood vessel lined in some part with two layers of the endothelial cells (*E*), and surrounded by protrusion of the pericytes (*P*). Note large, electron-dense inclusions inside the endothelial cell, and connection between endothelium and pericyte. Irregular, multilayered basal lamina (*asterisk*). Lumen of the vessel (*L*). (×24,750)
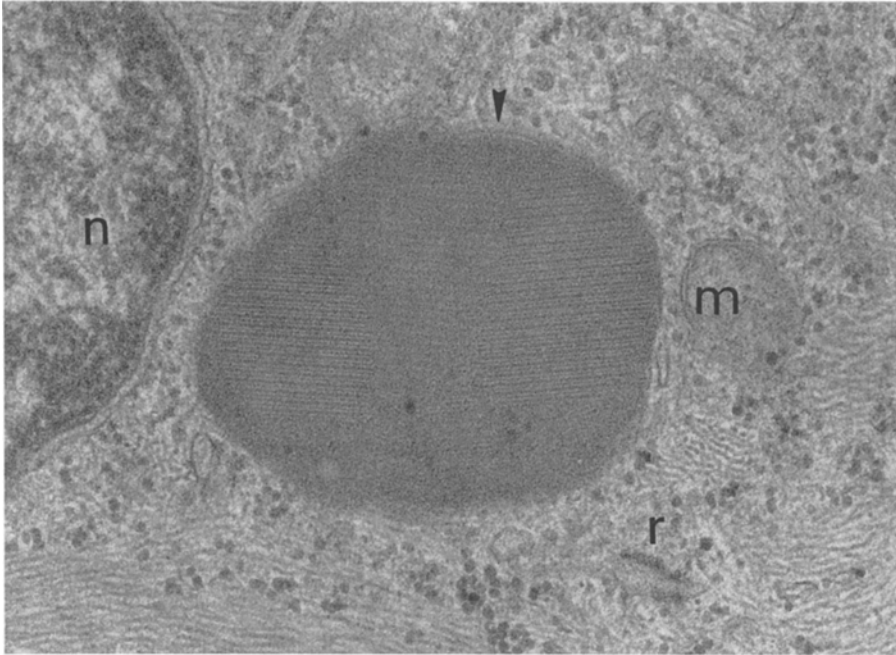
Fig. 8. Case 1. Part of the endothelial cell in the haemangioendotheliomatous area of the tumor with intracytoplasmic inclusion showing the granular and crystalloid character of the material. Note 3 layers of membrane surrounding the body (*arrow*). Nucleus (*n*). Mitochondrion (*m*). Ribosomes (*r*). ($\times$61,200)

2. In Areas With Open Vascular Lumen the endothelial cells were much more flattened and had fewer protrusions, but in some parts of the vessel wall the protrusions sometimes formed three layers (Fig. 13). Nuclei of the endothelial cells were mostly oval, without conspicuous invaginations and possessed one to two nuclear bodies. The cytoplasm showed plenty of fine filaments, a few mitochondria, pinocytotic vesicles and large, intracytoplasmic electron-dense inclusions. Weibel-Palade bodies were not seen. Pericytes were rounded, oval, or elongated with long processes which surrounded the endothelium. Their cytoplasm also had large masses of particles strongly resembling glycogen. The basal lamina was irregular, multilayered in some parts, and surrounded the pericytes completely (Figs. 14 and 15). In the lumen of these vessels numerous erythrocytes and, in some parts, plugs of platelets and fibrin fibers were seen. The intervascular spaces contained veil cells, loose dispersed collagen fibers and a very few mast cells and macrophages.

Discussion

Vascular tumors originate in collections of primitive mesenchymal cells which differentiate into endothelial cells and pericytes. The cell-rich, immature vascular tumors are composed of nearly all elements which, at one stage or another,
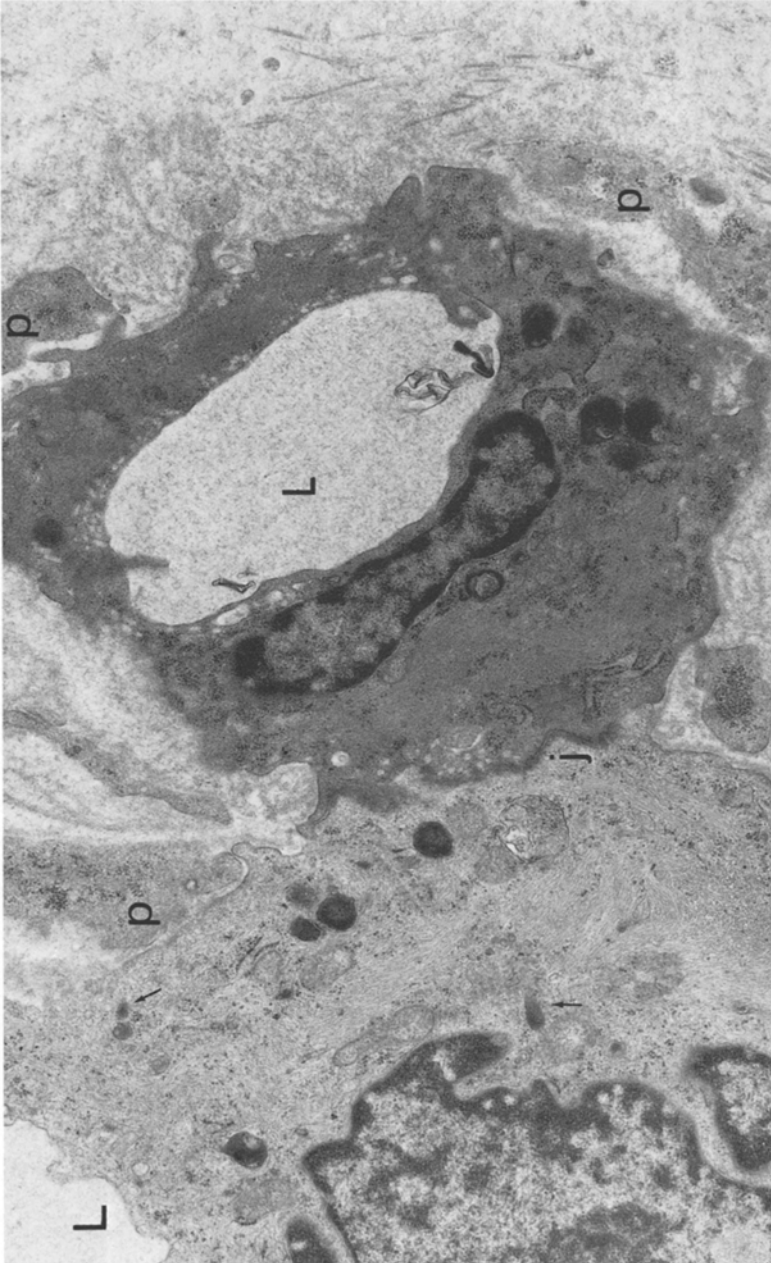
Fig. 9. Case 2. Haemangioendotheliomatous area. Huge endothelial cells (E) with a few electron-dense inclusions. In the cell with lighter cytoplasm immature Weibel-Palade bodies can be seen (*arrows*). Protrusions of pericytes (*P*) with glycogen-like particles. Note very scanty basal lamina around a new vessel with dark cytoplasm. Lumen of the vessel (*L*). Intercellular tight junction (*J*). (×18,270)
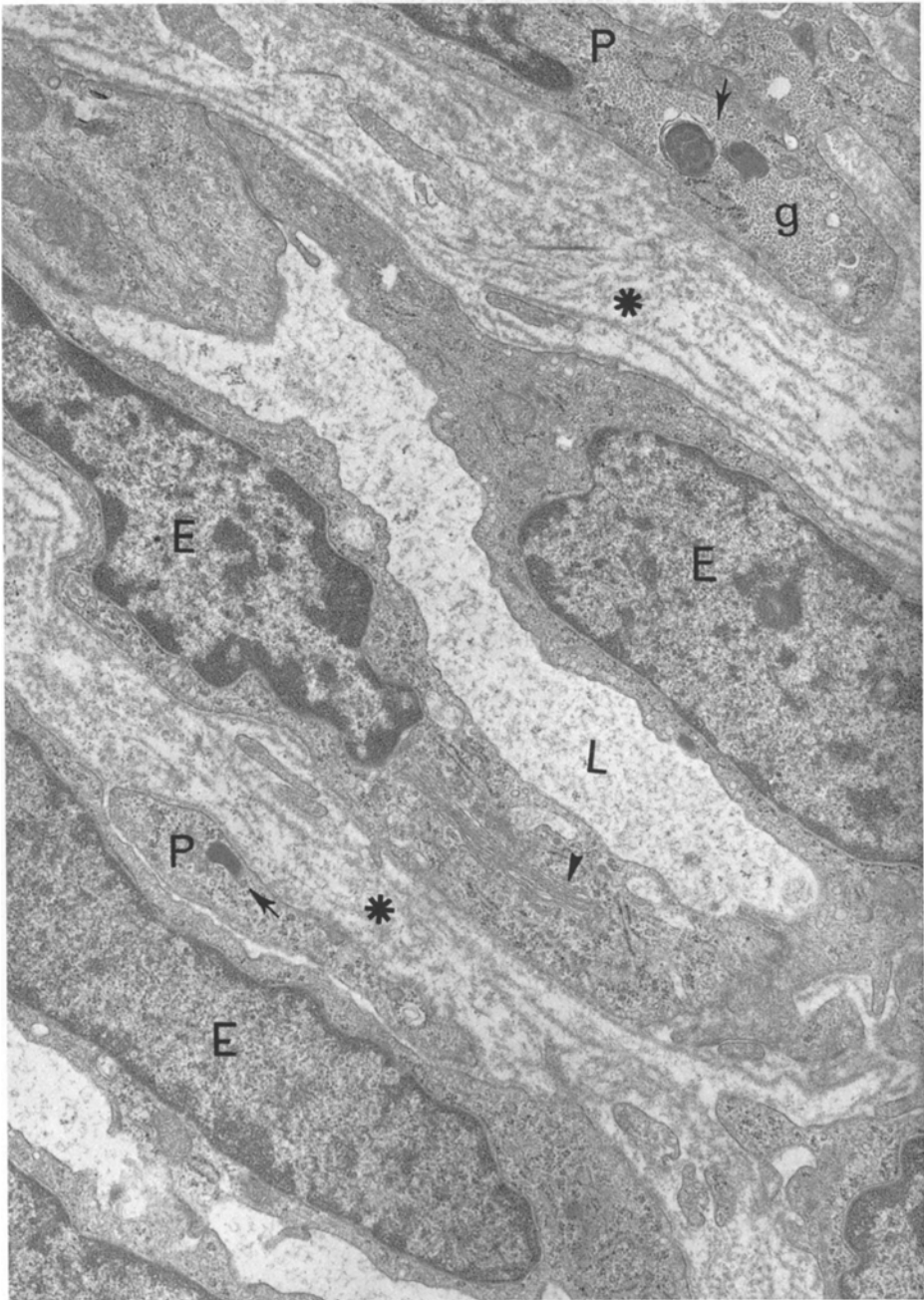
Fig. 10. Case 1. Haemangioendotheliomatous area of the tumor. Small blood vessels with very narrow lumens (*L*). Fusiform pericytes (*P*) with electron-dense and membranous inclusions (*arrows*) and a large amount of glycogen-like particles (*g*). Note irregular, multilayered basal lamina (*asterisks*) surrounding endothelial cells (*E*) and pericytes. Golgi zones (*head of arrow*). (×20,625)
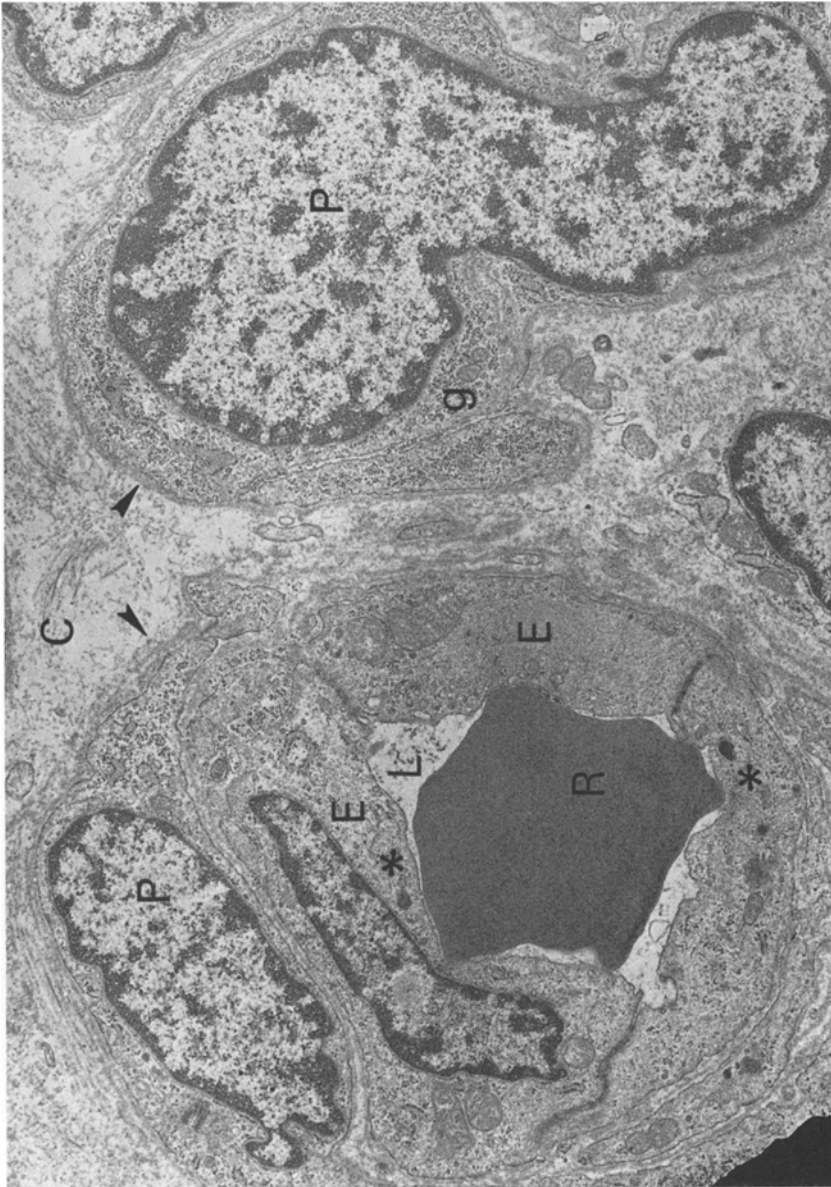
Fig. 11. Case 1. Haemangiopericytomatous area of the tumor. Small blood vessel with flattened endothelial cells (*E*). Large pericytes (*P*) with huge amount of glycogen-like particles (*g*). Note regular basal lamina surrounding pericytes and much more irregular, multilaminated basal lamina around the vessel (*head of arrows*). A few collagen fibers (*C*). Intracytoplasmic electron-dense inclusions (asterisks). Lumen of the vessel (*L*). Erythrocyte (*R*). (×15,000)

are formed in the embryonic development of the vascular bed. Von Albertini (1955) considered them to be immature mesenchymal tumors and as angioplastic reticulomas. The vascular tumor types do not represent sharply demarcated entities. Frequently, one type can be seen merging into another, or the characteristics of more than one type can be present in the same tumor. Histopathological classification of these tumors depends on whether the cellular components,
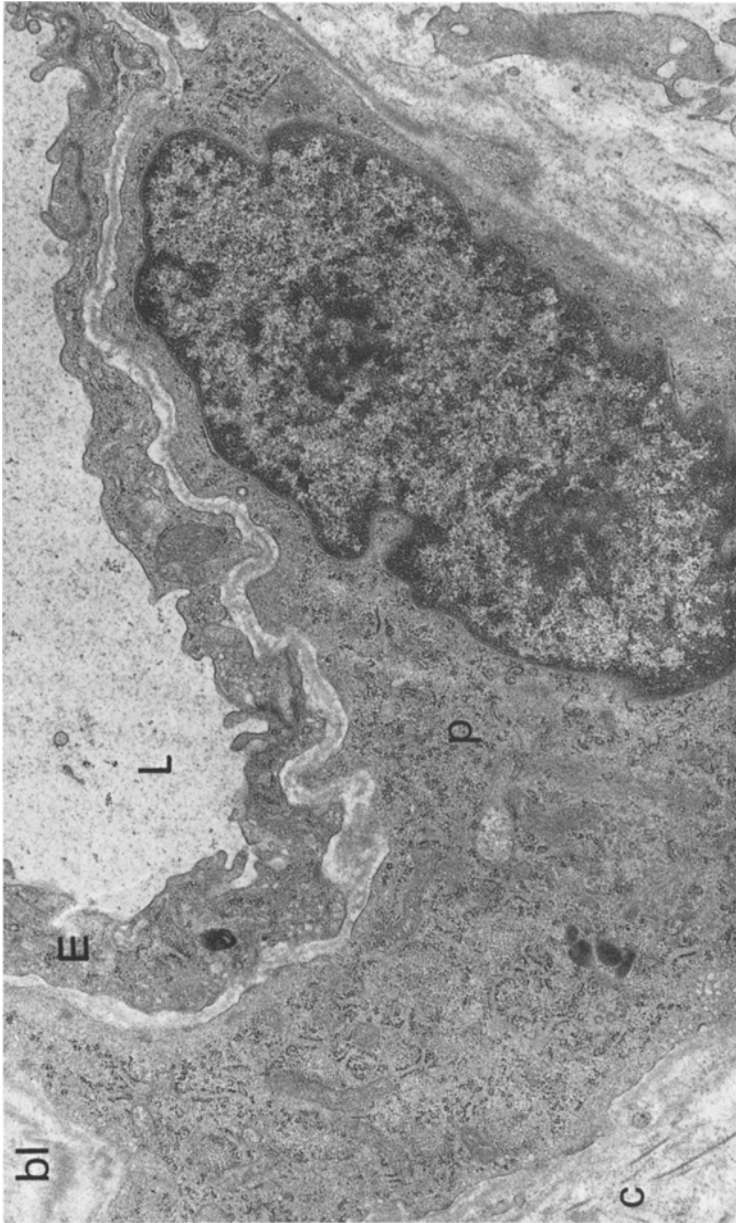
Fig. 12. Case 2. Haemangiopericytomatous area with large pericyte (*P*) showing glycogen-like particles, ribosomes, mitochondria, wide rough endoplasmic reticulum, Golgi zones and half desmosomes. Note electron-dense inclusions both in pericyte and endothelial cell (*E*). Basal lamina (*bl*). Lumen (*L*). Collagen fibers (*C*). (× 14,490)

especially the hyperplastic endothelial cells and/or pericytes, or the blood vessels are dominant. In our cases both cellular and vascular structures were present in the same mass. Histologically the most significant features of this cellular tumor suggest a transition between so called juvenile haemangiopericytoma and benign haemangioendothelioma (Enzinger and Smith 1976; Taxy and
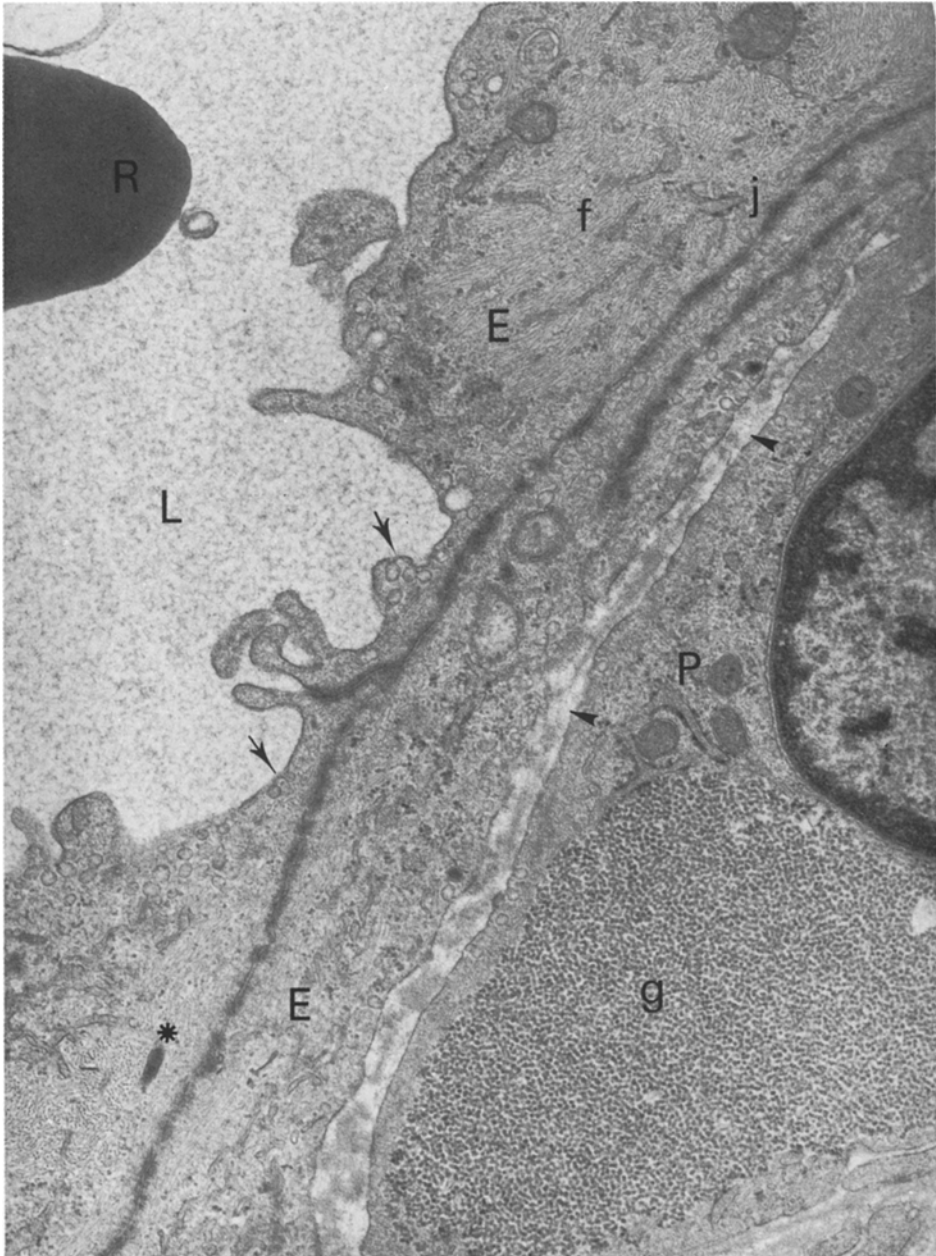
Fig. 13. Case 1. Part of the blood vessel's wall in the area with open lumen (*L*), filled with erythrocytes (*R*). Note three layers of endothelial cells (E), intercellular junctions (*j*), microfilaments (*f*), pinocytotic vesicles (arrows), and oval, electron-dense, Weibel-Palade body without characteristic tubular substructure (*asterisk*). Pericyte (*P*) with occasional pinocytotic vesicles and huge amount of the glycogen-like particles (*g*). Irregular and broken basal lamina (*head of arrows*) (×33,000)

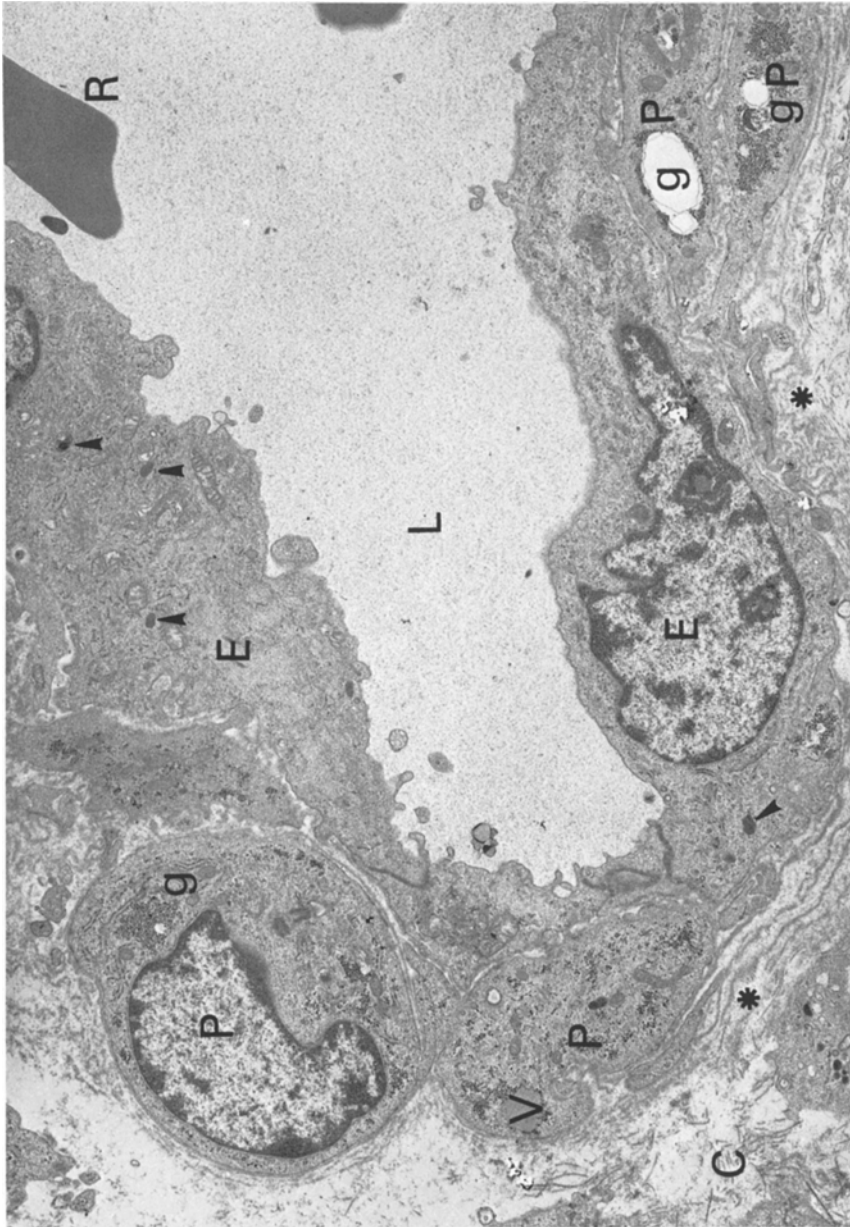**Fig. 14.** Case 1. Area with open vascular lumen. Endothelial cells (*E*) are much more flattened. Round shaped pericytes (*P*) in the close vicinity of the endothelial cells containing deposits of glycogen-like particles and empty spaces in the center (*g*), lipid vacuole (*v*) and a few mitochondria. Intracytoplasmic electron-dense inclusions are seen both in the pericyte and in the endothelial cells (head of arrows). Multilayered, irregular basal lamina (*asterisks*). Lumen (*L*). Erythrocyte (*R*). Collagen fibers (*C*). (9,900)

Gray 1979), and in the past have been interpreted as either juvenile haemangioendothelioma or juvenile haemangiopericytoma.

The distinction between the benign haemangioendothelioma and benign haemangiopericytoma with light microscopy is usually made by the identification of a proliferation of the endothelium with doubling or even tripling of this
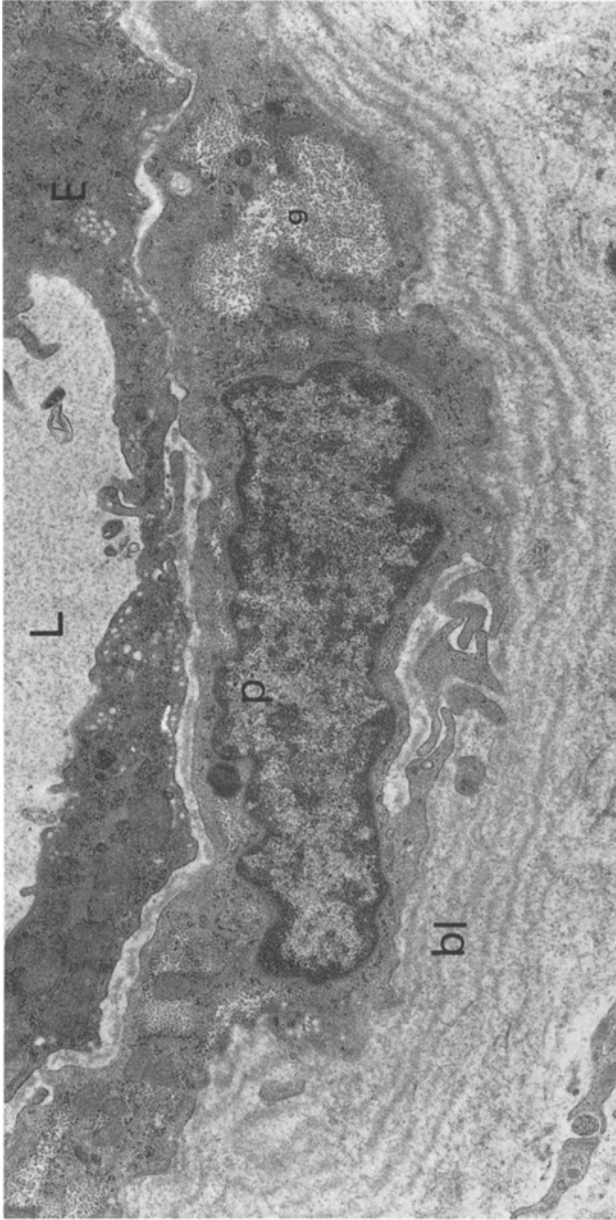
Fig. 15. Case 2. Pericyte (*P*) in area with open vascular lumen (*L*) with huge amounts of glycogen-like particles (*g*) and dark inclusion. Basal lamina (*bl*) shows multilamination in outer side of pericyte and discontinuation and irregularity between endothelial cell (*E*) and pericyte. (×14,490)

layer in haemangioendothelioma (Stout 1943). In haemangiopericytoma, however, there is a perivascular massing of the pericytes (Kauffman and Stout 1960). By using a silver stain, endothelial cells in haemangioendothelioma are seen inside the reticulin sheath and are not surrounded by reticulin fibers. In contrast, in haemangiopericytoma the pericytes are outside the reticulin sheath and each pericyte is surrounded by reticulin fibers (Dingman 1958; Stout and Lattes 1967).

It is unfortunate that there are no known reliable criteria that will distinguish

the malignant from the benign haemangiopericytomas (Kauffman and Stout 1960; Stout and Lattes 1967; Hajdu 1979). Abundant reticulum in benign haemangioendothelioma and haemangiopericytoma is not always seen. In fact it is quite sparse in some tumors, coming from the vessel walls and giving off thin twigs to individual cells, and in some cases providing small branches to enclose groups of cells. There is evidence that the less differentiated, malignant tumors have a poorly developed reticulin pattern. In both benign and malignant tumors, mitoses are few compared with the number found in many other tumors of mesenchymal origin. Most of the congenital tumors show no mitoses or at most a few in the entire histological section (Kauffman and Stout 1969). Hajdu (1979) decided that prognosis for this kind of tumor should be based on size, location, histological grade and age of patient.

In electron microscopy the endothelial cells of benign haemangioendothelioma occur in excessive numbers and have voluminous cytoplasm with many protrusions and irregular borders (Balazs et al. 1978; Feldman et al. 1978; Iwamoto and Jakobiec 1979; Taxy and Gray 1979), while the endothelial cells of juvenile haemangiopericytoma are of normal appearance and distribution along the vessel (Ramsey 1966; Eimoto, 1977). Pericytes are conspicuous by their absence in some cases of the benign haemangioendothelioma (Feldman et al 1978) and are numerous in others (Balazs et al. 1978). In the heamangiopericytoma multiple, layers of the pericytes surround endothelial-lined vascular channels (Hahn et al. 1973; Eimoto 1977). Extracellular material in haemangiopericytoma is a uniformly thin layer surrounding the vessels and extending as trabeculae segregating the cells into tightly packed masses. In haemangioendothelioma a much broader expanse of extracellular material permeates the tumor separating all cells from each other in an irregular scattered fashion (Ramsey 1966). Basal lamina around the pericytes is not identified in some instances (Ramsey 1966; Murad et al. 1968; Paullada et al. 1968).

In our study the endothelial cells in both tumors were recognized easily by electron microscopy when there were intercellular junctions between adjacent cells, when they contained micropinocytotic vesicles and abundant intracytoplasmic fine microfilaments, when they formed slit-like lumina and were surrounded by basal lamina. Rod shaped tubulated bodies, described by Weibel and Palade (1964), in the endothelial cells were absent in both solid cellular areas and in areas showing larger vascular lumens. Similarly Taxy and Gray (1979) found the apparent lack of typical Weibel-Palade bodies in two infants with cellular angiomas and theorized that these structures are manifested in more mature endothelial cells. However, in most of the vascular tumors they were absent. In angiosarcoma these inclusions in the tumor cells were only occasionally observed (Steiner and Dorfman 1972; Popoff et al. 1974; Rosai et al. 1976). Steinsiepe and Weibel (1970) reported a proportionate decrease in the number of Weibel-Palade bodies with decreasing vessel size. This may provide a clue to the possible function of this organelle, which at present remains unknown.

The pericytes of both our infants were located in close proximity to the endothelial cells and formed an integral part of the tumor. In the areas of the open vascular lumen of the tumor, the pericytes showed features similar to those in the solid cellular parts.

The ultrastructure of the pericytes indicated that they had characteristics

of undifferentiated cells and were similar to the mesenchymal cells of an embryo. They were larger than the normal pericytes described by many authors (Fernando and Movat 1961; Movat and Fernando 1964; Ashton and de Oliveira 1966; Rhodin 1968; Kuhn and Rosai 1969), and showed huge, lighter nuclei. Their cytoplasm contained moderately developed Golgi zones, few mitochondria, pinocytotic vesicles, extensive rough endoplasmic reticulum, free ribosomes, electron-dense inclusions and large amounts of glycogen particles. The abundant glycogen in the pericytes was also disclosed by the periodic acid Schiff stains before diastase digestion, whereas they disappeared after treatment. Examination with the electron microscope revealed that glycogen particles may occur in both monoparticulate and rosette form in human tissues (Biava 1963). In our cases monoparticulate glycogen found in the pericytes indicated their accumulative capacity. The reason for this accumulation of glycogen is not known. It is possible that it is a property of immature cells where glycogen has the function of maintaining development. Similarly, huge amounts of glycogen particles have been found in human embryonic epidermis in seven- and ten-week-old fetuses (Matsunala and Mishima 1969), as well as in human umbilical arterial endothelium at 10–12 $^1/_2$ weeks gestation (Parry and Abramovich 1972). Deposit of the glycogen particles in the pericytes were observed in neonatal haemangioendothelioma (Balazs et al. 1978), in cellular angioma of infancy (Taxy and Gray 1979), in juvenile haemangiopericytoma (Hahn et al. 1973; Eimoto 1977), and in haemangiopericytoma of adults (Ramsey 1966; Paullada et al. 1968; Silverberg et al. 1971; Battifora 1973; Pena 1975). They were also found in angiosarcoma of the skin (Rosai et al. 1976) and in pineal tumor (Ramsey 1965). Rarely has haemangiopericytoma been associated with ectopic hormonal syndrome. However, a few authors (Howard and Davis 1959; Lowbeer 1961; Crocker and Veith, 1965; Paullada et al. 1968) have described such cases where the patient also had hypoglycaemia.

In addition, present observation showed the possibility of producing a large pericellular deposition of basal lamina-like material by the hyperplastic pericytes. Bommer et al. (1976) postulated that pericytes play an important role in the formation of the basal lamina and of reticular fibers in the haemangiopericytoma. Moreover, according to Rhodin (1968) pericytes represent transitional forms between primitive mesenchymal and smooth muscle cells which are able to synthesize basal lamina substance and may participate in the formation of collagen fibers.

We frequently observed nuclear bodies in both endothelial cells and pericytes which were amorphous in form and measured 0.3 to 0.4 microns. These bodies have been reported in both normal (Farquar and Palade 1962; Weber and Frommes 1963) and abnormal tissue Zelickson and Lynch 1961; Robertson and Maclean 1965; Mottaz and Zellickson 1966), but their significance has not been established. Robertson and Maclean (1965) found that they occur with greater frequency in diseased tissue than in normal tissue and concluded that possibly they are associated with abnormal cell division.

A remarkable phenomenon which occured frequently in our cases was the presence of the intracytoplasmic, electron-dense inclusions in the endothelial cells and pericytes, which in higher magnifications showed crystalloid structures

in the endothelial cells and membranous features in the pericytes. This will be presented in more detail in a separate paper.

It is surprising that in both our cases of vascular tumors there were a very low number of mast cells compared to the number in normal skin and in the capillary and cavernous haemangiomas in the developing and involuting phase (Pasyk et al. unpublished data). In the previous publications of benign haemangiopericytoma and haemangioendothelioma in children there is no data about the number of mast cells. It has been known for a long time that mast cells are always fairly abundant along blood vessels (Ehrlich 1878; Jorpes 1939; Ham 1953; Riley 1953; Studer 1954). They have been shown to increase in number in many diseases with and without chronic inflammatory processes (Selye 1965; Bessis 1973), around malignant tumors (Benditt and Lagunoff 1963 and 1964; Rupe 1963) and in benign tumors (Belcher et al. 1974; Hajdu 1979). Ryan (1970) postulated that mast cells encourage vascular proliferation and Kessler et al. (1976) suggested an intermediate role for these cells in tumor angiogenesis.

Moreover, in our investigations much of the new blood vessels did not have fibrinolytic activity, factor VIII-related antigen synthesis or Weibel-Palade bodies in the endothelial cells. The studies of many authors (Todd 1959; Astrup et al. 1960; Pandolfi et al. 1962; Kwaan and Astrup 1964) indicate that high fibrinolytic activity is characteristic of proliferating and newly formed capillaries. We do not know what this absence of fibrinolytic activity implies it may be related to the reduced number of mast cells, lack of the Weibel-Palade bodies or absence of factor VIII-related antigen in the endothelium. Probably deficiency of these endothelial cell markers should be regarded as proof of the immaturity of the endothelial cells in these kinds of tumors. Moreover, these observations as well as our histologic and ultrastructural features showed that both endothelial cells and pericytes were immature and similar to the embryonic cells. These two tumors, with very high cellularity, were the most immature form of capillary haemangioma, which we prefer to call cellular haemangioma. We believe that the terms haemangioendothelioma and haemangiopericytoma that have been used to designate both benign and malignant tumors should be omitted because they may cause misunderstanding and confusion.

We want to emphasize that Case 1 presented an unusual clinical problem connected with localization of the tumor. For a number of years it has been known that most juvenile haemangiomas will resolve spontaneously in time without treatment (Lister 1938; Wallace 1953; Grabb et al. 1980) and are better left untreated (Lampe and Latourette 1959; Margileth and Museles 1965). In rare instances such as the present Case 1, when a large haemangioma of the eyelid obscures the visual axis, amblyopia may result (de Venecia and Lobeck 1970; McLeon 1976; Robb 1977; Pasyk et al. unpublished), therefore aggressive therapy is important. The tumor in our case was not completely sugically removed because of the risk of muscle damage. Eleven months after surgery the residual part of the tumor had completely involuted and visual acuity was not decreased.

In conclusion, on the basis of the light and electron microscopic studies of tumors in two infants, we established that they were the most immature

vascular tumors, showing vascular differentiation and both benign haemangioen-dothelioma and haemangiopericytoma in the same tumor.

Electron microscopic studies are much more helpful and decisive than light microscopy in establishing the diagnosis of these vascular tumors, which macro-scopically can resemble cavernous haemangioma or lymphangioma, and are therefore difficult to diagnose correctly.

We postulate that the term "cellular haemangioma" is the best suited for these kinds of immature vascular tumors in infants and children because it avoids further misunderstanding and confusion.

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