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Granular Changes in Vascular Leiomyosarcoma

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Summary. A 78-year-old male presented a tumor mass in the left arm which was surgically excised. Part of the tumor, when examined by light microscopy, showed the characteristic cytological features of a leiomyosarcoma. Other areas of neoplasm comprised layers of tumoral spindle-cells surrounding abnormal blood vessels. Nests of similar neoplastic cells were observed in the intima and media of these blood vessels. Wide areas of neoformation were made up by interlacing bundles of acidophilic polyedral cells with large irregular nucleus. Mitoses were frequent. The cytoplasm contained a great number of granules intensely PAS stained with and without prior diastase digestion. Electron microscopic examination revealed that the granular cells possessed a continuous basal lamina, numerous pinocytotic vesicles and abundant 80–150 Å microfilament bundles. Within the microfilament bundles, as well as apposed to the plasma membrane, electrondense bodies were often found. Granules contained degenerated organelles and probably corresponded to digestive vacuoles. In the intercellular spaces, fibrous long-spacing collagen was seen. The transition zone between the leiomyosarcoma cells and the granular cells showed intermediate cell types, with few granules and abundant microfilaments. The origin of granular cells from smooth muscle cells of blood vessels is discussed.

Key words: Granular cells – Leiomyosarcoma – Smooth muscle cells.

Since the original description in 1926 by Abrikossoff of the granular cell tumor (granular cell myoblastoma) as a distinct entity, identical or very similar lesions have been described in tongue, skin, breast, gastro-intestinal, respiratory and genital-urinary tracts, nervous system and elsewhere (Sobel et al., 1973; Weiser, 1978). The tumor generally is benign although rare cases of malignant granular cell tumors have been refered (Al-Sarraf et al., 1971; Ross et al., 1952). Both

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benign and malignant tumors are characterized by the presence of cells containing a large number of membrane-bounded granules, myeloid bodies and vacuoles. Granules usually give positive reaction to different histochemical tests, such as periodic-acid-Schiff (with and without diastase digestion), oil red 0 and nonspecific sterase, acid phosphatase and lipase activities (Sobel et al., 1973). However, variations in the results of these tests have been observed from some tumors to others.

The histogenesis of granular cell tumor has been subject of considerable controversy and the nature and origin of this tumor is far being settled. Of the various histogenetic theories proposed: myogenous (Abrikossoff, 1926; Christ and Ozzello, 1971), mesenchymal or fibroblastic (Aparicio and Lumsden, 1969), neurogenous (Fisher and Wechsler, 1962), the latter appears to be in current favour and is based on intimate relationship between tumor and nerves.

The present paper reports the light- and electron-microscope findings of a vascular leiomyosarcoma of the left arm which exhibits granular cells in some areas of the tumor.

Case Report

A 78-year-old male was admitted to the hospital because of a tumoral mass in the left arm. The mass was first noted as a small painless lump about 20 months before admission. It had fast enlarged during the preceding four months and was surgically excised.

The resected specimen was an irregular ovoid and not well circunscribed mass measuring about $10 \times 6 \times 5$ cm. The surface showed multiple nodules varying in size from several mm to cm. On section, cut surface showed anastomosing cords or fascicles with areas of haemorrhages.

Six months after surgery, local recurrence of tumor was observed. Eleven months later the patient died of metastases in the lung.

Material and Methods

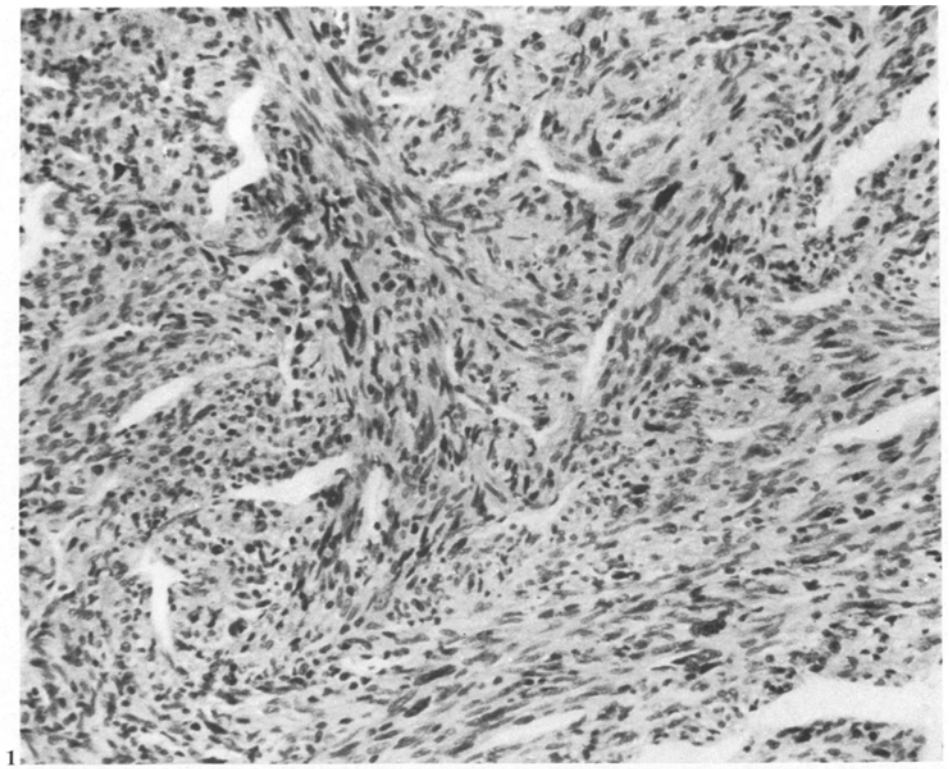
For light microscopy, the resected specimen was fixed in 10% formaline solution, dehydrated, embedded in paraffin and stained with haematoxylin-eosin, PAS (with and without diastase digestion), Masson trichrome and elastic van Gieson.

For electron microscopy, samples were cut into 1 mm cubes, fixed in the Karnovsky fixative (4 h), postfixed in 1% osmium tetroxide, dehydrated in serial ethanol, infiltrated with propylene dioxide and embedded in Epon-812 resin. The 1 μm thick sections were stained with aqueous touluidine blue solution for light microscopy observation. Ultrathin sections were mounted on copper grids, stained with uranyl acetate and lead citrate and examined with a Philips-300 electron microscope.

Results

Light Microscopy

The histological pattern of the tumor varied widely from one area to another. Part of tumoral tissue revealed a fascicular arrangement of spindle-shaped cells showing the characteristic cytological features of the leiomyosarcoma cells (Fig. 1). Most of these cells possessed an elongated euchromatic nucleus with



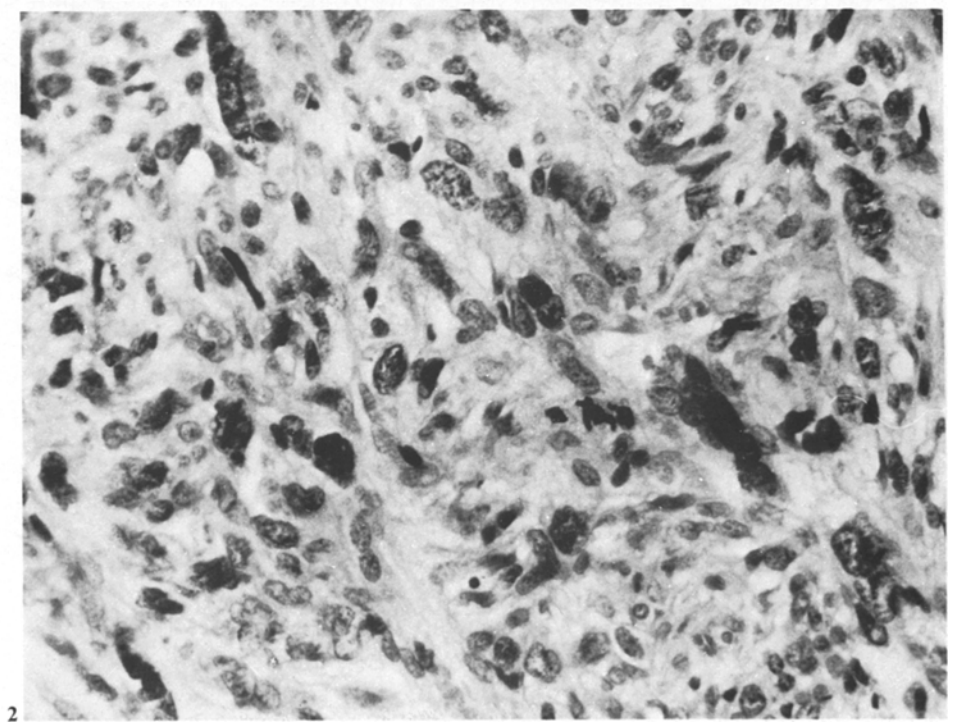


Fig. 1. Interlacing pattern of the bundles of spindle-shaped cells. H.E. × 150

Fig. 2. Tumoral cells showing bizarre nuclei, mitotic activity and eosinophilic cytoplasm. H.E. × 500

one or two prominent nucleoli. A palisade organization of nuclei was frequent. Tumor giant cells, with bizarre and hyperchromatic nucleus were also seen. Atypical mitotic figures were frequent (Fig. 2). The cytoplasm was eosinophilic and, in some cells, showed a slender longitudinal striation. The intercellular spaces were scarce and contained a few collagen fibres. Other areas of neoplasm comprised layers of tumoral spindle-cells surrounding abnormal blood vessels (Fig. 3). In several sections of the tumor, nests of similar neoplastic cells were often identified in the intima as well as in the media of the large calibre abnormal blood vessels (Fig. 4).

Wide areas of neoformation were characterized by the presence of interlacing bundles of acidophilic polyedral cells. They exhibited large, partly hyperchromatic nucleus, irregular in shape, with deep infoldings in their nuclear membrane and a distinct nucleolus. Mitoses were often observed. The cytoplasm contained a large number of granules which were intensely red with the trichrome stain and strongly PAS stained with and without prior diastase digestion (Fig. 5).

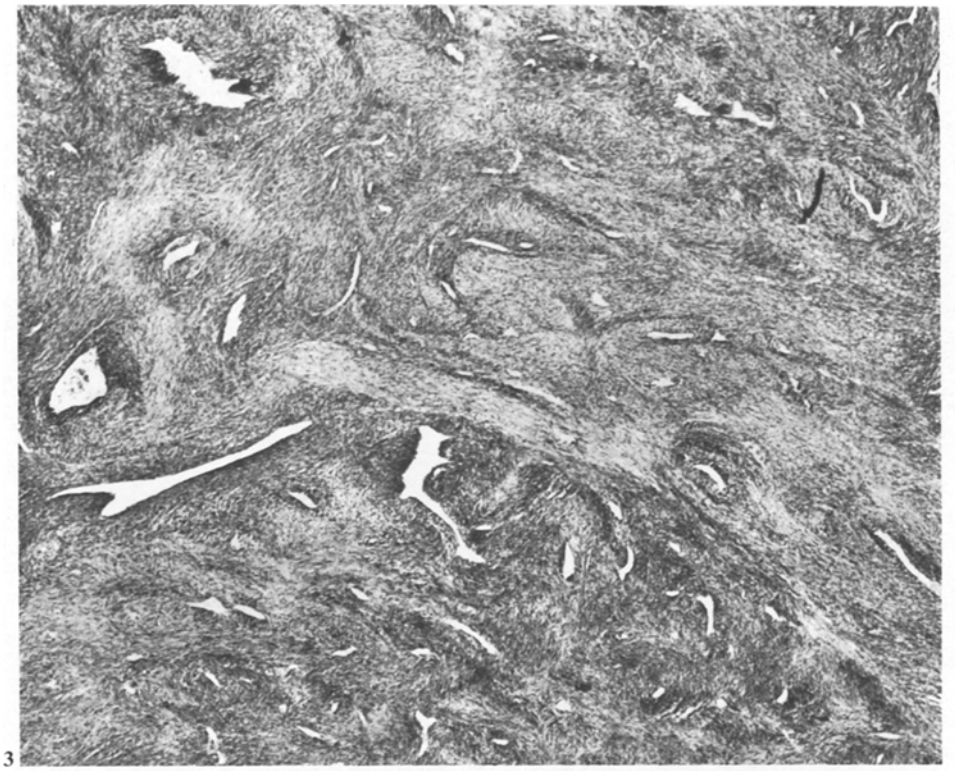
In the transition zone between the spindle-cell areas and the granular cell areas intermediate cell types were observed (Figs. 6, 7).

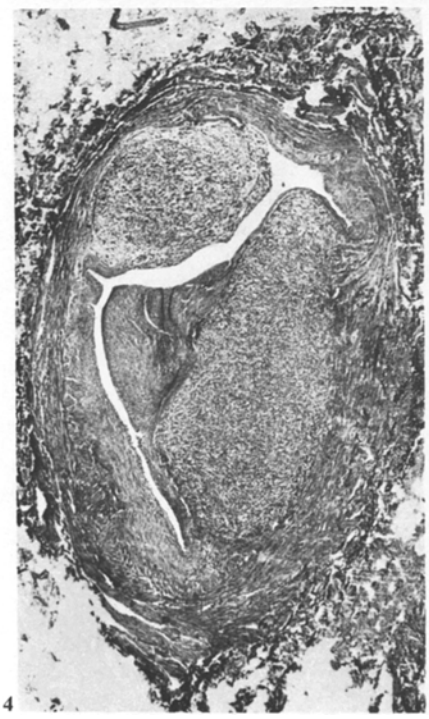
Electron Microscopy

The homogeneous tumor spindle-cell population by light microscopy revealed at the electron microscopy level a series of cells with different degrees of development towards smooth muscle cells. This cell population varied from undifferentiated and immature cells to myoblasts.

Immature cells possessed a round excentric nucleus, regular in outline, and abundant 80–100 Å microfilament bundles in the cytoplasm. Polysomes, microtubules, small mitochondria and a well-developed Golgi complex were also apparent. Myoblastic cells, had an elongated nucleus, with deep infoldings of the nuclear membrane. Their cytoplasm was characterized by the presence of numerous microfilament bundles showing electrondense zones. Two types of myofilaments could be distinguished: thin filaments (50–100 Å) and thick filaments (140–180 Å). Micropinocytotic vesicles were frequent along the plasma membrane.

In addition to light microscopy, ultrastructural examination of granular cells revealed that the cell membrane was covered by a continuous basal lamina. Intercellular spaces between adjacent cells were about 400 Å wide, and often contained fibrous long-spacing collagen with a banding of aproximately 1200 Å (Fig. 8). Near the plasma membrane, the cytoplasm axhibited abundant micropinocytotic vesicles and electrondense zones, opposite to those of the adjacent cells. The granules seen by light microscopy were delimited by a single smooth membrane by electron microscopy, and contained diverse structures, such as electrondense granules of variable size, membranous arrays, myelin-like figures, microfilaments and portions of cytoplasmic organelles, mainly mitochondria (Fig. 9). Most of the granular cells possessed in addition abundant microfilament bundles, either randomly oriented through the cytoplasm or confined to limited areas near the plasma membrane or in contact with it. The diameter of the





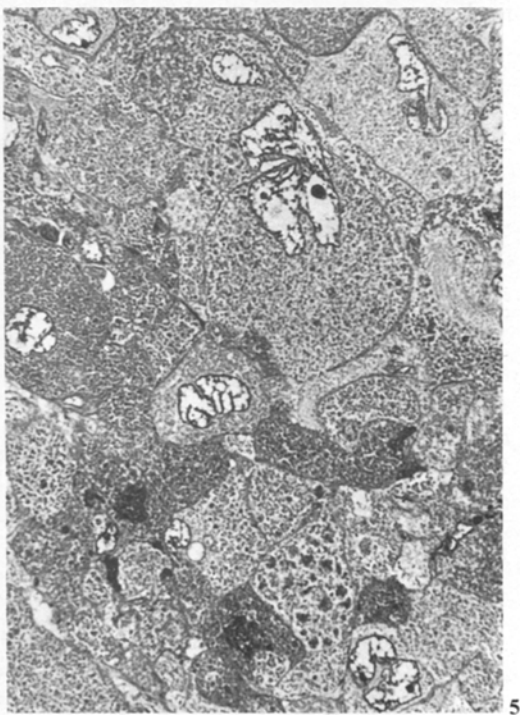
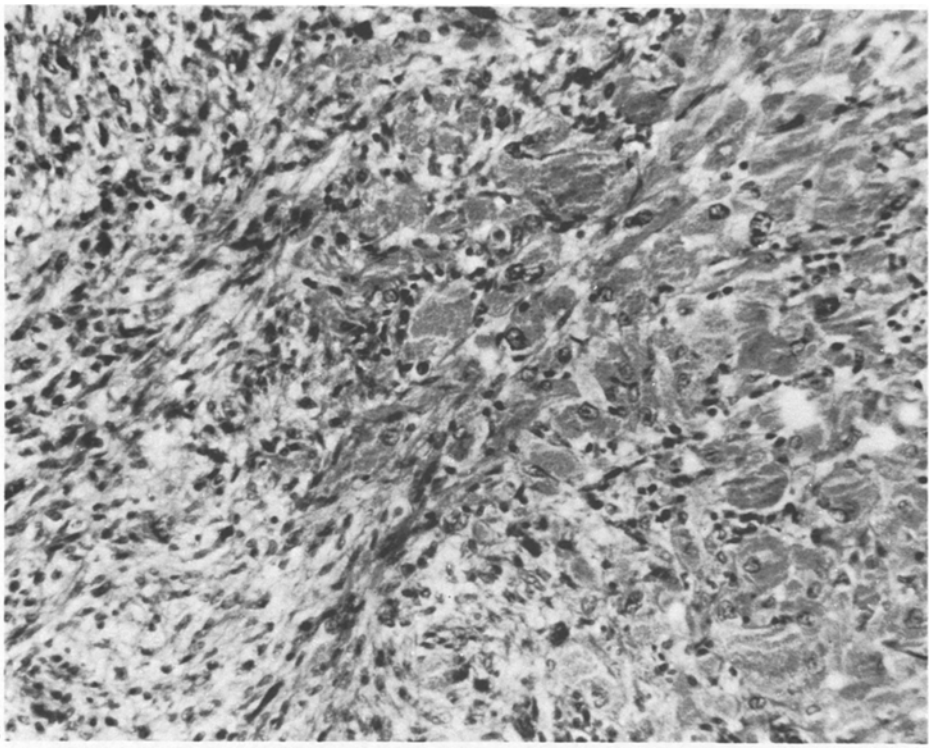


Fig. 3. Proliferation of tumoral cells around several displastic blood vessels. H.E. × 40

Fig. 4. Cross section of a blood vessel showing nests of tumoral cells in the intima and media. H.E. × 20

Fig. 5. Polyedral cells with nuclear polymorphism containing numerous granules of different size. Toluidine blue. × 950



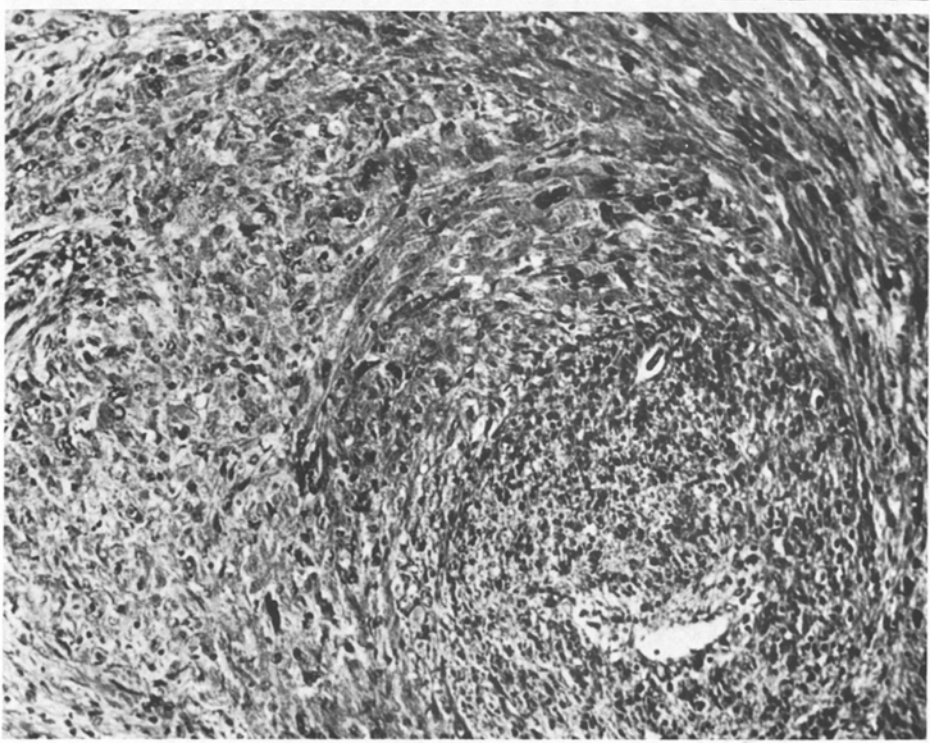
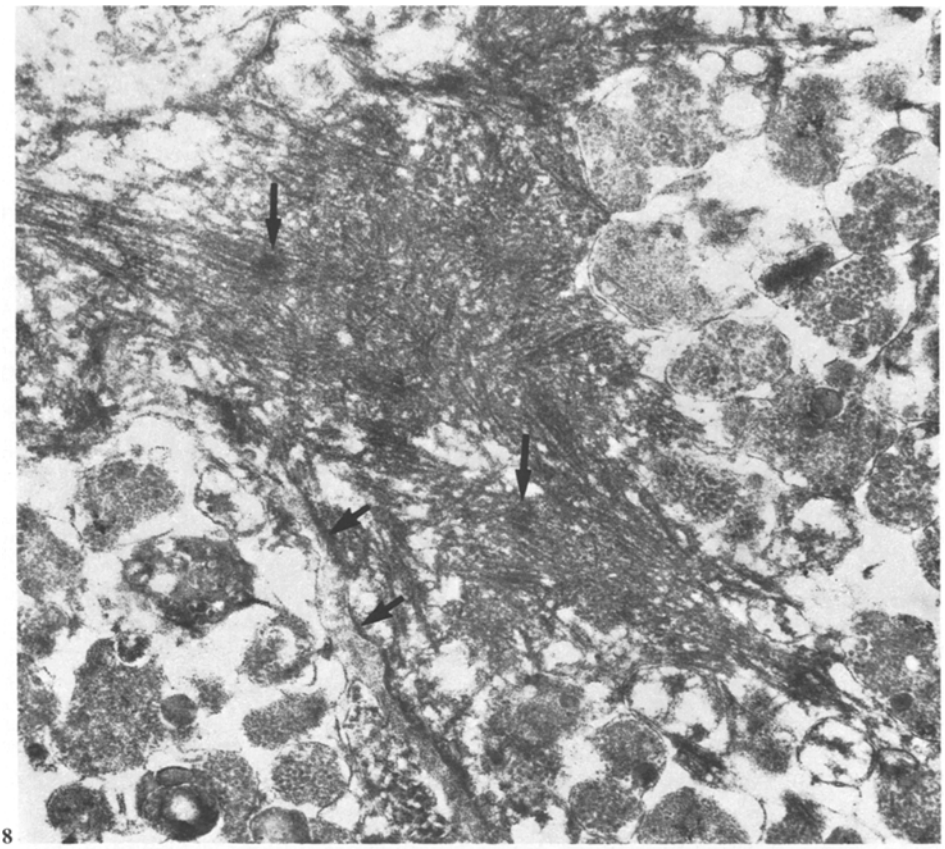


Fig. 6. Granular cells intermingled with fusiform cells. H.E. × 150

Fig. 7. A blood vessel is surrounded by spindle cells. At the periphery, a transition zone from spindle cells to granular cells is observed. H.E. × 150



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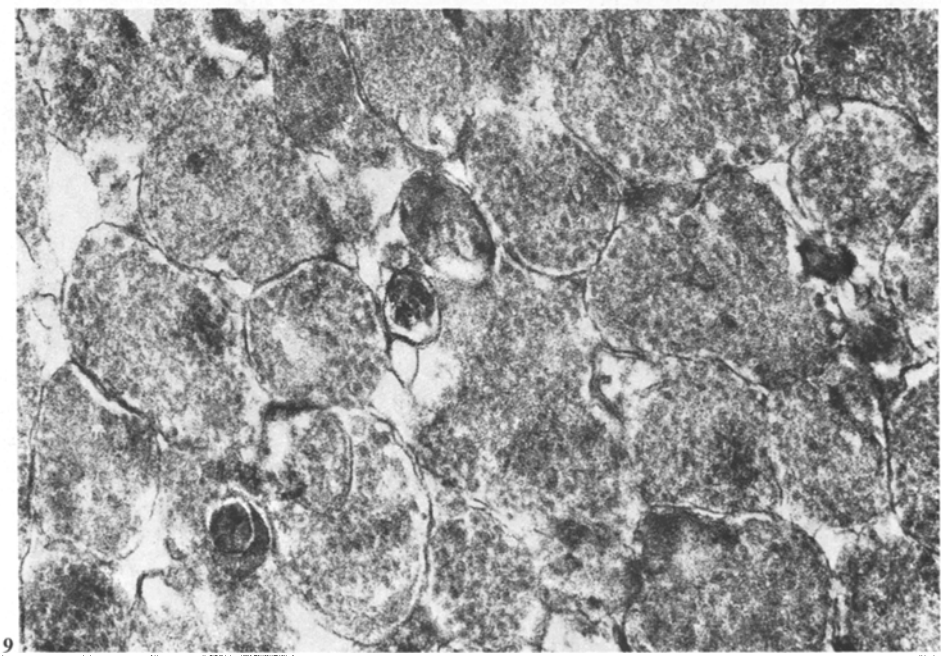

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Fig. 8. Electron-micrograph of granular cells showing a continuous basal lamina. Electrondense bodies are in close apposition to the plasma membrane (*small arrows*). Irregularly arranged microfilament bundles with electrondense bodies (*large arrows*) are observed in the cytoplasm. ×31,500

Fig. 9. Granules show a limiting smooth membrane and contain a variety of electrondense structures as well as membranous arrays. ×50,000

microfilaments varied from 80 to 150 Å. Within the microfilament bundles, electrondense zones similar to those apposed to plasma membrane were often found (Fig. 8). Scattered mitochondria with few cristae, some cisternae of rough endoplasmic reticulum, free ribosomes and glykogen granules were the other structural components most often observed in the granular cell cytoplasm.

The number of microfilment bundles was inversely proportional to the number of granules. Cells showing many microfilaments and few granules were located in the vicinity of myoblastic cells, forming the transition zone, whereas the cells with abundant granules and scarse microfilaments were found far from muscle cells.

Discussion

In the first description of the granular cell tumor, Abrikossoff (1926) stated that the cell, origin of granular cell myoblastoma (so he called it), was the embryonic muscle cell or myoblast. Since then, because of the lack of a conclusive evidence, the myogenous origin of granular cell tumor has been questioned and other histogenetic theories have been proposed. Many authors have reported the origin of granular cell tumor as being from nerve structure (Fust and Custer, 1949; Fisher and Wechsler, 1962). Other authors suggested that this tumor is derived from an undifferentiated mesenchymal cell that might also be the precursor cell of the Schwannoma as well as the myoblastoma (Sobel et al., 1973). The Schwann cell origin of this tumor is currently accepted (Weiser, 1978) inasmuch as peripheral nerves are commonly entrapped by granular cell tumor, and there is a marked similariry between the Schwann cells of the degenerating peripheral nerves and the granular tumor cells. However, no firm evidence has been concluded and tissue cultures have not conclusively revealed their histogenesis.

Christ and Ozzello (1971) stated the myogenous origin of a benign granular cell tumor of the urinary bladder, based upon the presence of myofilaments in the granular cells. This is in contrast to the ultrastructural features found by these authors in other granular cell tumors (two chest wall tumors), and interpreted as being indicative of a Schwannian origin.

Fibrous long-spacing collagen is a frequent finding in granular cell tumors (Al-Sarraf et al., 1971; Sobel et al., 1973). Since it has been refered that this variety of collagen fibres is present in damaged nerves as well as in Schwann cell tumors (Luse, 1960), it has been claimed that this observation could be suggestive of the neurogenous origin of granular cell tumor (Sobel et al., 1973), However, many authors have failed to find fibrous long-spacing collagen in granular cell tumors (Al-Sarraf et al., 1971; Christ and Ozzello, 1971). On the other hand, long-spacing collagen has been reported in tissues, other than neural, and tumors other than schwannoma, such as thimoma, seminoma, rabdomyosarcoma and fibrohistiocytoma (Navas Palacios, 1978), and even within the muscle cells in different pathological conditions (Abrikossoff, 1926; Staubesand, 1977). Therefore, long-spacing collagen might only be the result from an altered aggregation of tropocollagen, caused by the presence of abnormal proportion of

a number of factors, including mucopolysaccharides (Sobel et al., 1973), without a special relation to nervous compoents.

Some investigators have questioned the neoplastic nature of the granular cell tumor, which has also been considered as: a degenerative process (Abrikossoff, 1926), a reactive process (Chung, 1978), a reaction to anoxia (Cooper and Goodman, 1974), a metabolic storage disorder (Moscovic and Azor, 1967) and a lysosomal defect of Schwann cells (Garancis et al., 1970).

The present tumor exhibits different areas. This feature might lead us to a different diagnosis if each of these areas were separately interpreted. There are structural and cytologic features which suggest that a portion of the tumor corresponds to a leiomyosarcoma (Böcher and Strecker, 1975). The topographic relations of the tumor cells with the muscle coat of the blood vessels indicate that we are dealing with a vascular leiomyosarcoma. On the other hand, portions of the tumoral tissue show acidophilic polyedral cells with cytoplasmic granules and irregular nucleus suggesting a granular cell tumor. This observation leads to two different hypothesis: 1) it is a true granular cell tumor arised from a vascular leiomyosarcoma; 2) it is a vascular leiomyosarcoma focally undergoing granular changes.

We have observed that most of leiomyosarcoma cell areas and granular cell areas are not separated but forming interlacing bundles where both cell types are intermingled. Interestingly enough, the ultrastructural study reveals intermediate cell types between smooth muscle cells and granular cells. These cells possessed abundant microfilament bundles with electrondense zones as well as granules. However, in these cells, microfilaments were less abundant than in tumor smooth muscle cells, and granules were more numerous than in granular cells. This feature leads to think that the granular cells do not constitute a specific entity (granular cell tumor) but they probably represent the result of a peculiar transformation of some smooth muscle cells.

Morphologic and cytochemical studies about the nature of granules carried out in granular cells have not yet provide definitive criteria to differentiate between granular cell tumors and cells undergoing granular changes originating from several pathologic processes. Most authors coincide in asserting the lysosomal nature of the granules in all granular cells examined. They correspond to digestive vacuoles (autophagosomes) which show progressive steps of development (Al-Sarraf et al., 1971; Christ and Ozzello, 1971; Sobel et al., 1973). Similar lysosomal bodies, as result of an autophagic activity, have been shown in different cell types under several physiological and pathological conditions (Trump and Ericson, 1965), and they may be interpreted as a cellular response to different stimuli (Christ and Ozzello, 1971). In agreement with Christ and Ozzello (1971) and other previous authors (Shear, 1960; Sobel and Churg, 1964), we feel that granular cells may arise from more than one cell type, including Schwann cells, myoblasts and mesenchymal cells.

We consider that when a tumor showing granular cells is present, it would be recommendable to investigate the presence of other tumors, not only for a better knowledge of the histogenesis of granular cells but also for determinating the precise nature of the process.

References

Abrikossoff, A.: Über Myome, ausgehend von der quergestreiften willkürlichen Muskulatur. Virchows Arch. Path. Anat. **260**, 215–133 (1926)

Al-Sarraf, M., Loud, A.V., Vaikevicius, K.V.: Malignant granular cell tumor. Arch. Pathol. **91**, 550–558 (1971)

Aparicio, S.R., Lumsden, C.E.: Light- and electron-microscope studies on the granular cell myoblastoma of the tongue. J. Pathol. **97**, 339–349 (1969)

Böcker, M., Strecker, H.: Electron microscopy of uterine leiomyosarcomas. Virchows Arch. A Path. Anat. and Histol. **367**, 59–71 (1975)

Christ, M.L., Ozzello, L.: Myogenous origin of a granular cell tumor of the urinary bladder. Am. J. Clin. Pathol. **56**, 736–749 (1971)

Chung, H.D.: Granular cell tumor of the spermatic cord: A case report with light and electron microscope study. J. Urol. **120**, 379–382 (1978)

Cooper, P.H., Goodman, M.D.: Multilayering of the capyllary basal lamina in the granular cell tumor. A marker of cellular injury. Hum. Pathol. **5**, 327–337 (1974)

Fisher, E.R., Wechsler, M.: Granular cell myoblastoma- a misnomer. Cancer **15**, 936–954 (1962)

Fust, I.A., Custer, R.P.: On the neurogenesis of socalled granular cell myoblastoma. Am. J. Clin. Pathol. **19**, 522–535 (1949)

Garancis, J.C., Komorowski, R.A., Kuzura, J.F.: Granular cell myoblastoma. Cancer **25**, 542–550 (1970)

Luse, S.A.: Electron microscopic studies of brain tumors. Neurology **10**, 881–905 (1970)

Moscovic, E.A., Azor, H.A.: Multiple granular cell tumors ("myoblastomas"). Cancer **20**, 2032–2047 (1967)

Navas Palacios, J.J.: Characteristics, incidence and significance of fibrous long spacing collagen (FLSC). Morf. normal y pathol. B **2**, 123–133 (1978)

Ross, R.C., Miller, T.R., Foote, F.W. Jr.: Malignant granular-cell myoblastoma. Cancer **5**, 112–121 (1952)

Shear, M.: The histogenesis of the so-called "granular-cell myoblastoma". J. Pathol. Bactol. **80**, 225–228 (1960)

Sobel, H.J., Chrug, J.: Granular cells and granular cell lesions. Arch. Pathol. **77**, 132–141 (1964)

Sobel, H.J., Schwarz, R., Marquet, E.: Light- and electronmicroscope study of the origin of granular-cell myoblastoma. J. Pathol. **109**, 101–111 (1973)

Staubesand, J.: Intracellular collagen in smooth muscle- the fine structure of the artificially occluded rat artery and ureter, and of human varicose and arteriosclerotic vessels. Beitr. Pathol. **161**, 187–197 (1977)

Trump, B.F., Ericson, J.L.E.: Some ultrastructural and biochemical consequences of cell injury. In: The inflamatory process, B.W. Zweifach, L. Grant and R.T. McCluskey (eds.). New York: Academic Press 1965

Weiser, G.: Granularzelltumor (Granuläres Neuron Feyrter) und Schwannsche Phagen. Virchows Arch. A Path. Anat. and Histol. **380**, 49–57 (1978)

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