Virchows Archiv [Pathol Anat] (1985) 405:253–261

Virchows Archiv A

Atypical lipomatous hamartoma of the lung

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Summary. An unusual lipomatous tumour discovered accidentally in the right middle lobe of a 34-year old woman is described. The tumour was associated with an intrapulmonary typical chondromatous hamartoma in the same lobe but separate from the first lesion.

The lipomatous tumour was primarily an intrapulmonary lipoma but in a few of the numerous sections made minute islands of cartilage and bone were discovered along with a few epithelial-lined clefts. These justify the diagnosis of a lipomatous hamartoma.

Dispersed among the mature fat cells were a few immature cells with atypical nuclei. Cellular atypia in predominantly lipomatous hamartomas has not previously been reported. As the occurrence of atypical lipoblast-like cells might lead to an erroneous diagnosis of liposarcoma, this case is thought worthy of reporting.

Key words: Lipomatous hamartoma – Atypia – Lung

Introduction

Fat is often present in small amounts of benign neoplasms of the lung (Watts et al. 1946). True lipomas or predominantly lipomatous hamartomas, however, are rare. They are thought to arise from fat, normally present in bronchi containing cartilage, or from small amounts of fat which can be found beneath the pleura. Depending on their site of origin lipomas are divided into endobronchial and peripheral or subpleural lipomas, the latter being exceptionally rare; very few cases have been reported in the literature (Plachta and Hershey 1962; Shapiro and Carter 1954; Spencer 1977; Staub et al. 1965; Touroff and Seley 1951).

We wish to report a peripherally located lipomatous tumour. The presence of very small areas with cartilage, bone and epithelial-lined clefts cause us to term the tumour a lipomatous hamartoma rather than a lipoma. Cellular atypia has not been reported previously in these tumours. The

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occurrence of atypical cells in the present case lead to the diagnosis of liposarcoma, but the subsequent follow-up and the clinical course proved otherwise.

Case report

A 34-year old nurse with no previous medical history and no symptoms whatsoever was admitted to hospital, because a routine X-ray examination of the chest had revealed a coin-lesion in the right lung field. Mediastinoscopy and bronchoscopy were normal.

Thoracotomy was performed, and in the middle lobe of the right lung two tumours were found. The smaller of the two macroscopically a typical hamartoma, located subpleurally close to the lung hilus, was easily enucleated. The other tumour, located subpleurally on the lower aspect of the lobe was reported to be goose-egg-sized, smooth, well-encapsulated, with a cut-surface resembling fatty tissue. The tumour was readily enucleated. The impression was that the process was benign. The tumour was supposedly totally removed, and there were not signs of invasion into surrounding lung tissue.

The histological report, however, suggested liposarcoma, and re-operation with lobectomy was performed a few days later. The patient made an uneventful recovery, and remains trouble free four years after the operation.

Materials and methods

Tumour tissue from the first and second operation was fixed in 10% neutral buffered formalin, embedded in paraffin and sections were stained with haematoxylin-eosin, van Gieson-Hansen's connective tissue stain, Masson-trichrome and Gordon and Sweet's method for reticulin.

Selected sections were stained with anti-sera against α_1-antitrypsin, α_1-antichymotrypsin, lysozyme and S-100 protein. The indirect immunoperoxidase method was used as described previously (Nielsen et al. 1983). All anti-sera were raised in rabbits and obtained from DAKO, Copenhagen, Denmark. The anti-sera were used in the following dilutions: α_1-antitrypsin 1:50, α_1-antichymotrypsin 1:100; lysozyme 1:100 and S-100 protein 1:100. Control sections were incubated with non-immune rabbit serum replacing the anti-sera in the first step.

Results

Gross pathology

The smaller of the tumours measured $3.5 \times 2.5 \times 2$ cm. It was firm, greyish-white, lobulated, and the cut-surface appeared cartilage-like with dispersed calcifications.

The larger tumour measured $6.5 \times 6 \times 4$ cm. It was soft, with an even yellowish, somewhat greasy appearance on the cut-surface.

The lobectomy specimen revealed a large operation cavity with soft, yellowish, ill-defined tissue on the lateral aspect of the lung. In addition, the anterior edge of the operational cavity contained small, ill-defined, irregular, firm areas. The bronchi were without tumours. The lung parenchyma otherwise appeared normal.

Light microscopy

After de-calcification of the smaller tumour sections showed predominantly cartilaginous tissue surrounded by a fibrous capsule. No epithelial elements

were present. The findings were consistent with those of a cartilaginous hamartoma (chondroma).

The second tumour was composed of predominantly univacuolated fat cells centrally, surrounded by a capsule of fibrous connective tissue (Fig. 1). The fibrous capsule contained spindle-shaped cells along with a few large atypical cells (Fig. 2). Among the mature fat cells a few multi-nucleated tumour cells, resembling lipoblasts, were found. A very small percentage of the univacuolated cells had atypical nuclei, sometimes centrally located (Fig. 3). The nuclei were enlarged, hyperchromatic and moderately polymorphic. At the margin of the fibrous capsule the tumour became more cellular mainly due to proliferation of spindle-shaped cells with hyperchromatic nuclei. No mitoses were seen. Foci of lymphoid tissue were located in the connective tissue making up the capsule.

Sections from the operational cavity in the lobectomy specimen showed, that the tumour had no been totally removed during the first operation. Apart from granulation tissue remains of the mesenchymal tumour were found (Fig. 4). In addition to the dominating fatty component a few small islands of cartilage and osseous tissue were seen in a couple of the numerous sections examined (Figs. 5 and 6). Located in the same area were a few thick-walled arteries and small irregular clefts with epithelial-lined infoldings. The epithelial cells were of a benign cuboid or columnar type. Here again a few large, lipoblast-like cells were found among the mature fat cells. No mitoses were seen.

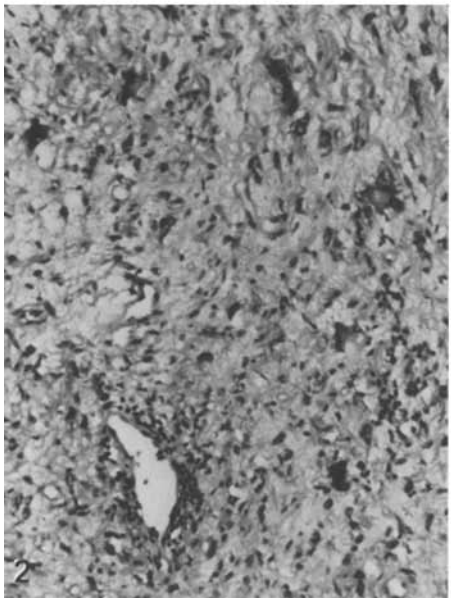
Immunohistochemistry

The tumour tissue showed no staining reaction when antisera against α_1-antitrypsin, α_1-antichymotrypsin and lysozyme were employed. The chondrocytes in the cartilage of the bronchi and the few small islands of cartilage in the tumour were the only components which showed a strongly positive staining reaction with anti-serum against S-100 protein. No specific immunostaining was observed in the control sections.

Discussion

The term hamartoma was introduced by Albrecht (1904) to designate lesions composed of tissue elements normally present within a given organ, but lacking normal organization. The majority of pulmonary hamartomas are solitary, and of chrondromatous type. The origin or cause of these lesions has been the subject of considerable debate. A congenital malformation has often been suggested. Bateson (1973) presented an alternative theory regarding all pulmonary hamartomas as true neoplasms of fibrous connective tissue of the bronchi, while the epithelial elements frequently present in these tumours were suggested to represent inclusions of bronchial epithelium.

A few pulmonary hamartomas have been studied by electron microscopy. Stone and Churg (1977) reported two chondromatous hamartomas in



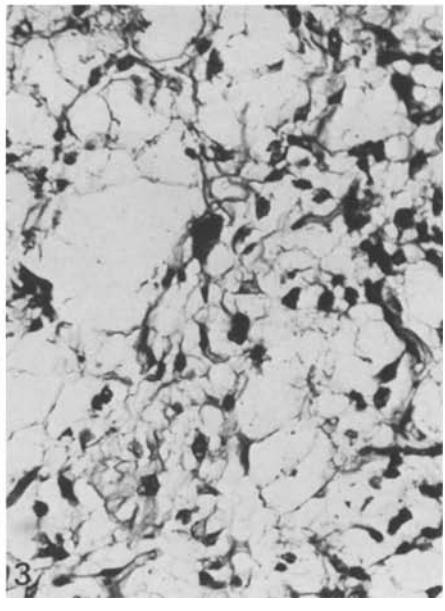
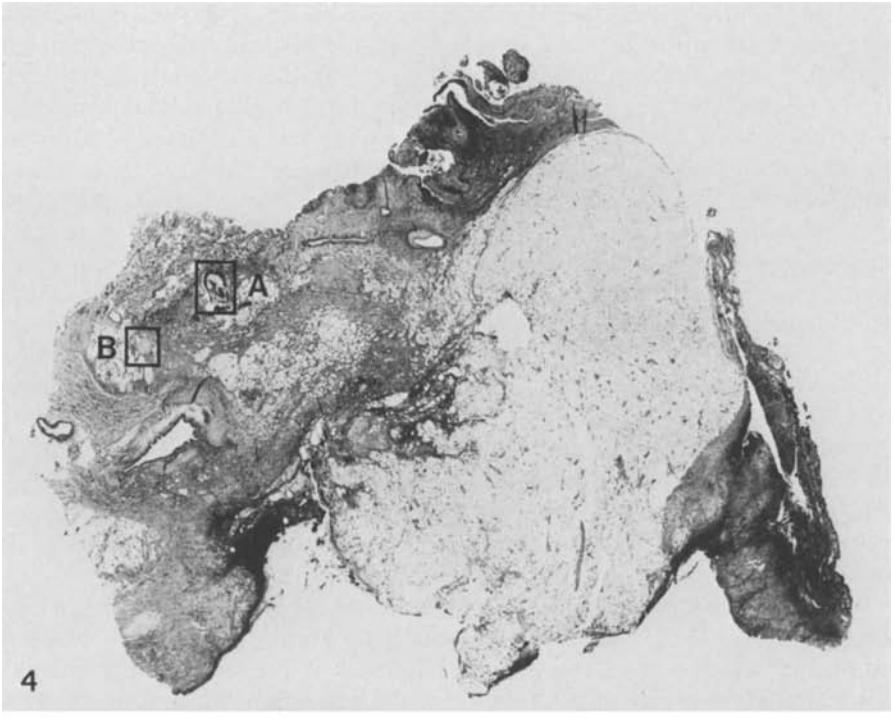
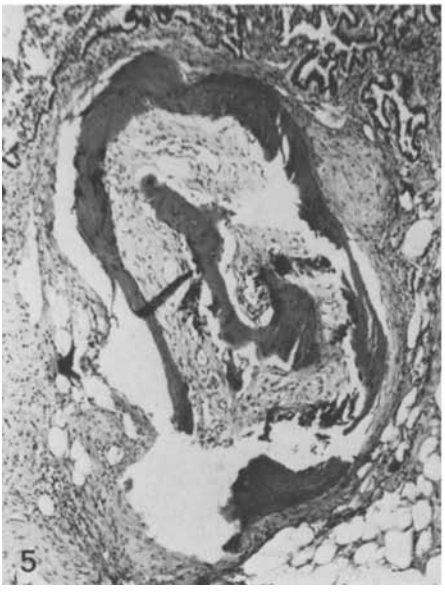


Fig. 1. Low power photomicrograph illustrating the fatty tumour with a fibrous capsule (H&E $\times 5$)

Fig. 2. The fibrous capsule showing spindle-shaped cells along with a few large atypical cells (H & E $\times 160$)

Fig. 3. The fatty tumour composed of adipocytes with large hyperchromatic nuclei, some centrally placed. (H & E $\times 300$)





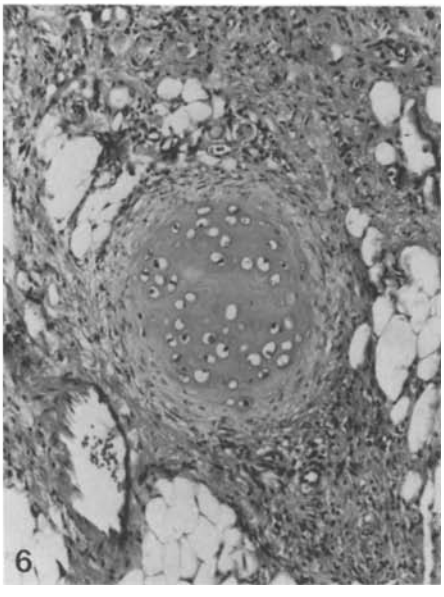


Fig. 4. Low power photomicrograph of the remaining tumour tissue in the operational cavity. (H & E $\times 5$)

Fig. 5. Islands of osseous tissue from the boxed area A in Fig. 4. (H & E $\times 65$)

Fig. 6. Islands of cartilaginous tissue from the boxed area B in Fig. 4. (H & E $\times 100$)

which they found the epithelial component to be similar to the epithelium lining the distal broncioles and the alveoli of the adult lung when examined ultrastructurally. The stromal cells beneath the epithelium were mostly stellate, but others were spindle-shaped resembling fibroblasts and deeper in the stroma typical chondrocytes were identified. The authors argued in favour of a simultaneous metaplasia of both meso- and endodermal elements of the lung. Perez-Atayde and Seiler (1984) reported three cases of histologically different pulmonary hamartomas, one consisting mainly of mature cartilage, the other consisting only of loose myxoid fibrous tissue, while the third showed a mixture of these two elements. The epithelial component was morphologcially identical to the epithelium of terminal bronchioles and alveoli, but in contrast to the former report, a distinct basal lamina was always found present. Ultrastructurally, the undifferentiated mesenchymal cells observed by light microscopy were of two types: cells showing features of smooth muscle and cells showing features of fibrocytes. Transition from undifferentiated mesenchymal cells to chondroid tissue was frequently observed. This ultrastructural study supports the above mentioned theory of Bateson (1973). In these two studies there was no mention of stromal cells showing a lipoblastic differentiation.

Whether the larger tumour in the present case should be called a lipomatous hamartoma or a peripheral lipoma with chondromatous and osseous metaplasia, is only of interest if one chooses to regard lipomas only as true neoplasms and not as a variety of pulmonary hamartomas along with chondromas and leiomyomatous hamartomas. Two writers (Bellin et al. 1971; Som and Feuerstein 1951) reported three cases of endobronchial lipomas with cartilaginous metaplasia. They stressed the fact that metaplasia is commonly seen in lipomas in other locations and may therefore be expected in lipomas of the lung and that these tumours should not therefore be regarded as hamartomas.

In the present case the mixed tumour elements were found only in the wall of the operational cavity, and could represent the "base" or origin of a lipoma. It seems likely that similar areas in the very few cases of peripheral lipomas examined could have escaped attention, because they represent only a very small proportion of an otherwise typical lipoma. The only reason that so many sections were made in our case was the uncertainty about possible malignant change.

In the fibrous capsule spindle-shaped cells along with a few large, atypical cells were identified. These cells showed no content of α_1-antitrypsin, α_1-antichymotrypsin or lysozyme with the immunoperoxidase method. These substances are claimed to be markers for tumours of histiocytic origin (Meister and Nathrath 1981, and Kindblom et al. 1982) for example malignant fibrous histiocytoma, which recently has been reported as a primary tumour of the lung (Paulsen et al. 1981, Jundt et al. 1983, and Lee et al. 1984). The positive staining of chondrocytes for S-100 protein is in accordance with other reports (Nakajima et al. 1982, Kahn et al. 1983). Cocchia et al. (1983) reported, that S-100 protein labelled neoplastic cells in liposarcomas. In our case the lipoblast-like cells and the adipocytes showed no

positive reaction with antiserum to S-100 protein, which is in agreement with other reports concerning adipose tissue (Nakajima et al. 1982; Kahn et al. 1983).

Single hamartomas are commonly found in men, the male to female ratio has been reported as 4:1 with a peak incidence in the sixth decade (Koutras et al. 1971).

Multiple hamartomas are, however, very rare. Nili et al. (1979) reported a case and reviewed the literature finding only 11 additional cases all occurring in females, the mean age being considerably lower than in cases of single hamartomas. All these tumours were fibroleiomyomatous hamartomas and most of the women had a history of leiomyomatous disease of the uterus.

Two cases of pulmonary multiple fibroleiomyomatous hamartomas have been studied by electron microscopy. In one case the stromal component was dominated by mature smooth muscle cells (Silvermann and Kay 1976) and in the other case a mixture of fibroblasts and smooth muscle cells was identified (Shirakusa et al. 1979). A case of multiple chondromatous hamartomas was reported by King et al. (1982) in a middle aged male. A fibroleiomyomatous hamartoma has also been reported coexisting with a chondromatous hamartoma in a 39-year old male (Vella et al. 1982). A case similar to ours was reported by Jones et al. (1973). They found an intrapulmonal peripheral lipoma associated with a typical hamartoma located intrabronchially in a different lobe. They suggested the case as possibly representing multiple hamartomas with development of a lipoma in one of these. We have not found other reports of multiple hamartomas, where a chondromatous hamartoma coexists with a lipomatous hamartoma as in the present case.

Single pulmonary hamartomas are usually recognized as asymptomatic coin-lesions on chest X-ray examination or as incidental postmortem findings. Clinical interest in hamartomas concerns the differentiation from malignant lesions, and in the rare cases of multiple lesions metastatic tumour is often suspected primarily. Endobronchial hamartomas may give symptoms secondarily to obstruction, but peripheral hamartomas can grow to large size without giving cause to symptoms.

Hamartomas are essentially benign tumours. They have been known to increase in size when followed radiographically over periods of many years, but malignant transformation has not been proved in these tumors, although recent report has suggested an association with malignant neoplasms and chondromatous hamartomas (Karasik et al. 1980).

An unusual feature in the lipomatous tumour of the present case was the finding of atypical lipoblast-like cells with enlarged, hyperchromatic, polymorphous nuclei. Cellular atypia of this kind has not previously been described in pulmonary lipomatous tumours, but atypia has been reported in lipomas located intramuscularly or subcutaneously by Kindblom et al. (1982). They reviewed a number of these tumours previously diagnosed as lipomas or well differentiated liposarcomas and found, that some of these could be characterized by a moderate nuclear atypia in a small number

of cells. The tumours with atypia showed a clear tendency to recur, but never showed sign of malignant change. The significance of atypical cells in this lipomatous tumour is not known, but the benign course and no signs of recurrence supports the conclusion, that the tumour was benign. It seems important to point out, that atypicality can be found in lipomatous tumours of the lung, in order to prevent these tumours being misdiagnosed and treated as liposarcomas.

Acknowledgement. The atuhors thank Professor H. Spencer, London for his comment on this case.

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Accepted September 24, 1984