Histol Histopath (1989) 4: 85-94

Histology and Histopathology

Hyperplastic cellular components of a hemangiopericytoma. An ultrastructural study

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Summary. Based on ultrastructural features of cellular components of a hemangiopericytoma, hyperplastic cells are classifiable into fibroblast-like (group I), endotheloid (group II) and pericyte-like (group III) cells. The transformation of the group I cells to the group II, or to the group III cells, is pronounced in our electron micrographs and this may imply that the group I cell is the principal cell of origin in this neoplasm.

The smooth muscle-like (group IV) cells comprising the media of the arteries and veins in this neoplasm may represent modified, possibly de-differentiated smooth muscle cells reacted to the neoplastic proliferation of the surrounding adventitial (group I) cells.

Key words: Ultrastructure, Hemangiopericytoma, Undifferentiated mesenchymal cell, Vasoformative cell

Introduction

Since the first description by Stout and Murray (1942), hemangiopericytoma has gained a definite entity in vascular tumors by the subsequent clinicopathological studies (McMaster et al., 1975; Enzinger and Smith, 1976; Lattes, 1976). Despite detailed histological examination, including electron microscopy (Ramsey, 1966; Murad et al., 1968; Kuhn and Rosai, 1969; Silverberg et al., 1971; Battifora, 1973; Hahn et al., 1973; Popoff et al., 1974; Reyes et al., 1977; Goellner et al., 1978; Nunnery et al., 1981; Pasyk et al., 1982), histogenesis of this neoplasm is still controversial, and the widely accepted «pericytic origin», first claimed by Stout and Murray (1942), is now questioned by several electron microscope studies (Ramsey, 1966; Murad et al., 1968; Paullada et al., 1968; Pasyk et al., 1982). Such a controversy may have arisen in part from the wide range of degree of development of the hyperplastic cellular components from area to area in the tumors ever examined: In one area the predominant tumor cells are apparently characterized by ultrastructural features of so-called pericytes, and surround vascular channels in a similar manner to pericytes, while in another area those similar in ultrastructure to «undifferentiated mesenchymal cells» or «fibroblasts» as often encountered in the adventitia of normal adult vessels are grouped near the vessels occasionally showing cell to cell contacts by simple attachment devices. If we could assume that the latter cell group represents a less-advanced phase in the tumor cell development, it seems quite reasonable to question whether hemangiopericytoma arises only from abnormal proliferation of capillary pericytes under effects of certain stimuli.

This paper describes several ultrastructural findings of a hemangiopericytoma. Electron micrographs provided here strongly suggest that the tumor is originated from the abnormal proliferation of undifferentiated mesenchymal cells.

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Materials and methods

Case Report

A 29-year-old female came to our hospital on October 23, 1985 for diagnosis of a purplish-red nodule on the great trochanter region of the left thigh. She stated that the lesion had been noted approximately during the previous 4 years and had become enlarged as much as thumb sized about a year prior to hospitalization. She had no spontaneous pain and urtication. Physical examination revealed an elastic-soft, well-demarcated nodule in the subcutis. There was no bleeding. Biopsy was performed and the diagnosis of hemangiopericytoma was made. The lesion was excised and O-Z plasty was performed.

Pathology

The surgical specimen submitted to the laboratory contained a 29 by 21 by 9 mm tumor. The tumor was firm in some limited areas but there was no calcification, necrosis, hemorrhage and cystic degeneration.

Specimens for light microscopy were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin. Some sections were stained with Watanabe's silver stain technique with a slight modification. Frozen sections from the formalin-fixed specimens were stained with Sudan III.

Methods for Electron Microscopy

Portions of the surgical specimen were fixed in 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer at 4° C for 2 hours, postfixed in 1% osmium tetroxide in the buffer, dehydrated in graded concentrations of acetone, and embedded in epoxy resin.

Ultrathin sections were made on Porter-Blum MT-1 microtome, stained with uranyl acetate and lead citrate, and examined in a JEM 100 CX electron microscope.

Results

Light microscopic examination provided essential criteria for the histological diagnosis of hemangiopericytoma: These include abundant small vessels including capillaries possessing a slit lumen throughout the tumor, tightly packed and elongated oval tumor cell groups around these vessels, and an extensive network of argyrophilic fibres surrounding both vascular walls below the endothelia and grouped tumor cells by the silver impregnation. Stainings of the tumor cells by Sudan III were occasionally positive. Prominent fibrosis mainly consisting of collagen bundles and a few fibroblasts was often intervened between each tumor cell cluster. There were considerable variations in arrangement and feature of the tumor cells from place to place. The tumor cells near the vessels with a wide lumen were tightly packed and often showed a marked epithelioid change, while those associated with capillaries with a slit lumen retained general features of immature mesenchymal cells and eventually formed solid cell cords.

As mentioned by light microscopy, there was also a great variety in ultrastructure of the cellular components. For convenience of descriptions as to such variations, the hyperplastic cells constituting the tumor were classified into the following groups although there existed many intermediate forms in such a classification.

1) Fibroblast-like cell group (Group I cells)

The cells belonging to this group were basically identical in ultrastructure with so-called undifferentiated mesenchymal cells occasionally encountered in the adventitia of differentiating vessels as well as mature ones. They often existed sporadically (Fig. 1) or aggregatively around small vessels with a slit lumen (Fig. 2). In addition, aggregations mainly consisting of this cell group were seen apart from the vessels (Figs. 3, 4).

They generally developed rough endoplasmic cisternae distended by electron dense substance in the interior and possessed a few cytoplasmic projections. Some cells which seemed to represent the most primitive type of this cell group were rather round in profile and were characterized by paucity of the cytoplasm including little rough endoplasmic reticulum in comparison with the large nuclear profiles (Fig. 5). The neighbouring cells occasionally made the plasma membrane to membrane apposition in a limited area of each cell surface and was realized with simple attachment devices, but the greater part of their surface was surrounded by abundant collagenous fibrils (Fig. 4). The group I cells occasionally came into contact with cells of the other groups by focal attachment devices as shown in Fig. 6.

The most distinctive feature of this cell group was the presence of a considerable number of lipid droplets in the cytoplasm as indicated by Sudan III stained sections in the present light microscopy (Figs. 2-4). In some cells the cytoplasm was full of this inclusion of varying dimensions, having a close resemblance to lipoblastic cells (Figs. 3,4). The formation of cilium from diplosome was rarely seen exclusively in this cell group (Fig. 7).

2) Endotheloid cell group (Group II cells)

The cells classified into this group were characterized by lighter cytoplasmic appearance and less amount of rough endoplasmic cisternae than the group I cells. Furthermore, they were always in direct contact with like cells forming a slit lumen and conjugated with each other by many junctions like endothelial cells (Fig. 8). The existence of electron dense granules suggestive of Weibel-Palade bodies was the most reliable marker of this cell group. These features of the cells were quite the same as those found in so-called «endothelial buds» in fetal angiogeneses.

3) Pericyte-like cells (Group III cells)

The ultrastructure of this cell group was almost the same as that described as the principally neoplastic cells of hemangiopericytoma in the previous reports. The group III cells included irregularly arranged cytoplasmic filaments with focal condensations and fewer rough endoplasmic cisternae compared with the group I cells. Focal thickenings in electron density and abundant micropinocytotic vesicles of the plasma membrane, which was completely or partially enclosed by the basal lamina-like structure including a considerable amount of microfilaments, were evident also in our specimen. They were located at variable sites: Some cells appearing less-differentiated were associated with aggregations of the group II cells are shown in Figs. 8, 9, while others appearing well-differentiated existed in clumps of the group I cells but were almost completely separated from the group I cells by sheath of the basal lamina-like

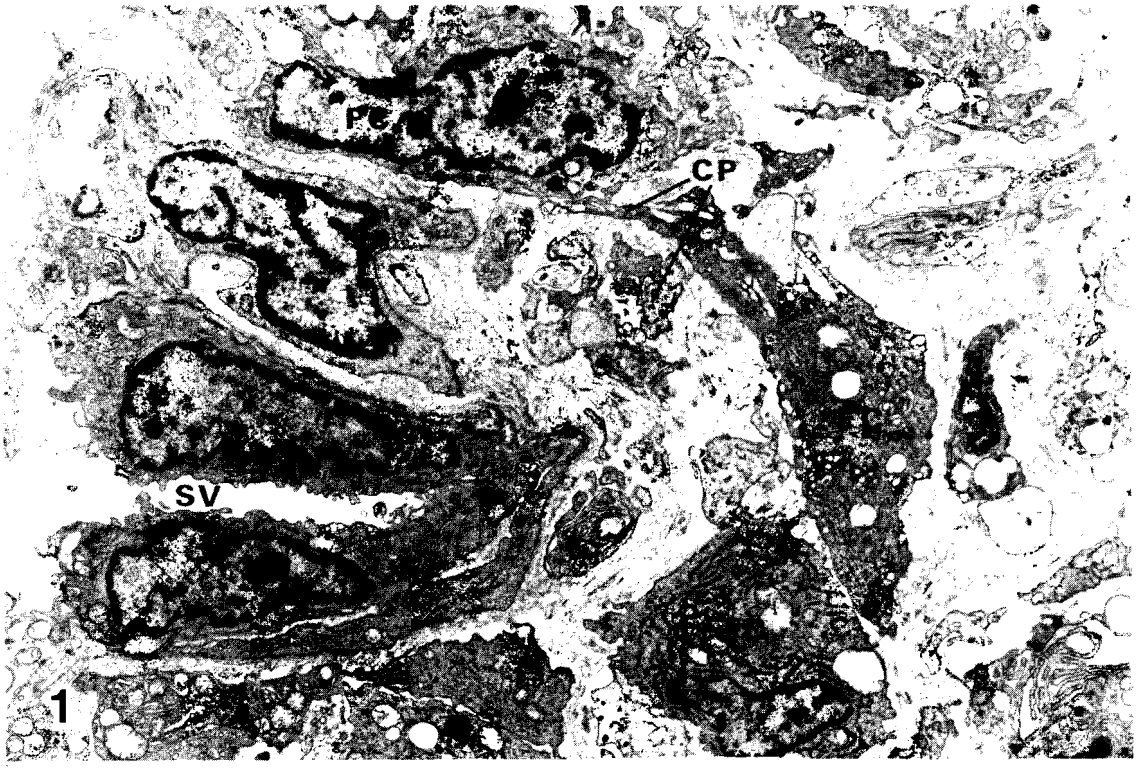

Fig. 1. Fibroblast-like (group I) cells (FC) are associated with a small vein (SV) in the tumor. The cells develop rough endoplasmic reticulum and possess abundant cytoplasmic projections (CP). × 5,000

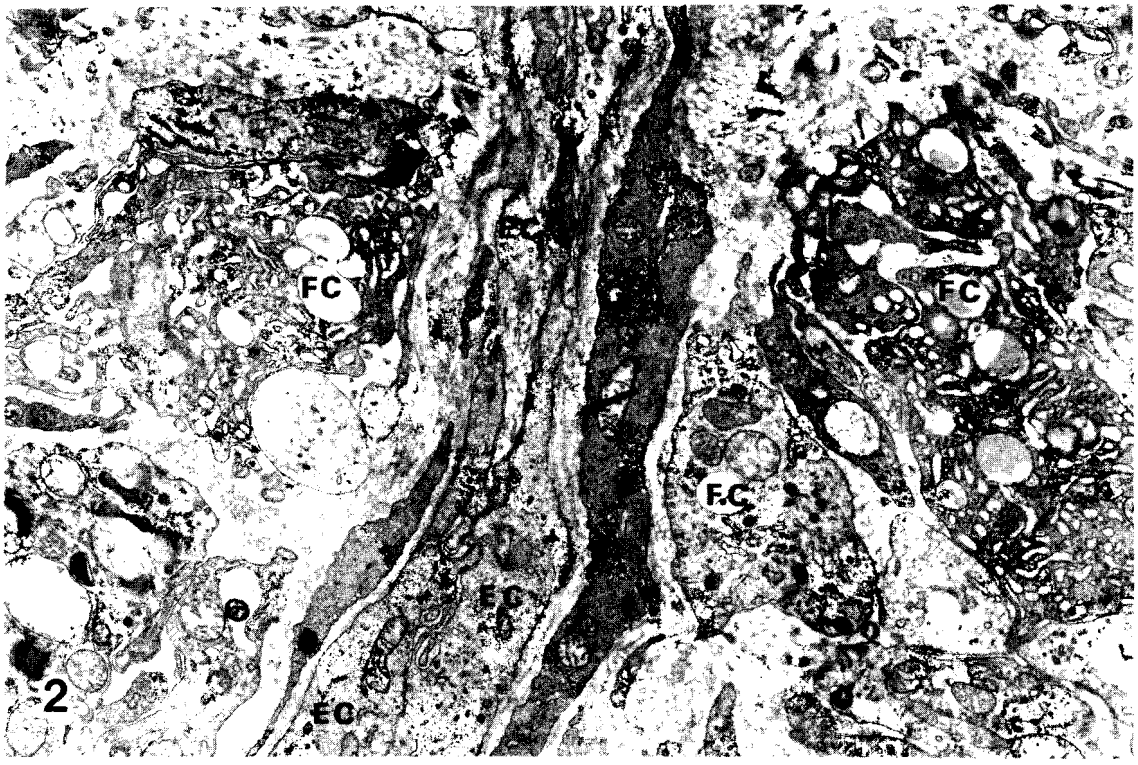

Fig. 2. A neoplastic vessel consisting of endotheloid (group II) cells (EC) is associated with well-differentiated pericyte-like (group III) (PC) and group I cells (FC). The vessel is surrounded by irregular, multilayered basal lamina-like structure (arrow). × 8,000

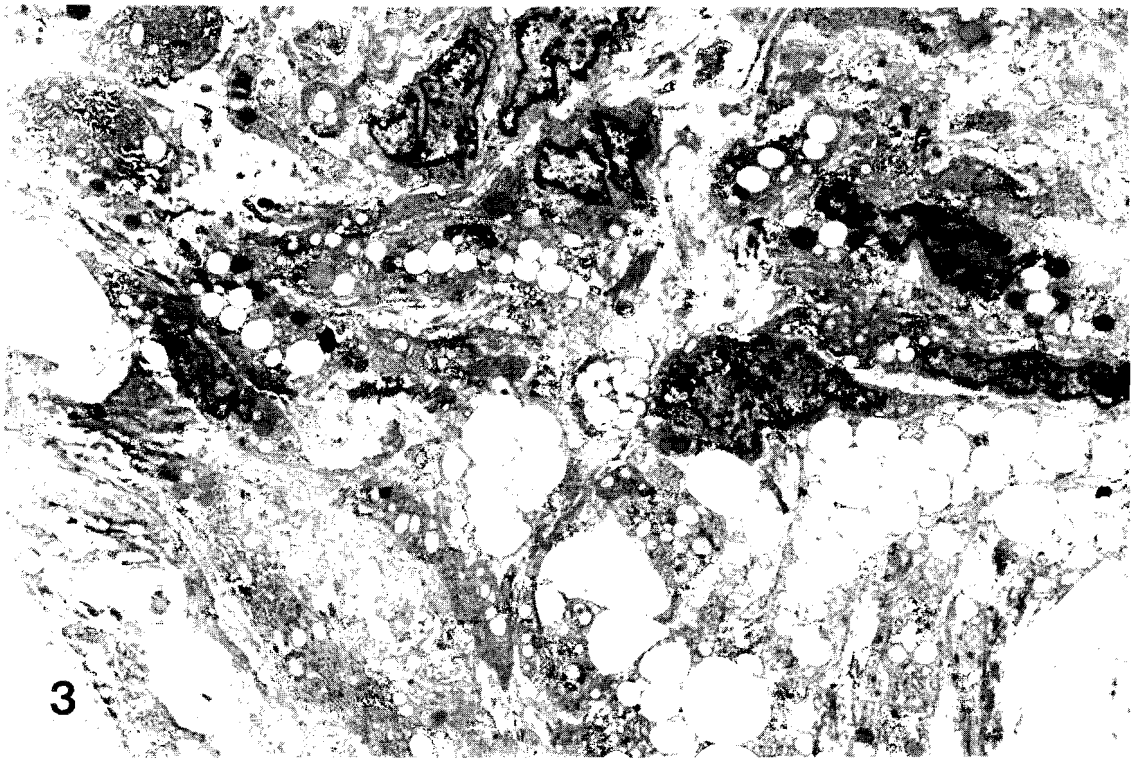

Fig. 3. Aggregated group I cells accumulate a considerable number of lipid droplets in their cytoplasm and produce abundant collagenous fibrils around their surface. × 3,000

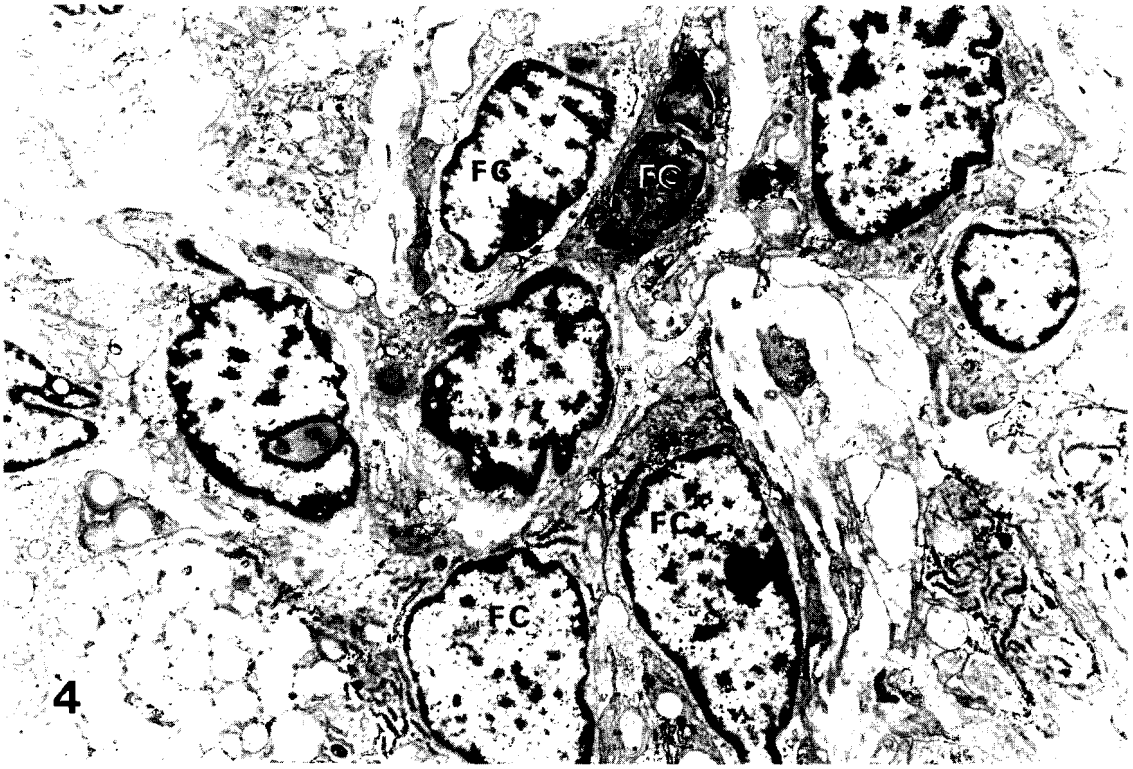

Fig. 4. In an aggregation of group I cells, the adjacent cells (FC) come into cell to cell contact in a limited area of each cell surface (arrows) but are surrounded by abundant collagenous fibrils in the other part of the cell surface. × 5,500

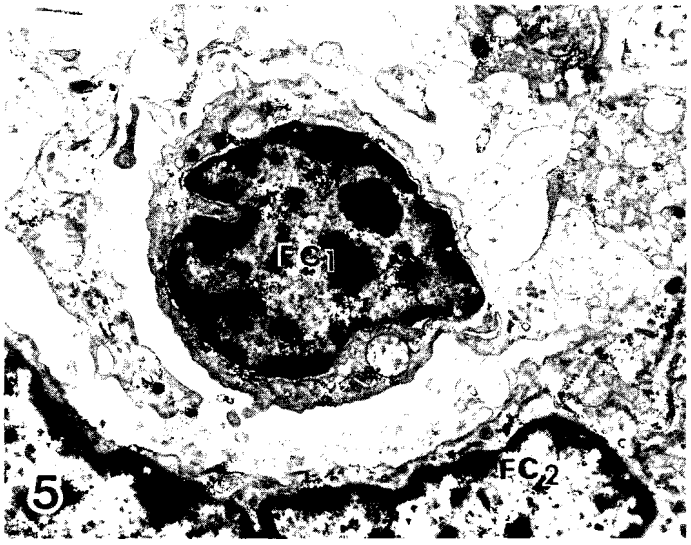

Fig. 5. A primitive group I cell (FC_1) possesses a large, chromatin-rich nucleus and the narrow cytoplasm containing little rough endoplasmic reticulum, while an adjacent, well-developed group I cell (FC_2) contains abundant rough endoplasmic reticulum. × 9,000

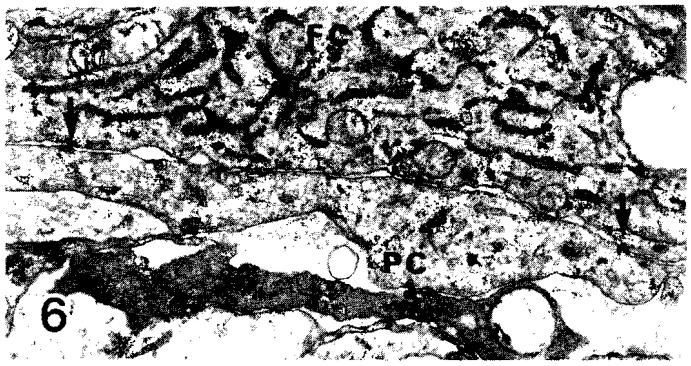

Fig. 6. A group I cell (FC) is in contact with an adjacent cell which appears to differentiate to a group III cell (PC) with simple attachment devices (arrows). × 13,000

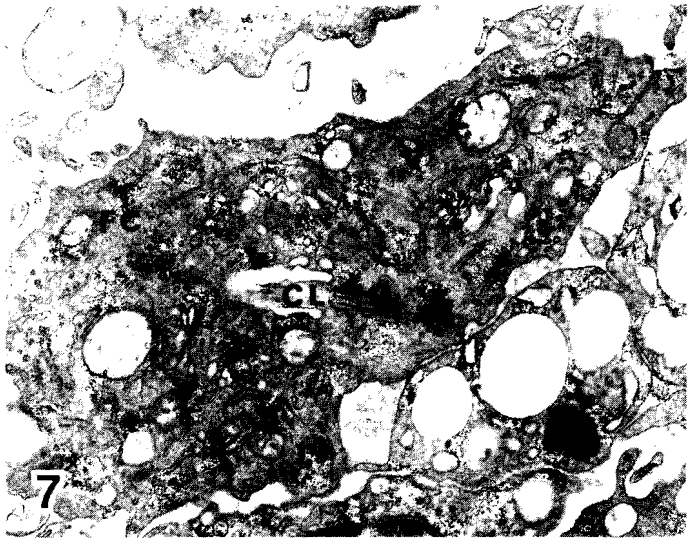

Fig. 7. A group I cell (FC) derives a cilium (CL). × 13,000

structure as shown in Fig. 10, or surrounded the vessels in the two or more cell layers in a similar manner to capillary pericytes as shown in Fig. 11.

4) Smooth muscle-like cell (Group IV cells)

These cells were found in the media of arteries and veins in this neoplasm. Although they retained many features of vascular smooth muscle cells, irregular arrangements of so-called dense patches (Fig. 12) and great variations in concentration of myofilaments were occasionally noticeable in these medial cells: Some cells were almost completely lacking in myofilaments and were occupied with developed rough endoplasmic reticulum (Fig. 13). Such altered muscle cells often contained lipid droplets and lacked the envelopment of the basal lamina in the greater part of the cell surface where adjacent ones were directly in contact with each other (Fig. 13). The extreme increase in number of Weibel-Palade bodies in the endothelial cells sometimes occurred in these vessels (Fig. 12). The group IV cells did not seem to be neoplastic judging from our electron micrographs as discussed later.

Discussion

In the present electron microscope survey of the hemangiopericytoma, there existed three groups of hyperplastic cells, namely the group I, II and III cells, which constituted variant patterns of growth from area to area in this neoplasm. The most numerous cells among these three groups, termed fibroblast-like (group I) cells in this article, were comparable in ultrastructure to so-called undifferentiated mesenchymal cells usually found in the adventitia of various vessels, especially of differentiating ones. The group I cells often aggregated around various kinds of vessels including capillaries with a slit lumen but some aggregations were also found apart from the vascular elements. The cells were partially or almost completely surrounded by extracellular fibrous elements such as collagenous fibrils and microfilaments like reticular fibres, possibly synthesized by their developed rough endoplasmic reticulum-Golgi system. The neighbouring cells occasionally made a direct contact with each other in a limited area with simple attachment devices and their cytoplasmic projections often made a honeycomb-like complex in these aggregations. Such a histological pattern is very similar to «histological type B» in the soft tissue hemangiopericytoma described by Battifora (1973) although he considered the predominant cells in this type to be less-differentiated pericytes (see Fig. 11 in his article).

The group I cells in our material seemed to possess the multipotentiality as vasoformative cells to differentiate not only to endotheloid (group II) but also to the pericyte-like (group III) cells since there existed many intermediate forms between the group I and II, or III cells. As shown in Figs. 8 and 9, both group II and III cells were often concomitant with the group I cells. A few group II cells were in a close apposition to each other,

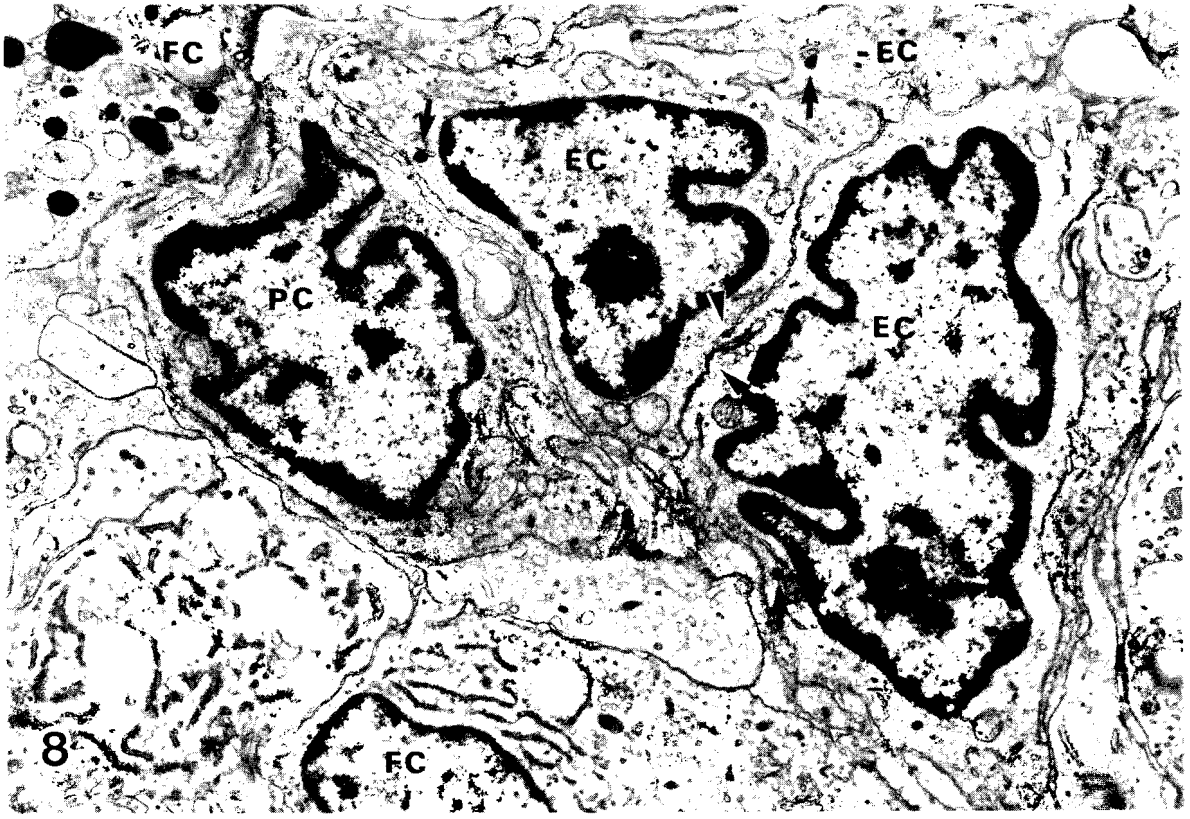

Fig. 8. Group II cells possessing electron dense granules suggestive of Weibel-Palade bodies (arrows) are closely apposed to each other with many junctions (arrowheads). A group III cell (PC) associated with the group II cells is enveloped by basal lamina-like structure which is contiguous to that of the group II cells. × 10,000

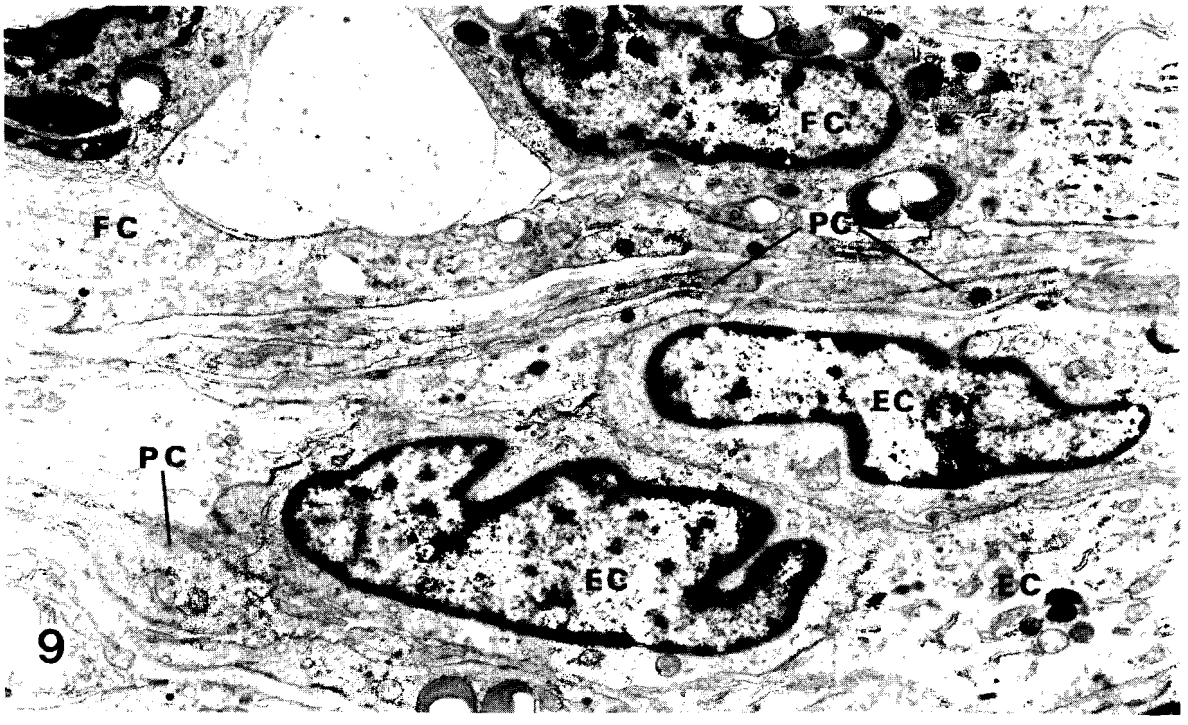

Fig. 9. A neoplastic vessel with a slit lumen consisting of group II cells (EC) is surrounded by group III (PC) and I (FC) cells. × 9,000

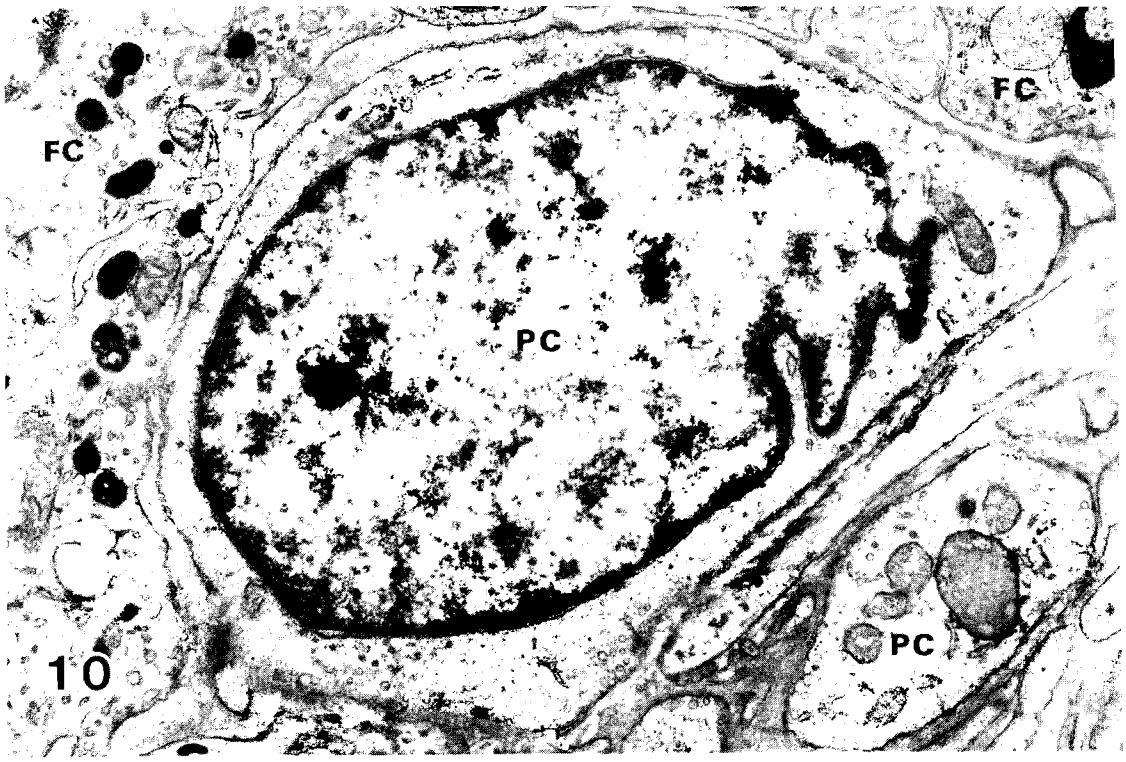

Fig. 10. Well-differentiated group III cells in an aggregation of group I cells (FC) are illustrated. The group III cells retain general features of pericyte, possessing a considerable number of cytoplasmic filaments and micropinocytotic vessels, and almost completely enclosed by the basal lamina-like structure. × 13,000

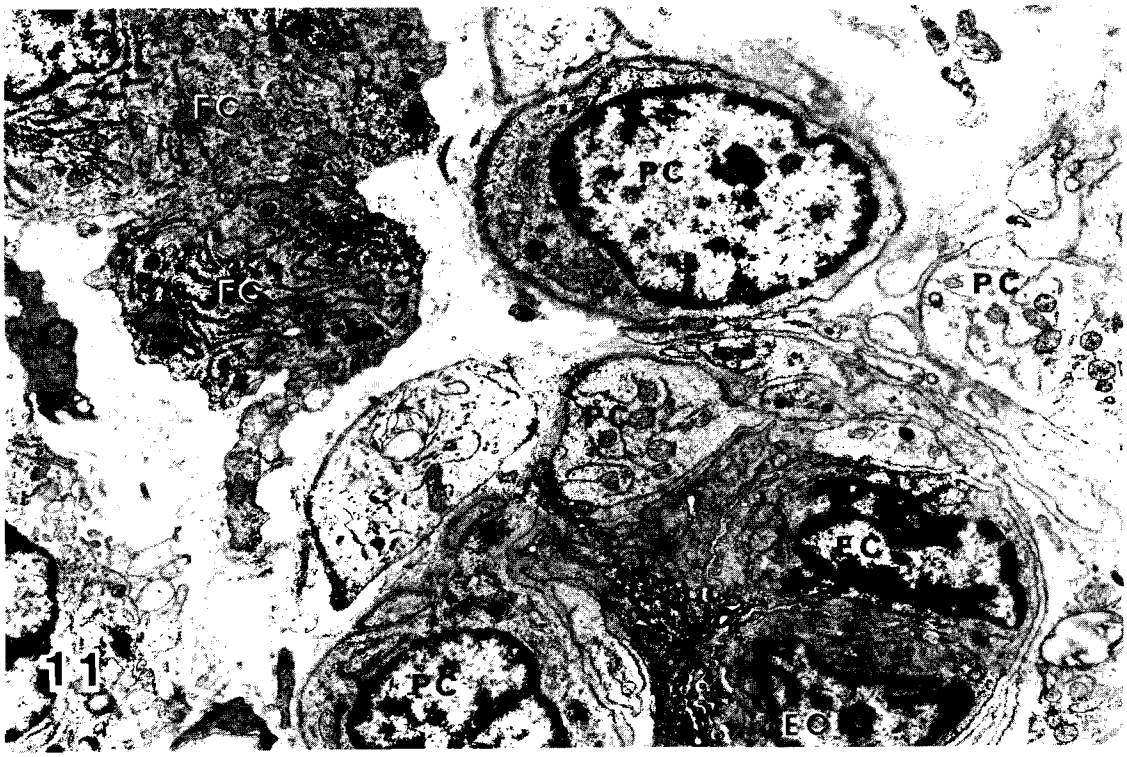

Fig. 11. A neoplastic vessel consisting of plump endothelial cells (EC) is surrounded by a few layers of well-differentiated group III cells (PC). The vessel is also associated with group I cells (FC). × 7,000

making a slit lumen at each apical portion, conjugated with adjacent cells by immature forms of junction like endothelia, and producing a basal lamina-like structure at each basal portion. Such features were basically identical to those of capillary tips in the fetal angiogeneses in our previous observations (Fujimoto et al., 1987; Maruyama et al., 1988).

The involvement of undifferentiated mesenchymal

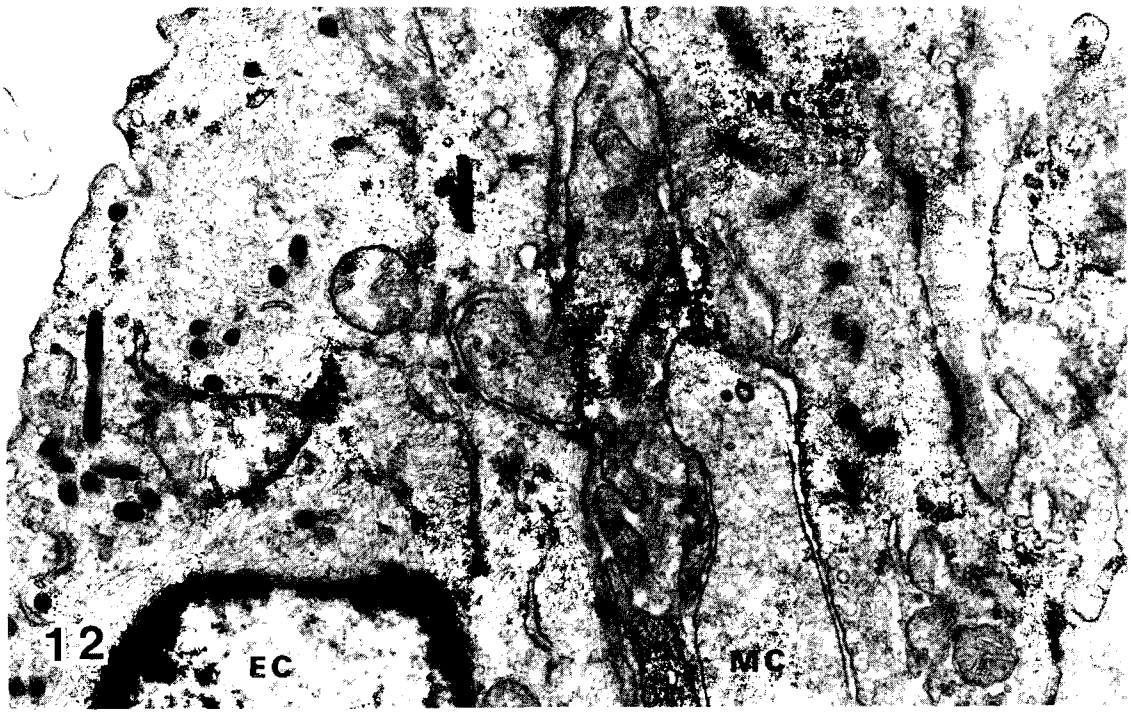

Fig. 12. Medial muscle cells (MC) of a vein decrease the number of myofilaments and are characterized by irregularly arranged dense patches. The endothelial cell (EC) increases the number of Weibel-Palade bodies. × 25,000

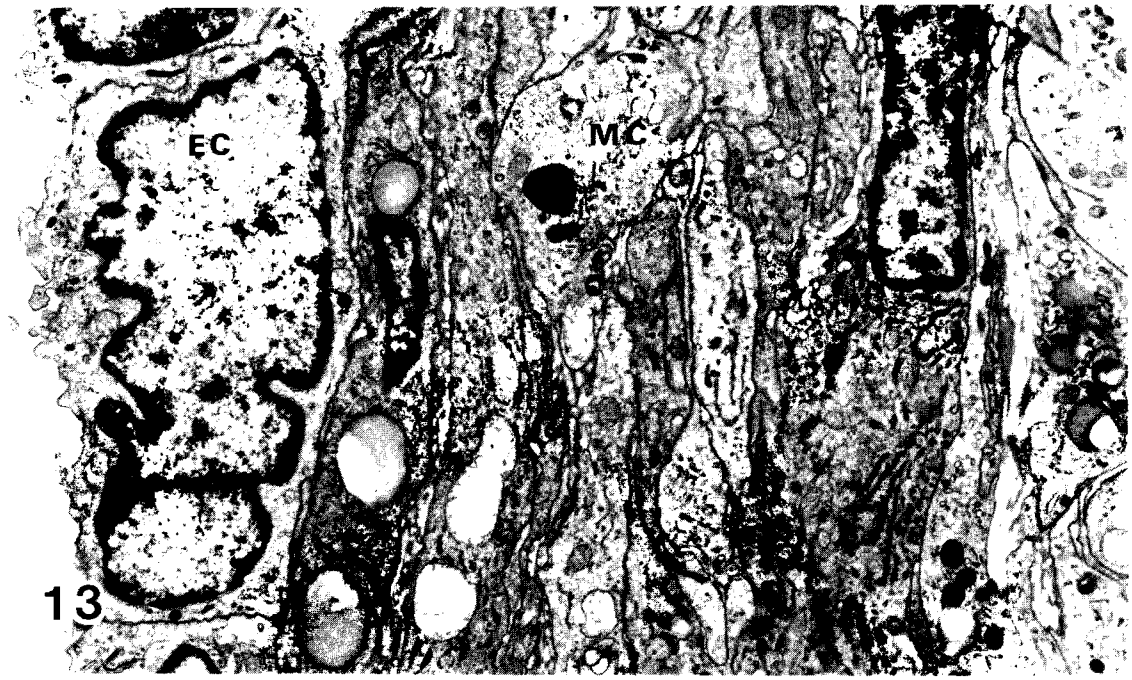

Fig. 13. The medial cells (MC) are almost completely lacking in myofilaments and contain lipid droplets. The cell to cell contact without intervening basal lamina is seen between the adjacent medial cells. Endothelial cells (EC) contain a considerable number of Weibel-Palade bodies. × 9,000

cells as vasoformative cells in a rapid neovascularization has been reported in several prenatal organs (Caley and Maxwell, 1970; González-Crussi, 1971; Fujimoto et al., 1987). Our latest study concerning the angiogenesis in the fetal rabbit dermis also reconfirmed the transformation of undifferentiated mesenchymal cells to vessel-forming cells in development of a capillary network in the dermis (Maruyama et al., 1988). Furthermore, Hammersen and his collaborators (1985) observed the incorporation of undifferentiated mesenchymal cells into capillary sprouts accelerating the growth rate in the tumor angiogenesis.

The group II cells suggestive of immature endothelial cells were characterized by lighter appearing cytoplasm, by decrease in number of rough endoplasmic cisternae, and by more smoothness of outline with an almost

complete loss of their cytoplasmic projections. However, the most reliable identification of their endothelial character was the existence of Weibel-Palade bodies in the cytoplasm as proposed by Carstens (1981). Cuevas et al. (1982) and Fujimoto et al. (1987) observed a considerable number of Weibel-Palade bodies in the neoendothelium. The appearance of Weibel-Palade bodies exclusively in the group II cells and their manner of aggregation like «endothelial buds» strongly suggested that an active neoplastic vascularization by the transformation of the group I to II cells happened in a certain developmental stage of the hemangiopericytoma as previously observed by Battifora (1973) and Pasyk et al. (1982).

We had no basic inconsistencies in our pericyte-like (group III) cells with capillary pericytes first described by Zimmerman (1923). However, the present electron microscopy revealed a wide variation in ultrastructure and distribution of this cell group. Apparent forms of transition between the group I and III cells were very common in our material as shown in Fig. 6. Such cells were still devoid of the continuous envelopment of the basal lamina-like structure around the cell surface but decrease of rough endoplasmic cisternae with inverse increase in number of cytoplasmic filaments and micropinocytotic vesicles were pronounced as in the case of capillary pericytes. The close apposition of the group III cells to the group II cell cluster is also frequent in our material as shown in Fig. 8. Such groups III cells appear to be less differentiated forms of pericytes and are partially surrounded by the basal lamina-like structure which was contiguous to that of the group II cells.

On the other hand, well-differentiated forms of the group III cells were completely surrounded by the basal lamina-like structure and uniformly distributed in the two or more cell layers alongside the endothelium with a wide lumen. The ultrastructural features of such well-differentiated pericyte-like cells surrounding the plump (possibly neoplastic) endothelial cells closely resembled those of epithelioid smooth muscle cells in the arteriovenous anastomoses (Fujimoto and Takeshige, 1975). A considerable number of cytoplasmic filaments similar in diameter to those of actin filaments with focal condensation, abundant micropinocytotic vesicles, and a complete sheath by the basal lamina-like structure in such well-differentiated pericyte-like cells may also imply the existence of apparent forms of transition between undifferentiated perivascular cells including pericytes and epithelioid smooth muscle cells as observed by Fujimoto and Takeshige (1975). In this sense, it seems possible to assume a histological transition as hybrid tumor between hemangiopericytoma and glomus tumor as mentioned by the previous workers (Murray and Stout, 1942; Fischer et al., 1952; Kuhn and Rosai, 1969).

The present electron microscopy indicated that the group I cells were a kind of vasoformative cell which had a capability of differentiation for either group II or III cell. Their active mitotic proliferation during the earlier stages of the tumor growth seemed to be likely judging from their occasional derivations of cilium from the diplosome as previously discussed by Yamamoto and Fujimoto (1980). If it may be correct to consider abnormally proliferated group I cells to be the principal cell of origin in soft tissue hemangiopericytomas, the extreme accumulation of lipid droplets in such cells seems to be one of early morphological signs of their neoplastic character.

The present hemangiopericytoma were composed of almost all cellular elements found in embryonic developments of the vascular bed. As cited by von Albertini (1955), the cell-rich vascular tumors such as hemangioendothelioma and hemangiopericytoma may not represent distinct entities, frequently showing the transformation of one type to another and the concomitance with more than one type in the same tumor and, thus, morphological characteristics of hemangiopericytoma may become greatly varied by whether predominently hyperplastic cellular components are fibroblastic, endothelial or pericytic in nature. In this sense, the terms «angioplastic reticuloma» by von Albertini (1955) and «cellular hemangioma» by Pasyk et al. (1982) should be re-evaluated in morphological analyses of these vascular tumors.

The group IV cells seemed to be neither neoplastic nor originated from the other cell groups. Conversely, the decrease or loss of myofilaments and the cell to cell contact with a loss of the intervening basal lamina may imply a simple reaction of the medial muscle cells of the arteries and veins to the neoplastic proliferation of the surrounding adventitial cells, although we did not prove these altered muscle cells to be «de-differentiating».

Acknowledgements. The authors wish to express their thanks to the late Prof. Kazukata Nishio, Department of Dermatology, for his giving an opportunity to this work. They thank Miss Toyono Nobukuni, Department of Anatomy, for her secretarial assistance.

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Accepted August 18, 1988