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Pathogenesis of the so-called cystic adventitial degeneration of peripheral blood vessels

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Summary. Eleven cases of cystic adventitial degeneration of peripheral blood vessels were examined by light and (in three instances) by electron microscopy. Eight cases were in arteries, three were detected in veins. In six cases a cellular lining of the cysts was observed. Ultrastructurally the lining cells resembled synovial mesothelial cells. In three cases a pedicle connection was detected between the adventitial cysts and an adjacent joint. In one case such a pedicle could be followed to its junction with the knee joint capsule and was also lined by synovial mesothelium. These findings indicate that the so-called cystic adventitial degeneration is not a primary dysplasia of the blood vessel wall but originates from ectopic tissue of a joint capsule or bursa.

Key words. Cystic adventitial degeneration of blood vessels – Pedicled joint ganglia – Synovial mesothelium in cysts – Joint ganglia imitating vascular dysplasia

The aetiology and pathogenesis of cystic adventitial degeneration of peripheral blood vessels is still uncertain. In an earlier publication we agreed with Rüppell et al. (1971) that the cysts probably correspond to ganglia of adjacent joints (Leu 1977). In a recent publication based on ultrastructural findings, Ulrich et al. (1983) suggest that the disease might belong in the group of primary dysplasias of the media. The present investigation demonstrates that light microscopic, electron microscopic and surgical findings in eleven cases are in agreement with the opinion of Rüppel et al. (1971).

Material and methods

The surgical specimens were obtained from the surgical clinic B, division of peripheral vascular surgery (head: Prof. Dr. U. Brunner), University of Zürich.

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Table 1

	Histology number	Age	Sex	Localization	Cellular lining	Pedicle
1)	20841/75	32	M	popliteal a.	+	–
2)	18299/76	58	F	popliteal a.	+	+ to knee joint
3)	14444/76	62	F	popliteal a.	+	–
4)	3395/79	53	M	popliteal a.	–	–
5)	6199/83	27	M	popliteal a.	–	–
6)	29088/83	32	M	popliteal a.	–	–
7)	22659/83	49	F	popliteal a.	+	+ to knee joint
8)	11898/75	64	M	common fem. a.	+	–
9)	5576/67	29	F	forearm vein	–	–
10)	2362/78	43	M	iliac vein	+	+ to coxa
11)	3860/84	21	M	forearm vein	–	–

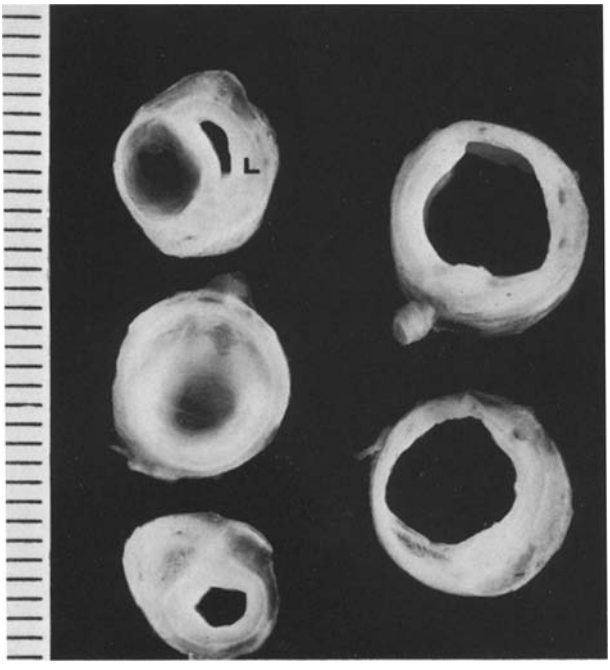

Fig. 1. Gross anatomy: cross section through an artery with large adventitial cysts and compression of the arterial lumen (*L*). Popliteal artery, case 5

Examination by the light microscope and in three cases by transmission electron microscopy, was carried out on the cysts, the surrounding tissue and if possible the arterial wall, if the entire arterial segment had to be removed. Haemalaun-Eosin, van Gieson, Alcian-Blue, Periodic Acid Schiff and Elastin stains were used for light microscope examinations. The material for transmission electron microscope examination was fixed immediately after removal in phosphate-buffered glutaraldehyde solution and embedded in Epon 812. The sections were stained with uranyl acetate and lead citrate and examined with a Philips EM 201.

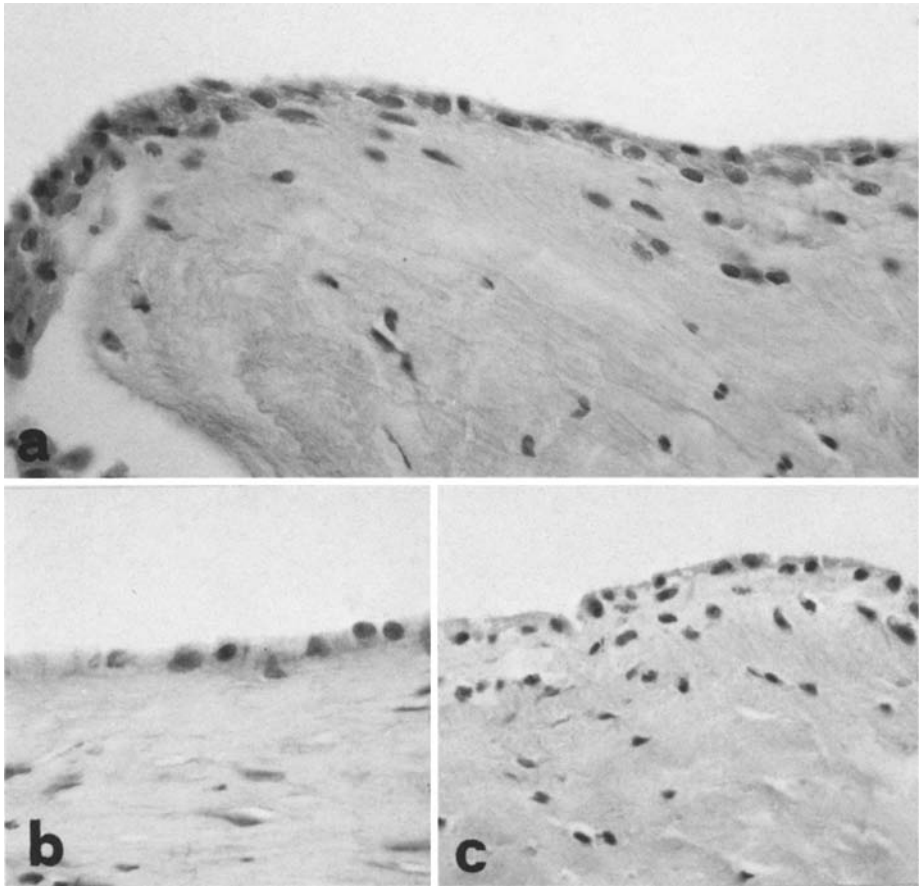

Fig. 2a–c. Cellular interrupted lining of adventitial cysts. **a** HZ 14 444/76, case 3. Haemalaun-Eosin, ×300; **b** HZ 18 299/76, case 2. Haemalaun-Eosin, ×300; **c** HZ 14 444/76, case 3. Haemalaun-Eosin, ×300

Factor-VIII-associated protein was identified immunohistochemically with a modified peroxidase-antiperoxidase (PAP) method of Sternberger et al. (1970), using both Ortho and Biogenex histosets. Examination for keratin was performed by a modified PAP-method of Sternberger et al. (1970) with polyclonal rabbit anti-human keratin antibodies (Dako) without and after unmasking of antigens by trypsin digestion.

Results

As seen from the table, our material consists of 11 cases with a mean age of 42.6 years, namely 7 men (mean age 39 years) and 4 women (mean age 49 years).

Case history and radiological findings of the 8 cases concerning arteries were typical (intermittent claudication and ischaemic symptoms in otherwise healthy, mostly young subjects, halfmoon-shaped stenosis of the artery without arteriographical signs of arteriosclerosis). The three cases concerning

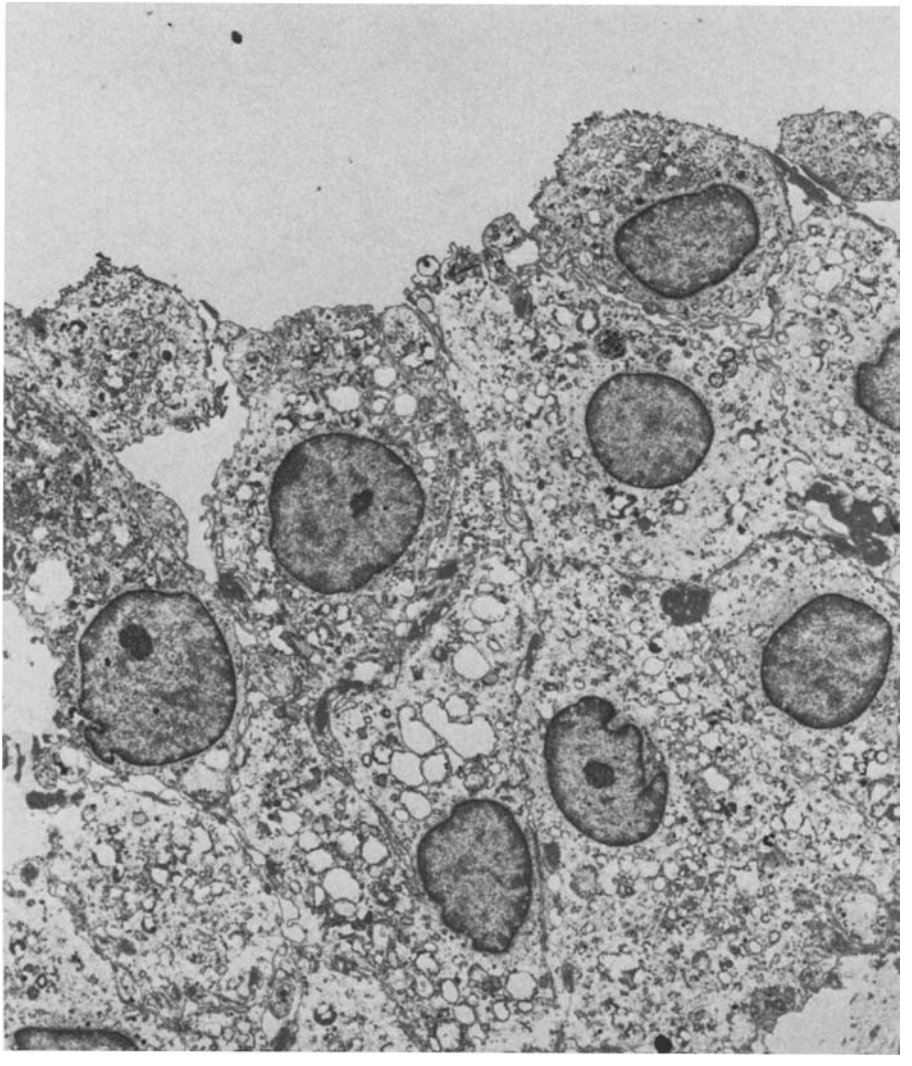

Fig. 3. Several cell layers lining an adventitial cyst. Large round nuclei with marginated chromatin, numerous vacuoles and inclusions of mucinous fluid. HZ 22 659/83, case 7. Neg. 3868/83. Phosphate-buffered glutaraldehyde, × 3,600

veins were unexpected findings in biopsy specimens which were sent in under the diagnosis of "tumours in connection with venous vessels".

Seven cases concerned the popliteal artery and one case the common femoral artery at the level of the coxa. Three cases were observed in veins: one in the iliac vein and two in superficial veins on the outside of the forearm near the radio-carpal joint. In three cases the surgeon detected a pedicle originating in the cystic area and leading toward an adjacent joint (twice to the knee joint, once to the coxa). In one case this pedicle could be followed to its connection with the knee joint capsule.

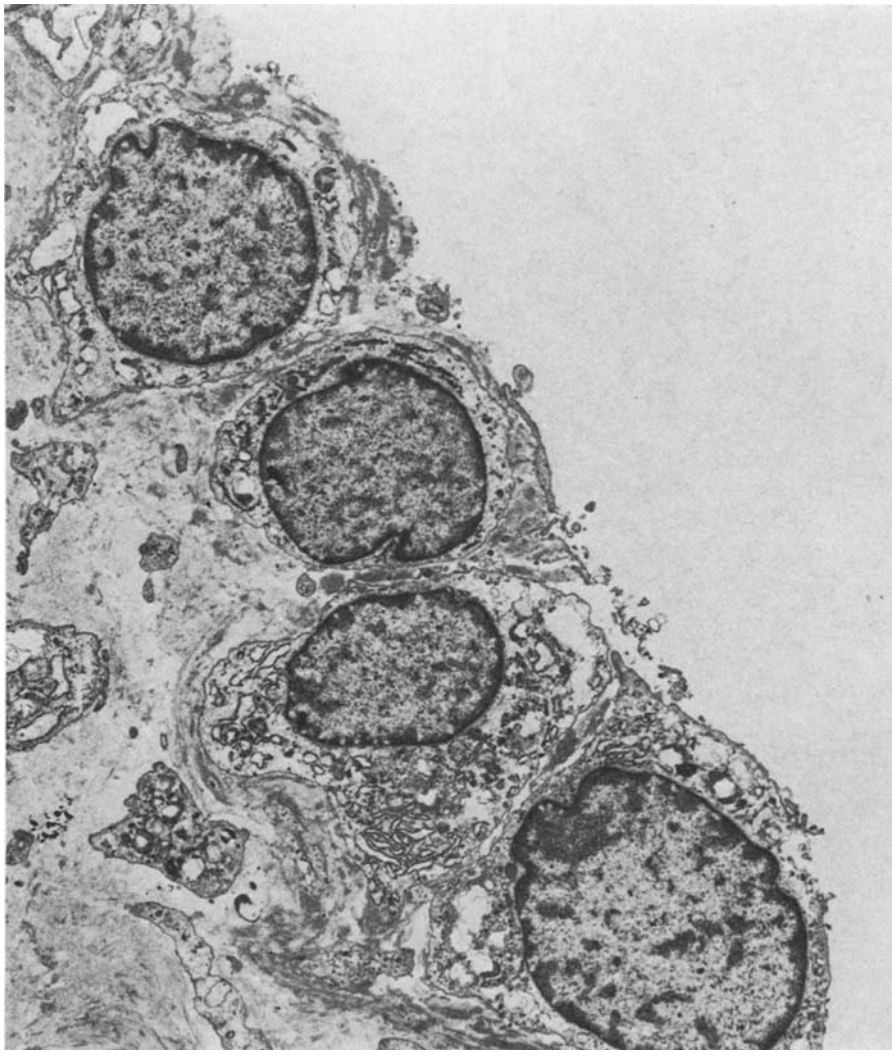

Fig. 4. Singular cell lining of an adventitial cyst. Large nuclei with marginated chromatin. Cells in loose connection. HZ 22 659/83, case 7. Neg. 3863/83. Phosphate-buffered glutaraldehyde, × 5,300

Light and electron microscopic findings

In all eleven cases the cystic alterations were situated within the adventitial layer clearly separated from the medial musculature. Alterations typical for a primary dysplasia of the media (such as cystic degeneration, focal necrosis of collagenous or muscular fibers, destruction of elastic fibers) were neither observed in the media adjacent to the adventitial cysts nor in more distal segments of the arterial wall. The media was built up of well-preserved smooth muscle cells of the k-type (contractile myocytes) with a moderate

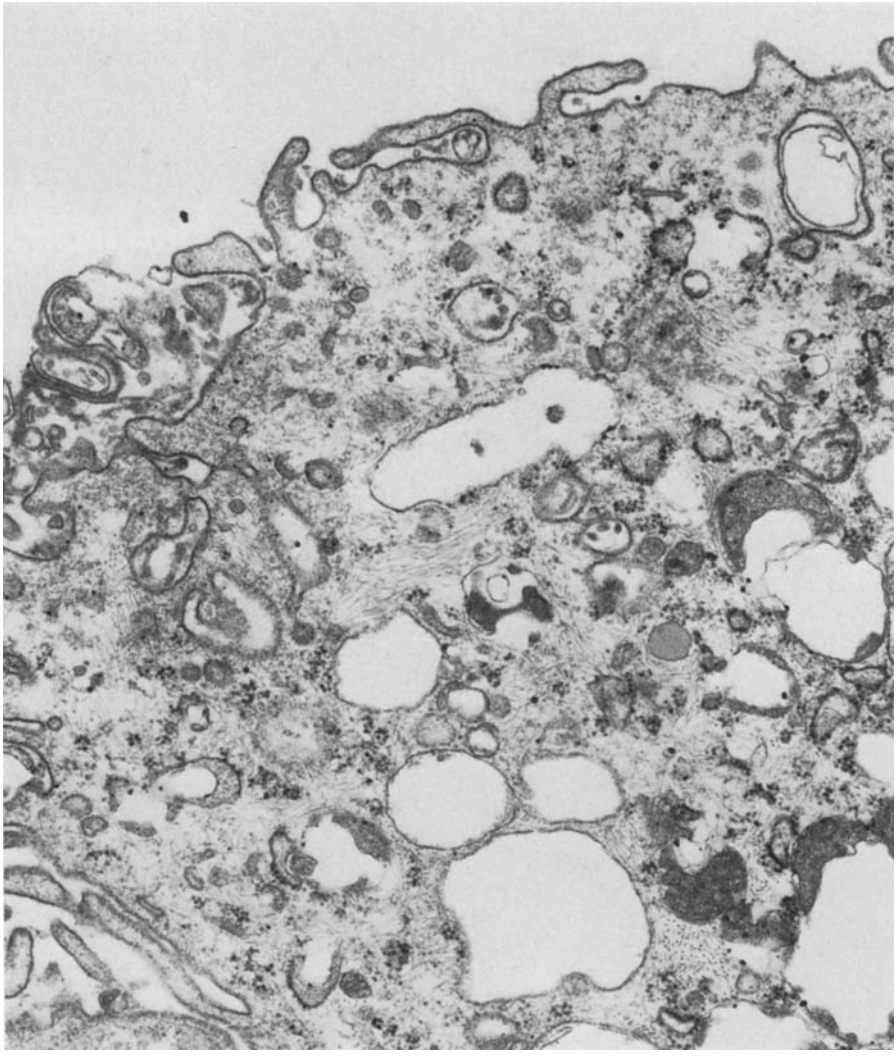

Fig. 5. Cell lining of an adventitial cyst. Cytoplasmatic pseudopodia and villi on the luminal surface. Vacuoles, coated vesicles and tonofilaments within the cytoplasm. HZ 22 659/83, case 7. Neg. 3919/84. Phosphate-buffered glutaraldehyde, × 27,300

amount of cytoplasmic organelles on both nuclear poles including a small Golgi apparatus, filamentous mitochondria, free ribosomes and a few small cisternae of rough-surfaced endoplasmatic reticulum. Abundance of myofilaments with dense areas and attachment points, micropinocytotic vesicles along the cell membrane and a broad and floccular basement membrane were always present. Interdigitations of myocytes were frequently seen. No accumulations of myocytes with increased numbers of cytoplasmic organelles suggesting an activation of the cell (Feigl et al. 1976; Riede and Staubesand 1977) were observed. Occasionally some cytolytic alterations such as

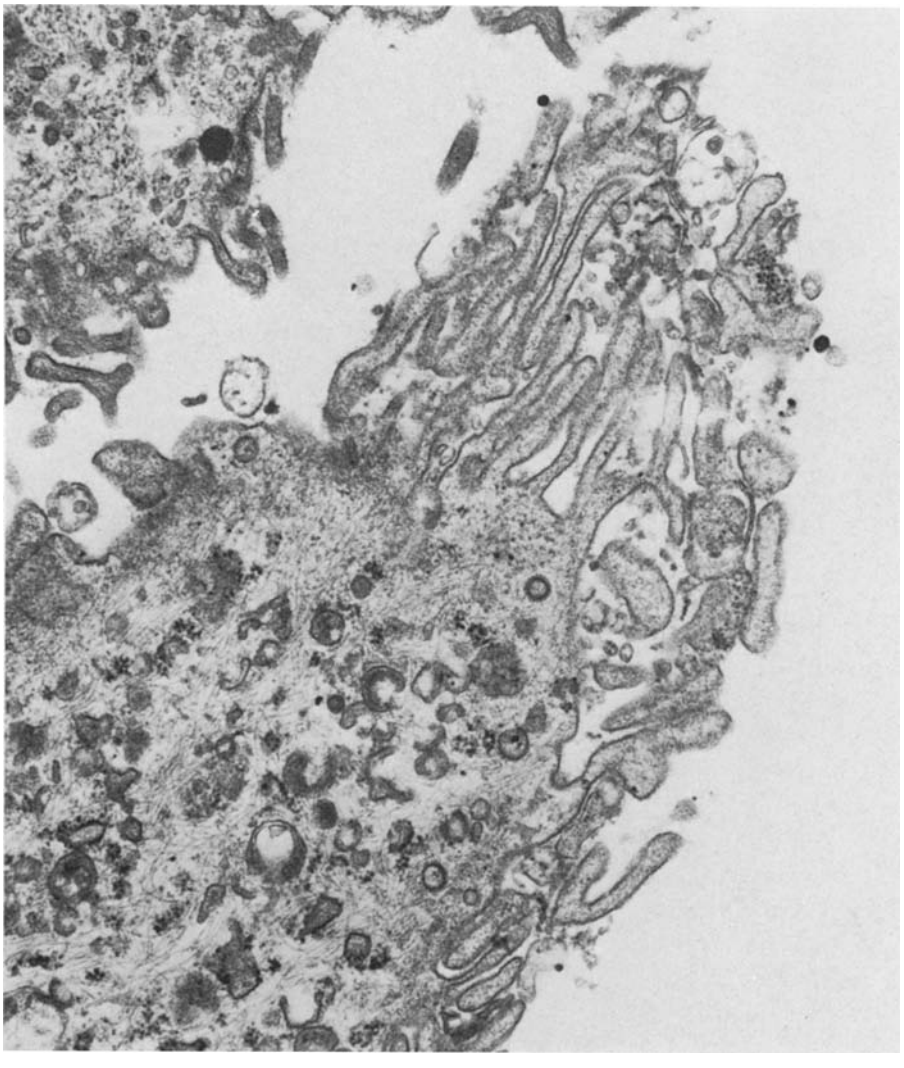

Fig. 6. Luminal surface of a mesothelial cell. Cytoplasmatic pseudopodia and villi, lysosomes and tonofilaments in the cytoplasm. No Weibel-Palade bodies present. HZ 22 659/83, case 7. Neg. 3914/84. Phosphate-buffered glutaraldehyde, ×27,300

vacuoles, swelling of mitochondria and dilatation of rough-surfaced endoplasmatic reticulum occurred. Occasional fibroblasts and collagen fibers of regular arrangement were lying between the smooth muscle cells. Necrosis of entire cells or nuclei was not detected. Mucin forming cells were lacking. The cysts were often multiple or multi-chambered. Their wall consisted of collagen without smooth musculature. The lumen of the cysts was filled by mucinous, alcian-blue-positive fluid. The interior surface of the cyst wall was either without a cellular lining or (in 6 out of 11 cases) partly covered by one or several layers of cuboidal cells with round nuclei (Fig. 2). Ultra-

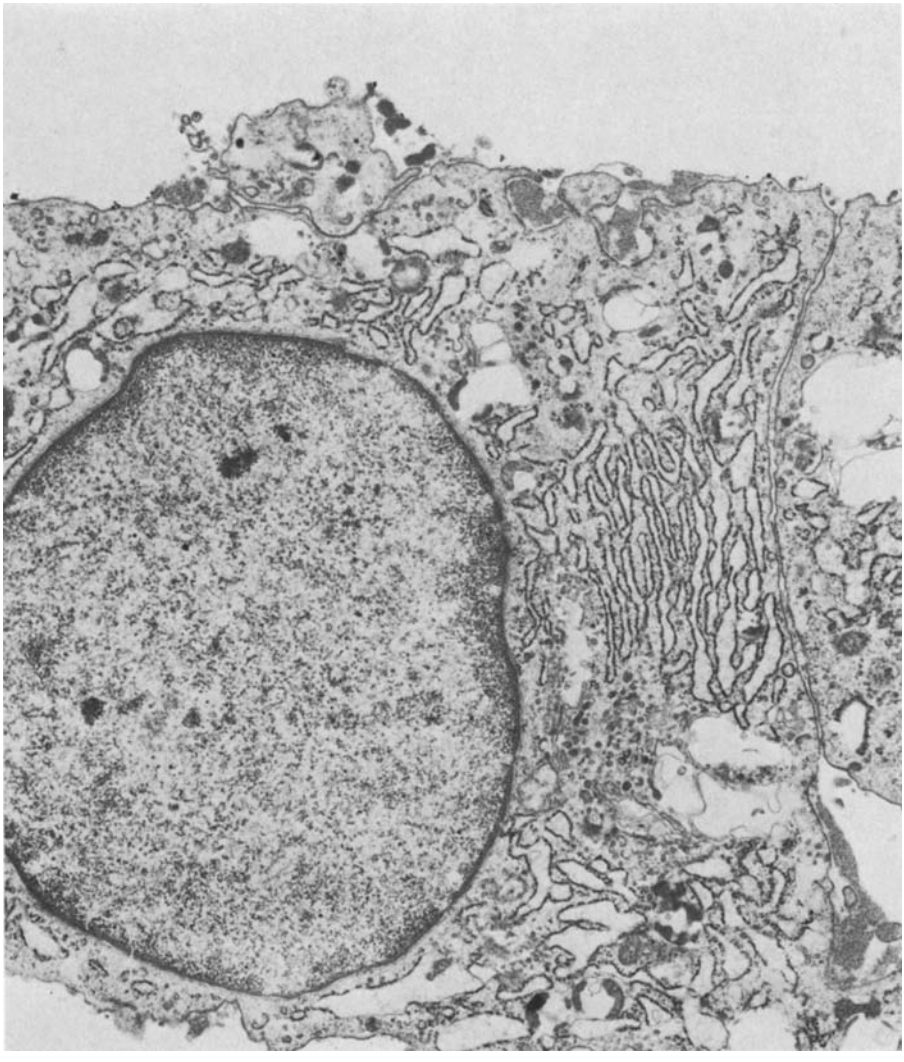

Fig. 7. Mesothelial cell resembling an F-cell (Fibroblast-like cell). Large round nucleus with dispersed chromatin. Numerous large Golgi lamellae and rough-surfaced endoplasmatic reticulum within the cytoplasm. No basement membrane. HZ 22 659/83, case 7. Neg. 3907/84. Phosphate-buffered glutaraldehyde, ×11,900

structurally these mesothelium-like cells were in loose connection with each other. They possessed large nuclei with either marginated or dispersed chromatin. Their luminal surface contained cytoplasmatic pseudopodia and villi. A basement membrane was not present. The cytoplasm contained numerous vacuoles, some lysosomes, coated vesicles and inclusions of muciform material. Most of the cells contained also large Golgi lamellae, some tonofilaments and a marked amount of rough-surfaced endoplasmatic reticulum. Micropinocytotic vesicles were rare. No Weibel-Palade bodies could be de-

tected. The pedicle had a tubular wall of collagen fibers. The interior surface of its wall was also partly covered by the same cell types as the cysts, strongly resembling synovial cells (Fig. 3–7).

The immunohistochemical examinations did not help in identifying the nature of the lining cells. No factor VIII could be detected, permiting the exclusion of an endothelial nature for the cellular lining. The examinations for keratin were likewise negative, excluding an epidermal origin. As far as we know a specific reaction for identifying synovial cells does not yet exist.

Discussion

Cystic degenerative alterations in the medial musculature of the aorta and other elastic arteries (Medionecrosis of Erdheim and Gsell) and also in muscular arteries (Doerr 1970) are well known. Similar lesions occur in experimental lathyrism (Doerr 1963; Hass 1963). They develop from vacuolar degeneration of smooth muscle cells (Doerr 1970) and contain alcian-blue-positive mucinous substances. Such lesions may be the cause of dissecting aneurysms (Hass 1963; Jülke 1984). They may occur anywhere in the arterial wall and are not accompanied by adventitial cysts. They do not possess a synovia-like lining or pedicles in direction of an adjacent joint. Furthermore the mucinous masses do not accumulate in large cysts with mechanical compression of the vascular lumen.

Cystic adventitial degeneration of arteries was first described by Atkins and Key (1947) and later received its name by Hiertonn and Lindberg (1957). Further cases have been described by Jaquet and Meyer-Burgdorff (1960); Meyer-Burgdorff (1961); Vollmar (1963); Haid et al. (1970); Powis et al. (1970); Sperling et al. (1972). The aetiology and pathogenesis have been widely discussed. The possible role of microtraumatic influences leading to haemorrhages has been emphasized by Meyer-Burgdorff (1961); Hiertonn and Lindberg (1957); Vollmar (1963); Sperling et al. (1972); Schramek and Hashmonai (1973). This is an unlikely explanation, however, as the disease is not more frequent in athletes and in heavy manual labourers (Powis et al. 1970; Haid et al. 1970) and may occur also in children (Silver 1983).

Slits and clefts of various origin are not uncommon within the connective tissue. They may be lined by interrupted cell layers. These cells, however, are spindle-shaped fibroblasts without any of the characteristics of synovial cells. Many of those slits are fixation artefacts. Cleftlike lymph channels can easily be distinguished from them by their uninterrupted endothelial lining. Neither of them possess pedicle connections with adjacent joints.

More convincing is the theory of Rüppell et al. (1971) who postulated a relationship to para-articular ganglia. Ganglia are due to dysontogenetic hyperplasia of persisting rests of scleroblastema and may develop synovial lining (Doerr 1974). The somewhat vague term of Baker's cysts is often used for any cystic formation within the popliteal groove, but should be reserved for cysts originating from a bursa (Fassbender 1975). Both ganglia

as well as cysts originating from a bursa may communicate with joints (Fassbender 1975) or with tendon sheaths, and their histology is identical. Both consist of a dense wall of collagen fibers with an interior interrupted lining of synovia-like cells of cuboid shape which produce a muciform fluid containing hyaluronic acid (Doerr 1974; Fassbender 1975). Their histological structure corresponds to that of the joint capsule (Bucher 1973). Watanabe et al. (1974) distinguished two types of synovia cells, the so-called M-cells (macrophage-like) and F-cells (fibroblast-like). According to these authors these cells are derived from mesenchymal cells and are responsible for production and resorption of synovial fluid.

In our cases the majority of the cysts possess an interrupted lining by one to several layers of cuboid cells which are clearly distinct from endothelial cells but resemble the synovial lining of joints. Ultrastructurally they do not contain any of the characteristics of endothelial cells (basement membranes, Weibel-Palade bodies, large amounts of micropinocytotic vesicles). They are similar, however, to the synovial cells described by Watanabe et al. (1974). They possess characteristics of both M-cells and F-cells. The nuclei either contain marginated (like in M-cells) or dispersed (like in F-cells) chromatin. In the cytoplasm numerous vacuoles, coated vesicles and inclusions of filamentous mucinous masses indicate M-cells, but usually there are also large Golgi lamellae, rough-surfaced endoplasmatic reticulum and tonofilaments which are characteristic for F-cells. This insufficient differentiation into the two cell types may be explained by their rudimentary function which cannot be compared with that of the cells lining a healthy joint.

The immunohistochemical examinations excluded an endothelial or an epidermal nature of the lining cells.

The cysts are always localized exclusively within the adventitia. We never observed the spreading of cystic alterations into the media. Examination of the media by light and in three cases also by electron microscopy revealed no lesions which might be interpreted as a primary dysplasia of the media. The observation of cytolytic alterations (vacuoles, degeneration of mitochondria, dilatation of the endoplasmatic reticulum) by Ulrich et al. (1983) might be due to artefacts which commonly occur within minutes after surgical removal of the specimens if the latter are not immediately fixed in glutaraldehyde. This phenomenon has been demonstrated by Staubesand et al. (1983) in animal experiments.

An accumulation of so-called modified or activated smooth muscle cells (Feigl et al. 1976; Riede and Staubesand 1977) was not observed. Even if such alterations were found, this would not necessarily indicate a primary dysplasia of the media as this non-specific alteration occurs in a variety of disorders and even in reactive muscular hyperplasia. The surgical experience also indicates that the cysts do not affect the muscular media, otherwise a local excavation, as is frequently performed, would risk rupture of the vessel wall. Such a complication, however, has never been reported. After insufficient surgical removal, the adventitial cysts tend to develop recurrences (Brunner and Soyka 1977; Burleson et al. 1956). This is also a well-known characteristic of ganglia.

The cysts contain large amounts of mucinous, alcian-blue-positive fluid.

It resembles the product of the synovial cells which is rich in hyaluronic acid (Bucher 1973). In case of an open communication between the cysts and an adjacent joint, the amount of fluid in the cysts may vary and cause an intermittent compression of the artery (Bollinger and Pouliadis 1977). This explains the frequently intermittent symptomatology. Cystic alterations in primary dysplasia of the media (Erdheim-Gsell's medionecrosis) or in mucoid degeneration of the aorta (Leu et al. 1978) do not contain comparable amounts of muciform fluid.

Cystic adventitial degeneration is localized exclusively in segments of arteries and occasionally also of veins (Mentha 1963; Leu 1977) which are adjacent to a joint. Pedicle connections between the cysts and a joint have been described before (Parkes 1961; Shute and Rothnie 1973; Brunner and Soyka 1977; Ohta et al. 1983). In one of our cases, such a pedicle could be followed from the cysts into the knee joint (Largiadèr and Leu 1984). Histology including electron microscopy of the pedicle showed a cellular lining analogous to that in the cysts.

By the term "cystic adventitial degeneration" we understand a clinicopathological entity which comprises large adventitial cysts, usually adjacent to a joint area, with half-moon-shaped compression of the vessel lumen. In arteries this compression causes ischaemic symptoms. We believe this entity to be caused by a ganglion or bursa-like ectopic tissue originating from scleroblastema which is responsible for the formation of joint capsules and bursae. The term does not include other microcystic degenerations as they may occur anywhere within the media of elastic and muscular arteries and which may possibly affect the adjacent adventitia. Such cystic or mucoid degeneration of the media may be the cause of dissecting or non-dissecting aneurysms.

Cystic adventitial degeneration is probably congenital. The growth of the cysts in later life is due to the slow accumulation of muciform fluid produced by the synovial-like mesothelial lining cells. Pedicles are not always found. In case of a persisting open connection with a joint, the amount of fluid in the cysts may vary and cause intermittent ischaemic symptoms by increasing and decreasing compression of the arterial lumen. If such a pedicle exists it must be followed and ligated at the level of the joint capsule in order to prevent recurrences.

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