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Multiple Pulmonary (Hamartomatous?) Leiomyomas

Light and Electron Microscopic Study

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Summary. The light and electron microscopical features of the lung tumors in a case of multiple pulmonary leiomyomas are described. The differential diagnosis of leiomyomatous tumors of the lung is discussed. They have to be differentiated from lymphangio-leiomyomatosis of the lungs. In the literature, multiple pulmonary leiomyomas are generally considered to be metastases from low grade uterine leiomyosarcoma or to be hamartomatous lung tumors. This is suggested by the glandular structures both within the tumor and on the surface. However, our ultrastructural observations showed these epithelia to have features of granular pneumocytes (type II), in particular they contain lamellar bodies and posess microvilli on their surface. Their formation is considered to be a secondary reaction of alveolar lining cells to tumor growth. A possible origin of multiple pulmonary leiomyomas from the contractile system of the lung acini (contractile interstitial cells) is discussed.

Key words: Pulmonary benign tumors – Leiomyoma – Hamartoma

Zusammenfassung. Die licht- und elektronenmikroskopischen Befunde an den Lungentumoren eines Falles mit multiplen pulmonalen Leiomyomen werden beschrieben. Die Differential-Diagnose der leiomyomatösen Lungentumoren und besonders die Abgrenzung von der pulmonalen Lymphangiomyomatose wird besprochen. Multiple pulmonale Leiomyome werden in der Literatur als Metastasen von "low grade" uterinen Leiomyomen oder aber als Hamartome der Lunge betrachtet. Letztere Annahme beruht auf der Tatsache, daß auf der Oberfläche der Tumoren und in ihrem Inneren sich kubisches, drüsenartiges Epithel befindet. Dieses weist jedoch nach unseren Beobachtungen Merkmale der granulären Pneumocyten (Typ II) auf, insbesondere lamelläre Körper im Zytoplasma und Microvilli an der Oberflä-

Dedicated to Professor Dr. G. Seifert on the occasion of his 60th birthday

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che. Die Ausbildung dieser epithelialen Bedeckung wird deshalb als Reaktion des Alveolarepithels auf das Tumorwachstum aufgefaßt. Als mögliches Muttergewebe der multiplen pulmonalen Leiomyome wird das kontraktile System der Lungenacini (kontraktile interstitielle Zellen) diskutiert.

Introduction

Benign pulmonary neoplasmas are mostly single and generally asymptomatic. Among benign lung lesions multiple pulmonary (hamartomatous) leiomyomas are extremely rare. We had the opportunity to study a case of multiple pulmonary leiomyomas in which the diagnosis could be verified by lung biopsy with light and electron microscopic studies of the tumor tissue.

Material and Methods

Open lung biopsy was performed in a 54 year old clinically asymptomatic woman, in whom progressive reticulo-nodular densities in both basal lung zones were observed for 3 years. The clinical course and radiographic record are described in detail separately (Kaukel et al., in preparation). The material for *light microscopic study* was fixed in Bouin's solution and stained with haematoxilin-eosin (HE), periodic acid-Schiff (PAS) and according to Masson-Goldner, Turnbull and van Gieson.

For *electron microscopy* small cubes of the biopsy specimen were immediately fixed in glutaraldehyde and routinely embedded in Epon 812. Ultrathin sections were contrasted with uranylacetate and examined with the Zeiss Elektronenmikroskop Em 9 S-2.

Results

Light Microscopic Findings

The light microscopic examination of the lung biopsy-specimen revealed the presence of multiple small (up to 4 mm in diameter) circumscribed, unencapsulated nodules which had developed in the alevolar interstices (Fig. 1a). The sharp delineation of the nodules was remarkable as was the absence of any major change in the surrounding alveolar tissue, which did not show inflammation, atelectasis or fibrosis. Only the directly adjacent alveoli exhibited "cuboidal transformation" of the alveolar lining cells. The nodules were covered by cuboidal to columnar epithelium, which in some places extended into cleft-like spaces within the nodule (Fig. 4). The nodules consisted of elongated spindle-shaped cells arranged in interlacing fascicles (Fig. 1b), which in differential stains were identified as smooth muscle cells. The cells contained blunt, elongated nuclei, no pleomorphism or mitotic activity was observed. Between the smooth muscle cells there were scattered collagenous fibers, but no myxoid, adipose or chondromatous tissue. Although the nodules contained few capillaries, no relation to larger vessels was observed; no haemosiderosis and no connection with bronchioles could be demonstrated. Besides these nodules foci of smooth muscle cells were found in the alveolar interstices (Fig. 2), which apparently are nodules "in statu nascendi".

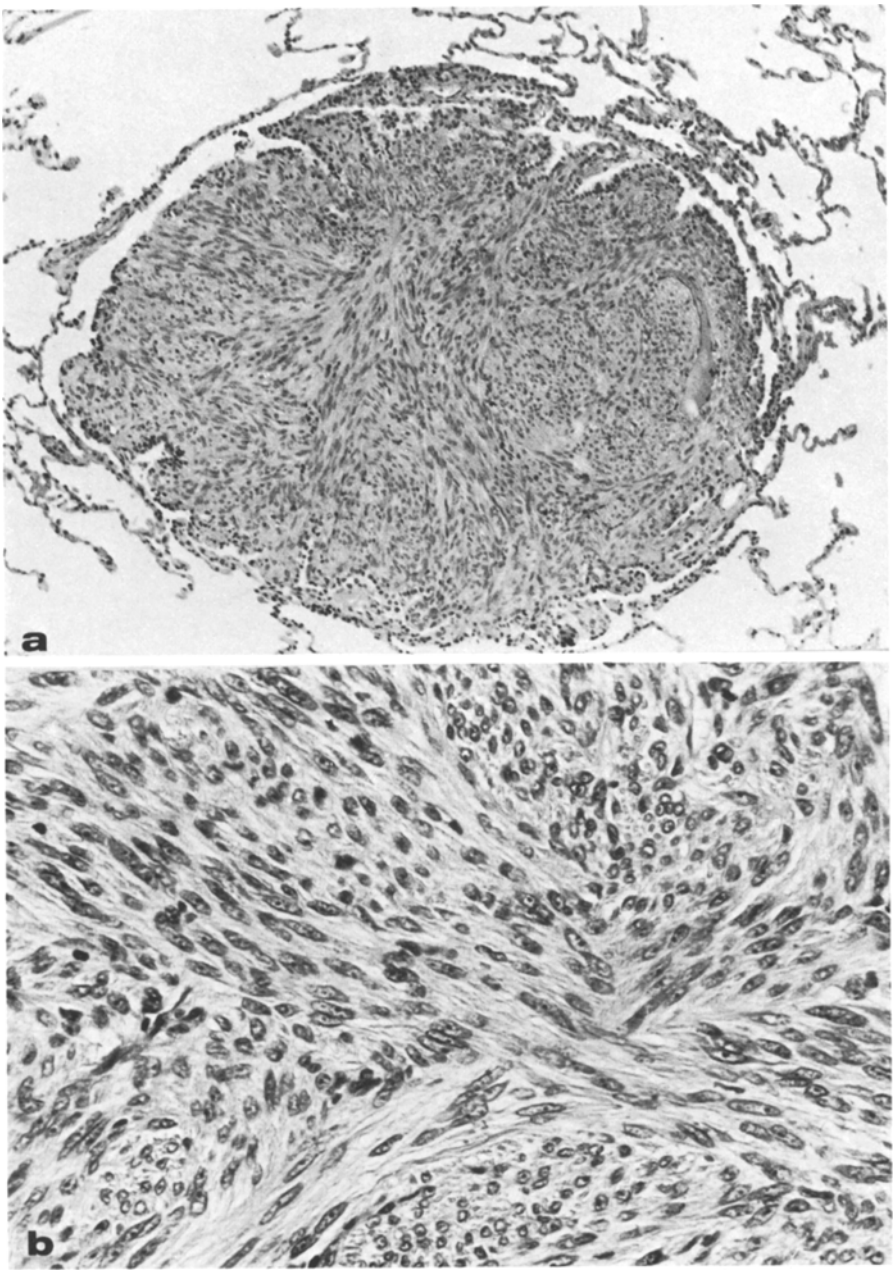


Fig. 1a, b. One of the multiple nodules in the lung. **a** The tumor is sharply delineated, but does not posess a capsule. The surrounding alveolar tissue appears normal, fibrosis of the alveolar interstices and atelectasis are absent. Haematoxilin-Eosin; ×75. **b** The nodule consists of elongated spindle-shaped cells arranged in interlacing fascicles. Haematoxilin-Eosin; ×300

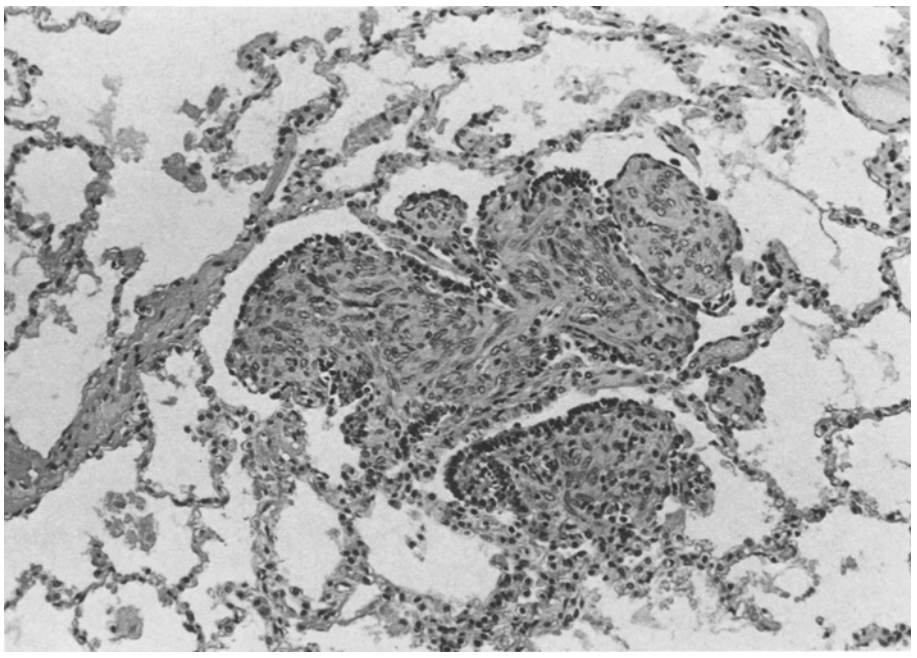


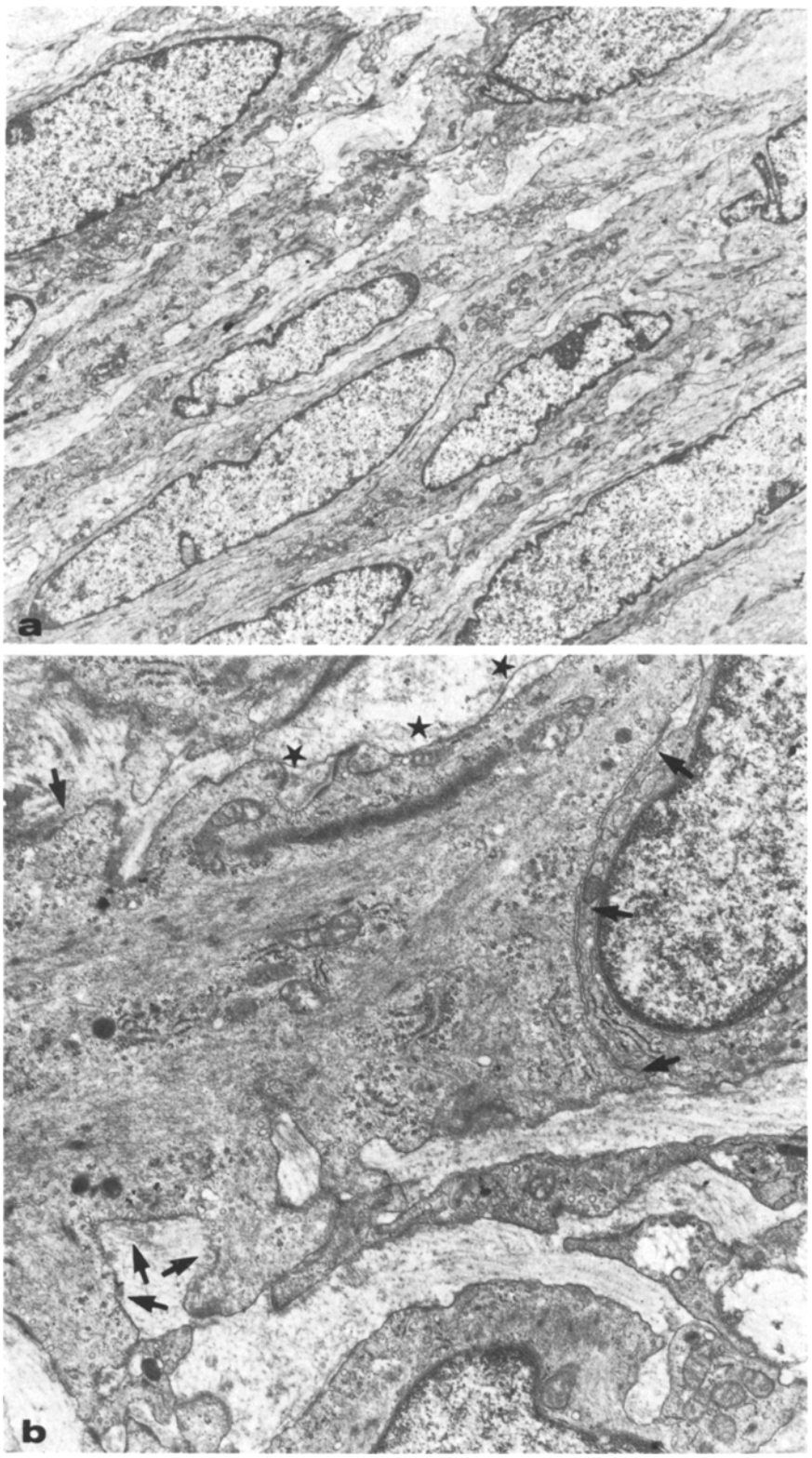
Fig. 2. Small foci of smooth muscle cells in the alveolar interstices, probably a nodule in an early stage of formation. The expansion of the tumor with compression of the alveoli and inclusion of alveolar lining cells can be seen. The pneumocytes in these areas are conspicious and show so-called "cuboidal" transformation. Haematoxilin-Eosin; × 120

Ultrastructural Observations

The smooth-muscle nature of the tumor was demonstrated by electron microscopy. The elongated cells were rich in microfilaments with dimensions appropriate for myofilaments, running parallel to the long axis of the cell (Fig. 3a and b). There were occasional interfilamentous electron dense condensations. Besides microfilaments there was granular endoplasmic reticulum, a few glycogen granules and a few lysosomal granules.

The cellular membrane showed many pinocytotic vesicles and occasionally the formation of a basal lamina (Fig. 3b). Apart from smooth muscle cells, a few fibroblasts with collagen fibers were present in the vicinity of the cells and very seldom inflammatory cells (lymphocytes, mast cells) could be found in the tumor. The epithelial cells covering the nodules and the clefts within the tumor contained rough endoplasmic reticulum, mitochondria, lysosomes, many large lamellar bodies and posessed microvilli on the cell-surface (Fig. 4).

Fig. 3a–b. Ultrastructural features of the tumor cells. **a** The cells are elongated with blunt nuclei and filamentous cytoplasm. In the interstitium are a few collagenous fibers. × 4260. **b** The cytoplasm of the tumor cells contains microfilaments, few lysosomes and granular endoplasmic reticulum. The cellular membrane shows pinocytotic vesicles (*arrows*) and formation of a basal lamina (stars). × 13,800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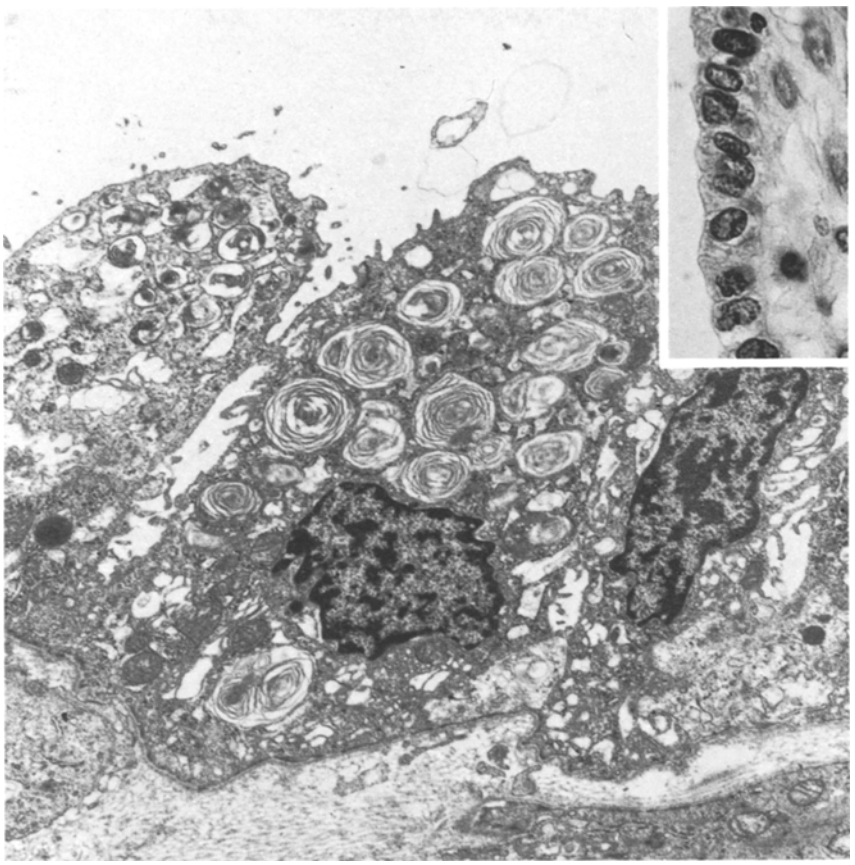

Fig. 4. Epithelial covering of the tumors. *Inset:* light microscopic appearance of the epithelial cells as a continous cuboidal cell layer. Haematoxilin-Eosin; ×650. Ultrastructurally the cells contain abundant lamellar bodies, few lysosomes and mitochondria. The surface shows few microvilli ×6,800

Discussion

Light and electron microscopic study of the tumors showed them to be leiomyomatous. Leiomyomatous lesions are the rarest benign tumors of the lung (Spencer 1977) and can occur in different forms.

Singular leiomyomas, fibroleiomyomas and leiomyosarcomas have been described both in men and women (Carpinisan et al. 1968; Inberg et al. 1969; Sweet 1969; Barthel and Eckert 1971; Guccion and Rosen 1972; Wang et al. 1974). In most cases it can be shown that they originate from bronchi (often endobronchial), bronchioles or larger blood vessels.

Lymphangioleiomyomatosis (Brandt 1952; Basset et al. 1976), lymphangiopericytoma (Enterline and Roberts 1955) or pulmonary and lymph node myomatosis (Vadas et al. 1967) is a diffuse "proliferation of the muscle cells associated with the lymphatics surrounding the acini" (Vázques et al. 1976), which occurs in adult women and usually also involves the lymph nodes of the mediastinum and retroperitoneum (Joliat et al. 1973; Corrin et al. 1975).

It has been considered to be a polytopic hamartoma of the lymph vessel system (Wuketich 1967). It is almost always associated with progressive cystic fibrosis (honeycombing) and haemosiderosis of the lung (Brandt 1952; Heppleston 1956; Vadas et al. 1967; Joliat et al. 1973; Corrin et al. 1975; Basset et al. 1976; Vázques et al. 1976).

Most authors consider the smooth muscle cells in this disease to be derived from the lymphatic vessels (Brandt 1952; Inglis 1960; Vadas et al. 1967; Joliat et al. 1973). However, Basset et al. (1976) and Kane et al. (1978) suggested an origin from pulmonary contractile interstitial cells (myoid stromal cells), myofibroblasts or pericystes.

The leiomyomatous tumors in the patient observed by us clearly do not belong to this entity. There were clinically no signs of involvement of the mediastinal or retroperitoneal lymph nodes. In the histological specimens a diffuse proliferative process or generalized fibrotic or cystic changes of the lungs were absent. Haemosiderosis was absent. The multiple lesions found were nodular and well demarcated and the surrounding lung tissue was normal.

The multiple nodular leiomyomatous process in the lung of the patient presented by us must be considered to belong to a third type of leiomyomatous lesion of the lung which has been designated *"multiple pulmonary leiomyomatous hamartomas"* by most authors.

Hamartomas (Albrecht 1907) are defined as tumor-like malformations containing an abnormal mixture of component tissue intrinsic to the site of origin. The majority of so-called pulmonary hamartomas are considered to be neoplasms of the bronchi (Bateson 1973; Stone and Churg 1977) and contain a mixture of chondromatous, fibrous, myxomatous, myomatous and lipomatous tissues, sometimes together with epithelial gland like structures and a covering of cuboidal sometimes ciliary epithelium (Roenspies et al. 1978).

Most authors consider the epithelial lining and the glandular structures of multiple pulmonary leiomyomas to be an integral and intrinsic part of the tumor ("fibroleiomyoadenomatous hamartoma, adenomyoma"; Keers and Smith 1960; Silverman and Kay 1976; Roenspies et al. 1978) and the resemblance to the epithelial component of other so-called hamartomas caused them to classify this multitopic tumor as a "fibroleiomyomatous hamartoma" (Dempster 1969).

Our ultrastructural study showed that the epithelial covering of the pulmonary leiomyomas consisted of cells resembling granular pneumocytes (II). An increase of pneumocytes II is a well known reaction in numerous pulmonary lesions which lead to a decrease of compliance (fibrosing alveolitis, pulmonary fibrosis, bronchopulmonary dysplasia; Burkhardt et al. 1977; Gebbers et al. 1977). In multiple leiomyomas this epithelial covering is probably a reaction of the alveolar lining cells of the preexisting alveoli (which in the adjacent tissue also exhibit increase in pneumocytes II) to the increasing rigidity of their substratum. The cleft like spaces in the tumor probably are remnants of alveoli occupied by the slowly progressive growing and expanding tumor (Horstmann et al. 1977; Piccaluga and Capelli, 1967; c.p. Fig. 2). The observation of this phenomenon in the vicinity of a number of benign lung tumors (probably also in other so-called hamartomas; Bateson, 1973) can be considered to be an expression of the benign behaviour of the tumor. A covering by

cuboidal or columnar epithelium does not by itself justify the classification of a pulmonary tumor as "hamartoma". The occurrance of fibrous tissue, capillaries and inflammatory cells in pulmonary leiomyomas cannot be considered to be "hamartomatous" as they are part of most tumors – and of course, of uterine leiomyomas. Kaplan et al. (1973) differentiated two types of multiple pulmonary leiomyomas, primary benign multiple fibroleiomyomatous hamartomas and "benign" metastasizing leiomyomas. However, Horstmann et al. (1977) clearly pointed out that pulmonary fibroleiomyomatous hamartomas and "benign" metastasizing leiomyomas cannot be distinguished and that they are not true hamartomas. He raised the question of whether they are simply metastasizing uterine leiomyomas (corresponding to low-grade leiomyosarcomas; cp. Ariel and Trinidad 1966; Pocock et al. 1976).

We believe that the hamartomatous nature of multiple pulmonary leiomyomas is unlikely and that the term hamartoma should be abandoned in this context. However, it is also uncertain whether all cases should be considered metastases from uterine leiomyomas. The lack of cellular pleomorphism and mitoses and the fact that metastases in other organs are absent in all cases of multiple pulmonary leiomyomas reported seems to contrast with cases of low-grade leiomyosarcomas of the uterus which metastasize into other organs (Steiner 1939; Pocock et al. 1976).

Surely leiomyomas of the lung could arise from the contractile system of the lung acini ("alveolar muscle" myoid stromal cells, contractile interstitial cells, myofibroblasts; Baltisberger 1921; Corrssen 1963; Collet and Des Biens 1974; Kapanci et al. 1979).

The multiple development of nodules in the alveolar interstices (cp. Fig. 2) where vascular or bronchiolar smooth muscle cells are absent suggests a "neoplastic diathesis" of this system. Apparently the growth potential of the single nodule is limited and the progression of the disease is caused by the formation of new nodules.

The aetiology of this rare benign pulmonary tumor is as little understood as the pathogenesis. A striking point, however, is the fact that the cases of multiple pulmonary leiomyomas reported to date and the case presented here were all in females, suggesting a hormonal dependency of the disease.

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