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Leiomyosarcoma of the Pulmonary Artery

A Light and Electronmicroscopical Study*

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Summary. A 25-year-old man with chest pain and shortness of breath was found to have a primary sarcoma of the pulmonary artery.

On light- and electronmicroscopy and immunofluorescence microscopy the lesion was found to be composed of cells of smooth muscle origin. It was diagnosed as leiomyosarcoma.

The cross and microscopic features of the tumor are described and the morphologic characteristics of previously reported vascular sarcomas are briefly reviewed.

Key words: Primary sarcoma of pulmonary artery – Light-electron and immunofluorescence microscopy findings – Myointimal cells.

Introduction

Although primary malignant tumors of the heart and the large vessels are extremely rare, reports of cases suffering from sarcomas of large veins have become increasingly frequent. Sarcomas of the arteries have been found mostly in the pulmonary arteries of which approximately 31 cases have been reported (Wackers et al., 1969; Hohlbach and Mall, 1977).

In most reports the classification of theses tumors has been purely descriptive and includes spindle cell sarcoma, malignant endothelioma, fibromyxosarcoma, polymorphic cellular sarcoma and emboliforme sarcoma (Froboese, 1928; Goedel, 1936; Martin et al., 1939; Green et al., 1964). To our knowledge only one report has presented an electronmicroscopical analysis (Wang et al., 1974).

This paper records a detailed light and electronmicroscopical analysis of a primary sarcoma of the pulmonary artery including immunofluorescence techniques.

*Dedicated to Prof. Dr. W. Doerr to his 65th birthday

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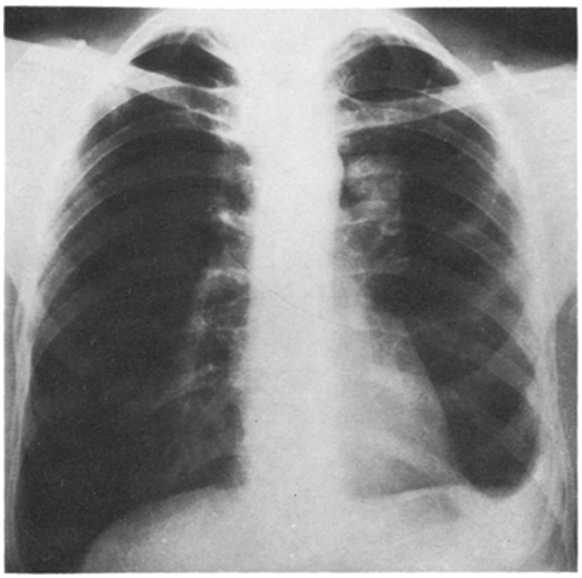


Fig. 1. A–P roentgenograph showing tumorous mass in the central part of the left hilus

Report of the Case

A 25-year-old man was admitted to hospital in November 1978 with complaints of chest pain of deep inspiration and expiration, shortness of breath and mild hemoptysis and sweating at night. These symptoms began 2 weeks prior to admission.

In January 1978 the patient had suffered from bronchopneumonia which recurred in May 1978. Between May and November 1978 he was in good health.

Results of the physical examination, lung function tests and biochemical profile were within normal limits, blood gas analysis following exercise revealed slight hypoxemia. An ECG showed a right axis deviation. The pulmonary arterial pressure was elevated. On chest X-ray films a distinct tumor mass was seen in the central part of the left hilus (Fig. 1).

Lung scan revealed multiple perfusion defects in the left lung and a poor perfusion of the upper lobe of the right lung. Bronchoscopy and cytology were negative.

At thoracotomy a solid tumor could be palpated in the central hilar portion of the left lung. The left pulmonary artery was obliterated by tumorous masses which extended into the pulmonary trunk just above the pulmonary valves. Resection appeared to be impossible. During the postoperative course the patient went into a shock-like state and died with signs of a pulmonary embolism.

Methods

Autopsy was performed 24 h after death. Multiple tissue samples were fixed in 4% neutral buffered formaldehyde solution processed routinely and embedded in paraffin. Sections were stained with haematoxylin-eosin, Verhoeff-Van Gieson and Masson Goldner stains.

For electron microscopy the tissue was fixed in 2.5% cacodylate-buffered glutaraldehyde for one hour and after washing, postfixed with 1% osmium tetroxide for 2 h and embedded in Epon®.

Semithin sections were stained with Toluidine blue. Ultrathin sections were stained with lead citrate and uranyle acetate, examined using a Siemens EM1 and documented on Scientia® photoplates.

For immunofluorescence cryostat sections were treated for 30 min with fluoresceine di-isothiocyanate (FITC)-labelled antiacytomyosin (Hofmann and Goger, 1974) in a moist chamber at room

temperature. The excess conjugate was then washed off by incubation with PBS for 30 min. The tissue preparation was mounted in a glycerol-glycine buffer at pH 6.8. Using a Leitz Ortholux fluorescence microscope with the filter combinations Bg 480/K 510 and a HG 200 W lamp the sections were examined and documented on a Kodak-Ectachrome high speed film.

Autopsy Findings

The enlarged heart (heart weight 380 g, body weight 72 kg) showed dilation of the right ventricle and a marked hypertrophy of the right ventricular myocardium (thickness 6 mm). The pulmonary valve cusps were thickened, and the other valves showed no evident alterations. Two cm distal to the pulmonary valves the pulmonary trunk contained a tumorous mass firmly adherent to the arterial wall and extended along the inner surface into the left pulmonary artery. The lumen of the left pulmonary artery was completely occluded by the solid mass which was partially covered with thrombus and extended into the right branch of the pulmonary artery, which was partially occluded. The tumor displayed entirely intravascular growth, more extensive on the left. The central part of the tumor showed necrosis. There were hemorrhagic infarctions of the left lung and of the right upper lobe. The hilar lymph nodes did not contain tumor, distant metastases were not found and there was no evidence of a primary tumor elsewhere. Liver, spleen and kidneys were severely congested and cerebral oedema was found.

Light Microscopy

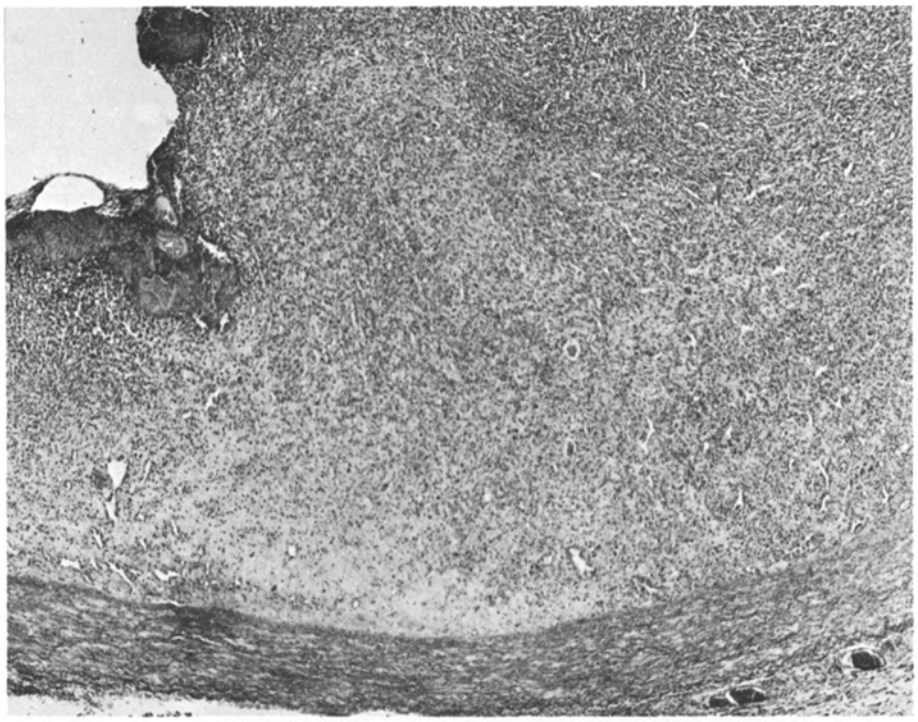
Histologically the tumor spread along the inner surface of the pulmonary trunk with complete destruction of the intima and the internal elastic lamina, other parts of the media were fully preserved (Fig. 2). Some smaller sized branches of the left pulmonary artery were completely obstructed by tumor, the lumina of the larger branches were merkedly narrowed by tumor and thrombotic masses of different ages.

The tumor was built up of irregular bundles of mostly spindle shaped cells with a marked pleomorphism. The nuclei were large, often lobulated, sometimes with dense and notched nuclear membranes and coarse chromatine clumps. Many cells seemed to be multinucleated. Mitotic figures were infrequent (Fig. 3).

In the interstitium bundles of collagen fibres were found. Vascularisation of the tumor tissue was marked. The central part of the sarcoma showed focal necrosis. The tumor was partly covered by thrombotic material. There was an infarct of the left upper lobe with extensive intraalveolar hemorrhage and apposed pleural surfaces were covered by a fibrinous exudate. Extensive hemorrhage was also found in the left lower lobe and the right upper lobe.

Immunofluorescence

Using immunofluorescence we found an intense specific fluorescence with fluorescein labelled anti-acto-myosin in the tumor tissue, the conjugates were bound



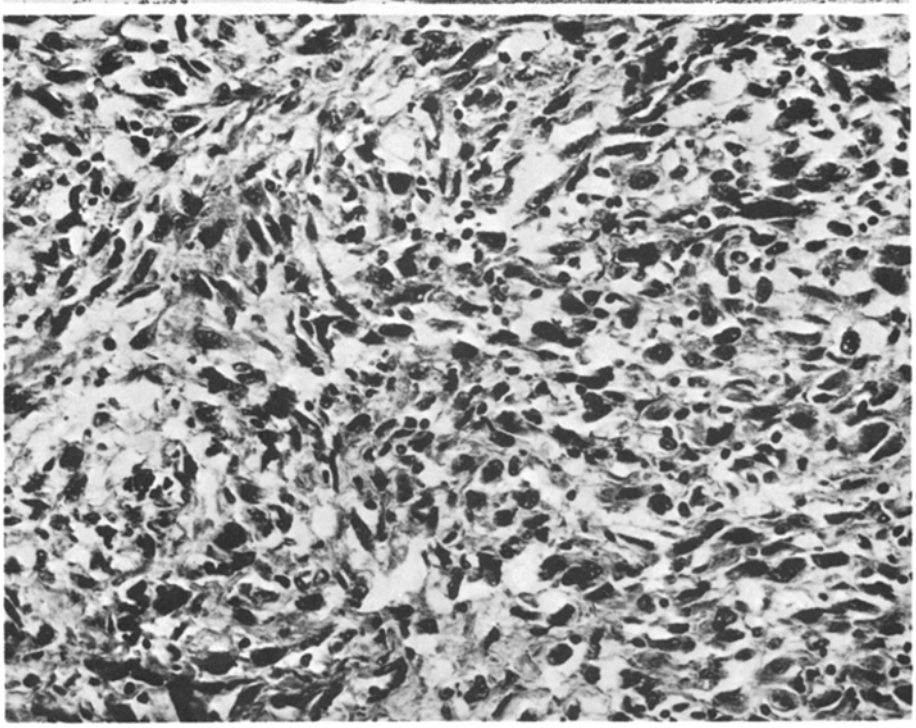


Fig. 2. Photomicrograph, H&E, 1:25, left branch of pulmonary artery. The intima is destroyed by tumor. Preserved parts of the arterial media in the lower portion of the figure. The luminal surface of the tumor is covered by thrombus. Note the marked vascularisation of the tumor

Fig. 3. Photomicrograph, Masson-Goldner, 1:250. Higher magnification of the tumor showing irregular bundles of spindle shaped cells with a marked pleomorphism and large irregular nuclei. Collagen fibres in the interstitium

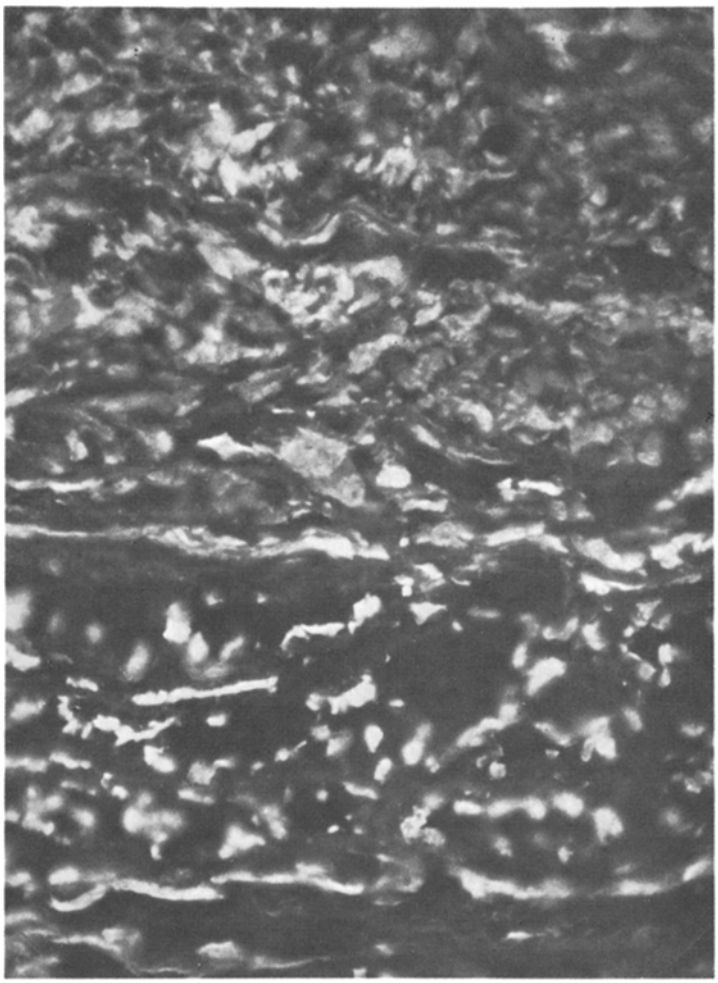


Fig. 4. Immunofluorescence-photomicrograph, FITC-labelled antiactomyosin, Leitz,Ortholux, filter combination Bg480/K 510, Hg 200 W lamp, 1:250. Specific fluorescence in the tumor tissue which is shown in the upper portion of the photomicrograph. In the lower portion of the photomicrograph are parts of the preserved arterial media. There is no difference in intensity of fluorescence between the two portions

in a fairly irregular pattern in the cytoplasm of the tumor cells leaving open nuclear spaces. Specific fluorescence was found only within the cytoplasm. The pattern of the fluorescence in the tumor was different to that in the vascular media without any difference in intensity (Fig. 4).

Electron Microscopy

At ultrastructural level parts of the original vessel wall could be identified, the media displayed a typical structure containing elastic lamellae and smooth

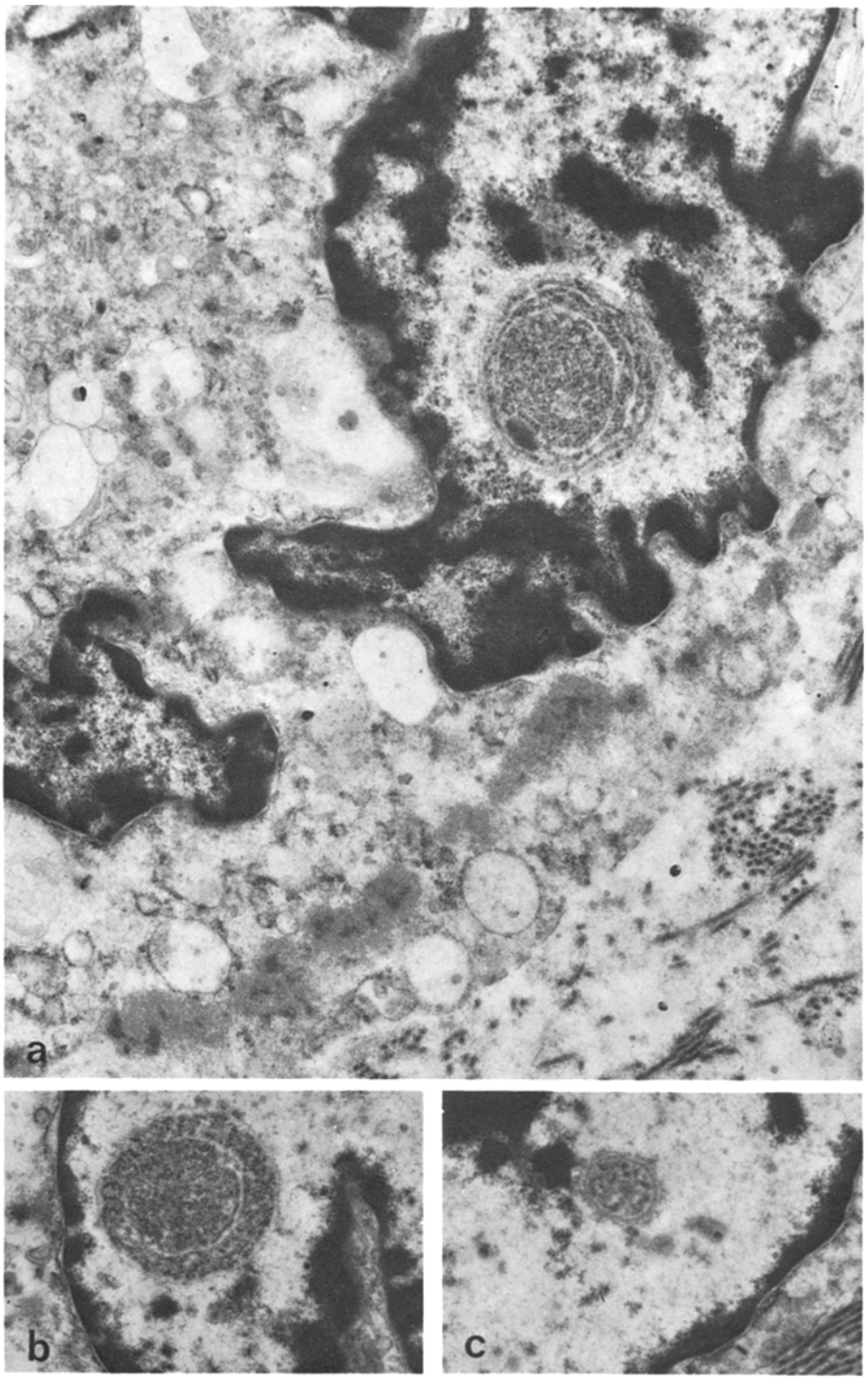
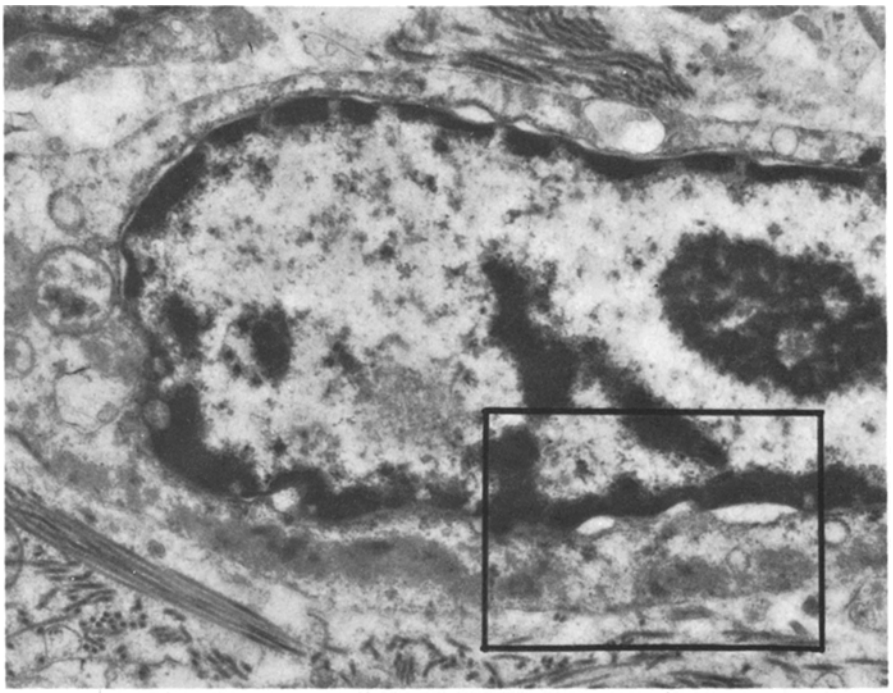


Fig. 5a–c. High power view of tumor cells, lead citrate and uranyl acetate, 1:15,000. Irregularly notched nucleus of a tumor cell with intranuclear inclusion body showing concentric structures. In the cytoplasm condensates of actomyosin (**a**). Figures (**b**) and (**c**) show nuclear bodies of different size and structure



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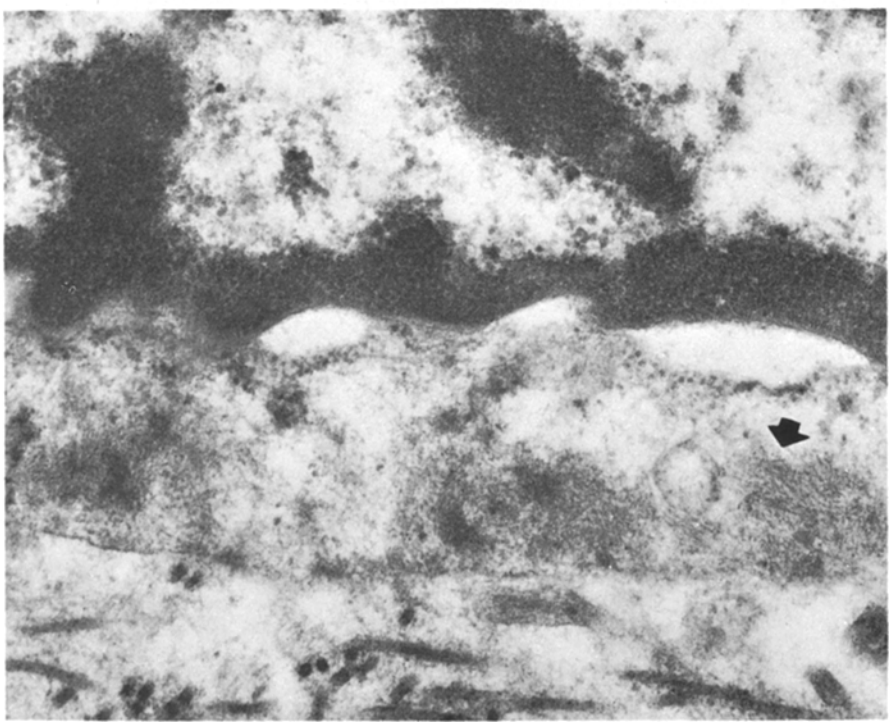

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Fig. 6. High power view of a tumor cell, lead citrate and uranyle acetate, 1:15,000. Coarse clumps of actomyosin in the cytoplasm. Collagen fibres in the interstitium

Fig. 7. Detailed view of Fig. 6, 1:60,000. Condensates of actomyosin in the cytoplasm showing microfilaments (*arrow*)

muscle cells. The tumor contained large, multipolar cells with electron dense rings at the margins of the irregularly notched nuclei and 1 to 3 prominent nucleoli. Intranuclear electron dense inclusion bodies were seen (Fig. 5). Occasionally these inclusion bodies were deliniated by distinct membranes and contained partly concentric, partly palisade-like structures. Those inclusion bodies which displayed a concentric structure had an average diameter of 1.4 μ. The second type displaying palisade-like patterns had an average diameter of 0.6 μ. The intranuclear inclusion bodies were either solitary or multiple and usually located in the paracentral region of the nuclei. In the cytoplasm of the sarcomatous cells large vesicles, degenerated mitochondria and fragments of endoplasmatic reticulum were seen and the cytoplasm contained microfilaments and coarse clumps of electron dense material, which was interpreted as actomyosin. Some of the tumor cells were surrounded by basement membranes (Figs. 6, 7). Apart from these cellular elements the tumor contained capillary endothelial cells which were connected with basement membranes but not always related to the vascular lumen. In their cytoplasm electron dense filaments
were loosly arranged. Intracytoplasmatic vacuoles of different sizes were common, the chromatin displayed thick electron dense rings at the margins of the nuclei; single nucleoli were seen. The interstitium was filled up with thick bundles of collagen fibres intermingled with large vacuoles. Elastin was not seen (Fig. 6).

Discussion

The morphologic study of our case revealed an intravascular sarcoma of the pulmonary artery involving intima, subintima and the internal elastic lamina of the media.

The light microscopical features were compatible with the descriptive diagnosis of spindle cell sarcoma or polymorphic cellular sarcoma.

Immunofluorescence and electronmicroscopy revealed a tumor with features of smooth muscle cell origin. Since autopsy was performed 24 h after death many autolytic changes were encountered. However, the tumor tissue had the distinctive features of smooth muscle cells such as intracytoplasmatic microfilaments, basement membranes and positive immunofluorescence to antiactomyosin.

Cytoplasmatic filaments and basement membranes have been reported in tumors of smooth muscle origin (Frenczy et al., 1971; Wolff, 1973; Wang et al., 1974). Since the tumor described here contained thick bundles of collagen one could possibly argue that it consisted of fibroblast-like cells and the clumps of actomyosin complexes were simulated by artifacts because of severe autolysis, although positive immunofluorescence seems to be rather unlikely in that case. The basement membrane which was found is a distinctive feature of smooth muscle cells (Jellinek, 1974). Cells of this type, resembling smooth muscle cells apear to be closely related to the myofibroblasts which are responsible for the contractile nature of granulation tissue (Gabbiani and Majno, 1972). They also closely resemble the cells which invade the intima of arteries after endothelial damage and have been termed "myointimal cells" (Buck, 1961). Cells of this

type have been reported to arise in thrombi (Davies et al., 1972) and to occur during the development of atheromatous plaques (Haust et al., 1960; Thomas et al., 1963). They are described by Rokitansky (1856) and Langhans (1866) and were called "Langhans-Cells" (Doerr, 1978) or "modified myocytes" (Pott and Staubesand, 1977) and have also been found in intimal fibrosis of the pulmonary artery (Balk et al., in press).

Many tumor cells contained nuclear bodies which have not been found in pulmonary arterial sarcomas previously. Nuclear bodies have been found in many different types of human diseases (Bouteille et al., 1967) and it has been suggested that they might be observed in any growing and rapidly multiplying cells (Robertson and Mc Lean, 1965). Nuclear bodies have also been found in myxofibrosarcomata displaying histiocyte-like cells (Kindblom et al., 1979). In our case the tumor seemed to arise in the intima of the pulmonary artery and showed a distinct growth within the intima and along the intimal surface, without infiltration of the deep media or adventitia. The center of tumor growth was clearly the intima of the pulmonary artery and one can argue that the tumor arose from intimal cells, possibly from those which are subsumed by the term "modified myocytes".

Since the tumor displayed features of smooth muscle cells we consider this tumor to be a leiomyosarcoma arising in the intima of the pulmonary artery. It seems appropriate "to designate this entity with a rather clearly established cellular origin to avoid confusion", as it was stated by Wang et al. (1974) who reported another case of sarcoma of the pulmonary artery.

A primary malignant tumor of the pulmonary valve was first described by Mandelstamm (1923). Froboese (1928) reported a case of sarcoma of the trunk of the pulmonary artery which was called emboliforme sarcoma because of severe concomitant pulmonary thrombosis.

Since then around 30 cases of primary sarcomas of the pulmonary artery have been reported (Wackers et al., 1969; Hohlbach and Mall, 1977). The tumors have displayed quite different histologic features; the majority has been interpreted as fibrosarcomas one has been diagnosed as chondrosarcoma (Hohlbach and Mall, 1977) and one tumor showed osteogenic sarcomatous elements (Murphy et al., 1976).

Clinically sarcomas of the pulmonary artery mimic pulmonary thromboembolism (Wackers, 1969) including cor pulmonale, dyspnea and cyanosis. Metastases are uncommon (Wang et al., 1974).

Sarcomas of large veins are reported to have become increasingly frequent (Kevorkian and Cento, 1973), those sarcomas originating in large arteries are rare; in pulmonary arteries sarcomas are reported to be twice as frequent as those found in other large arteries (Kevorkian and Cento, 1973).

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