Virchows Arch (1997) 430:181–184

CASE REPORT

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Pulmonary nodule caused by an alveolar adenoma of the lung

Received: 17 July 1996 / Accepted: 7 October 1996

Abstract Alveolar adenomas of the lung may be a rare cause of solitary coin lesions on chest radiographs. We report a case of this neoplasm, describe its morphological and immunohistochemical characteristics and give further evidence that alveolar adenomas of the lung represent a benign proliferation of both the alveolar epithelium and the septal mesenchyme.

Key words Lung adenoma · Immunohistochemistry · Case report

Introduction

Alveolar adenoma of the lung (AAL) is a benign tumour with distinct histological features, only nine cases of which have been reported in the literature to date. AAL is thought to represent the benign counterpart of the bronchiolo-alveolar carcinoma [6, 9] and is composed of proliferating alveolar pneumocytes within a neoplastic stroma. There is no convincing evidence to support the hypothesis that AAL represents a variant of the so-called "sclerosing haemangioma of the lung", although clinical and histopathological parallels between these entities undoubtedly exist [5, 6, 9]. The knowledge of AAL may be of practical importance in the differential diagnosis of solitary peripheral lesions of the lung. We report a new case of AAL, focusing on the histological and immunohistochemical profile of this tumour.

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Clinical history

A 52-year-old woman was examined for recurrent paraesthesiae and pain in her arms and back. On investigation, severe degenerative changes of her vertebral column were found and a cervical spine syndrome was diagnosed. As an incidental finding, the chest radiograph revealed a solitary peripheral nodule in the lower lobe of the left lung, which was interpreted as a hamartochondroma (Fig. 1). Clinically, an extrapulmonary malignancy was ruled out, and a diagnostic thoracotomy was performed. The nodule was found to be located in the postero-basal segment of the left lung and was removed with healthy tissue margins by a wedge resection. One year after tumour resection the patient is alive and well, without recurrent disease. The patient has received symptomatic treatment for the cervical spine syndrome.

Materials and methods

The resected lung specimen was fixed in 4% buffered formalin and embedded in paraffin. Sections were stained with haematoxy-

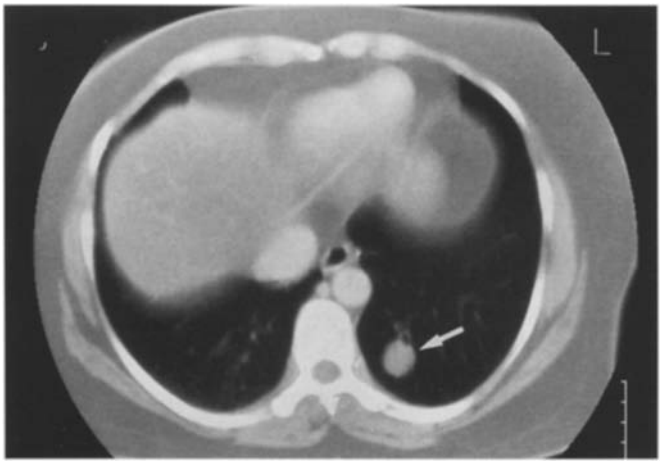


Fig. 1 Computed tomographic scan of the chest, showing a solitary tumour nodule in the basal periphery of the left lung (*arrow*)

Fig. 2 Alveolar adenoma of the lung. Non-encapsulated multicystic tumour with sharp borders and compression of the adjacent lung tissue. PAS, ×20

lin-eosin (H&E), elastic-van Gieson (EvG), and periodic acid-Schiff (PAS). Immunohistochemistry was performed with the alkaline phosphatase-anti-alkaline phosphatase (APAAP) technique; the chromogen was Fast Red (TR-salt [Serva, Heidelberg, Germany] and naphthol-AS-MX-phosphate [Sigma, St. Louis, Mo.]). Antibodies to the following antigens were used: cytokeratins CK AE1/3, CK7, CK19 (Progen, Heidelberg, Germany), CK18 (Sigma-Aldrich, Deisenhofen, Germany), epithelial membrane antigen (EMA), neuron-specific enolase (NSE), factor VIII, vimentin, desmin (Dako, Hamburg, Germany), carcinoembryonic antigen (CEA; Signet-WAK, Bad Homburg, Germany), Chromogranin A (Boehringer, Mannheim, Germany), MIB-1 (Dianova, Hamburg, Germany), and CD3, CD20, CD68 (Dako, Hamburg, Germany with the EPOS-kit, using diaminobenzidine [DAB] as chromogen). Positive and negative controls were used in every staining run.

Pathological findings

The tumour nodule within the peripheral lung parenchyma was well circumscribed, had a soft, greyish-red cut surface and measured 2 cm in size. There was no irritation of the overlying pleura by the tumour. Histologically, the nodule consisted of alveolar spaces which were two- to five-fold the size of non-neoplastic lung alveoli. The lesion had no capsule but was sharply demarcated from the surrounding compressed lung tissue (Fig. 2). The alveolar spaces were lined by a single layer of cuboidal cells without nuclear atypia. The alveolar lumina contained foamy histiocytes, erythrocytes and PAS-positive granular material. The septa between the alveolar spaces were thin, contained delicate collagen fibres but no elastic fibres, and were rich in capillary blood vessels. Focally, aggregates of lymphocytes were present (Fig. 3a, b). Within the tumour neither bronchioli nor larger blood vessels were found. Generally, the mitotic rate was very low (less than 1 mitotic figure/10 high-power fields [HPF]). Immunohistochemically, the lining cells of the alveolar spaces were reactive with antibodies against various cytokeratins (CK AE1/3, CK7, CK18, CK19; Fig. 4a, b) and epithelial membrane antigen (EMA). The proliferation rate as determined by the antibody MIB-1 (paraffin Ki-67) showed nuclear immunoreactivity of less than 1% among both lining cells and interstitial cells of the alveolar septa; the lymphatic cells in the septa consisted of a mixture of B-cells (CD20+) and T-cells (CD3+). The foamy histiocytes within the tumour and in the surrounding parenchyma were immunoreactive with CD68. Factor VIII and vimentin immunostaining was confined to endothelial cells. Within the tumour there were no cells that were immunoreactive with carcinoembryonic antigen (CEA), desmin, or the neuroendocrine markers neuron specific enolase (NSE) and chromogranin A.

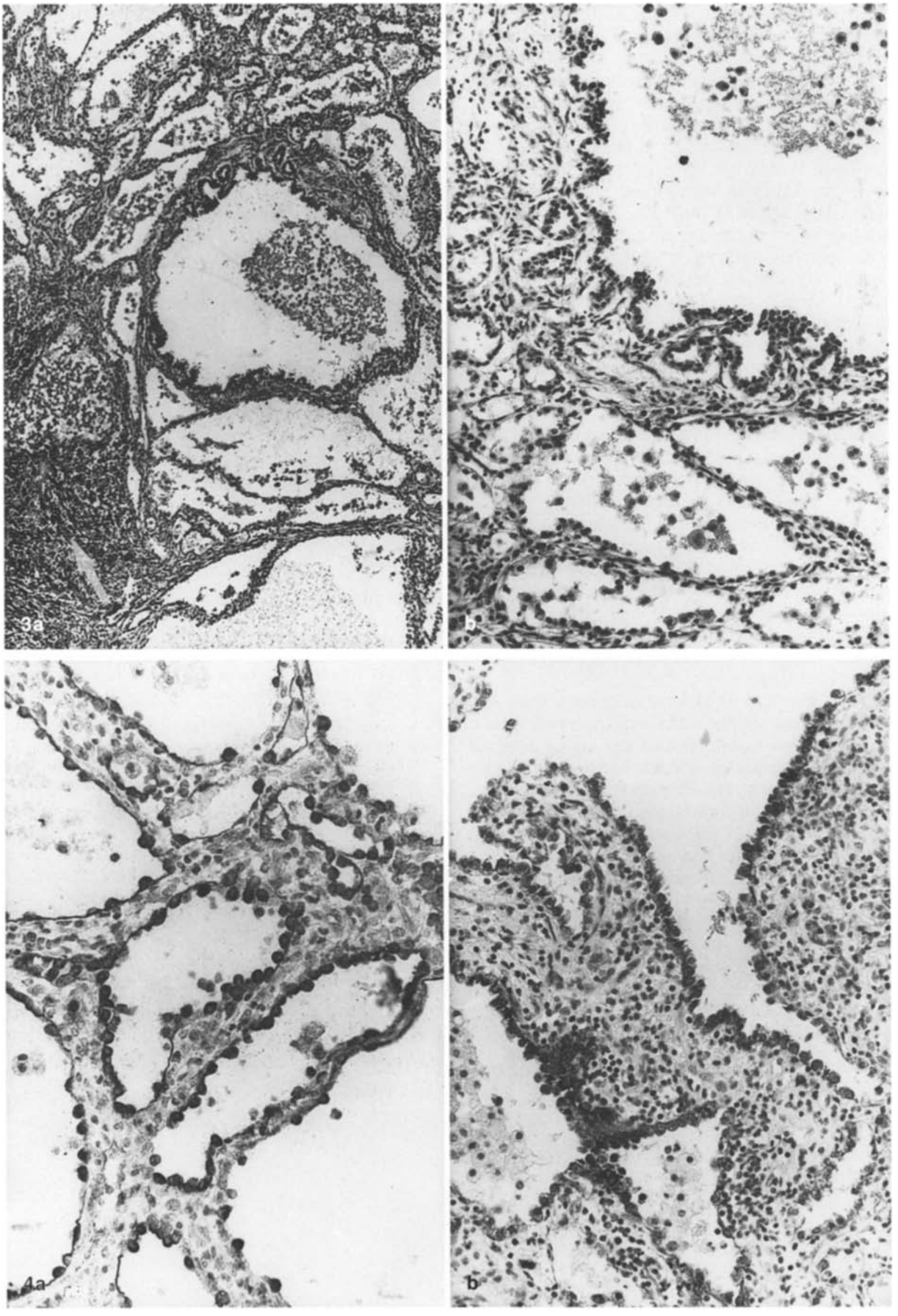
Discussion

Since the first descriptions in 1986, a total of nine cases of AAL have been reported in the literature [2, 5, 6, 9]. Some authors [1, 6, 9] speculate that another case of AAL was described in 1974 with the designation "lymphangioma of the lung" [7]. We here present another classic case of this entity, which has been described too recently to be listed in the 1982 WHO classification of lung tumours [8]. AALs occur as solitary lesions in older persons (age range: 45–74 years, mean age: 58 years), and mostly (70%) in women. All reported cases have been asymptomatic and have been incidentally. Owing to the subpleural location of the lesions, bronchoscopy is unlikely to reveal AALs. Macroscopically, these tumours manifest as well-demarcated spongy nodules (tumour size range: 1.2–2.8 cm; average size: 1.9 cm), which may be located in any lobe beneath an intact pleura. Microscopically, they possess unique histological characteristics, which allow diagnosis by light microscopy alone.

AALs are composed of multicystic alveolar spaces lined by a single layer of cuboidal cells. These lining cells sometimes appear hobnail-shaped or flattened, but they show no cytological atypia. The epithelial nature of the lining cells is reflected by their immunostaining with different cytokeratins and with EMA [5, 6, 9]. In our case, the lining cells showed the same immunohistochemical staining pattern as has been reported in the literature, with the exception of carcinoembryonic antigen (CEA), which we found to be completely negative. From the light microscopic appearance it has been suggested that the epithelial component of AAL is derived from

Fig. 3a Alveolar adenoma composed of neoplastic alveolar spaces separated by thin septa-like mesenchyme. Some of the alveolar lumina contain floccular material, foamy histiocytes and erythrocytes. There is a focal infiltrate of lymphocytes (*arrow*). H&E, ×60. **b** Higher magnification. Note bland overall cytology of the tumour cells. H&E, ×160 ▶

Fig. 4 Positive immunostaining for **a** cytokeratin AE1/3 and **b** cytokeratin 18 restricted to the epithelial lining of the neoplastic alveoli. Note hobnail shape of some of these lining cells. **a** ×200, **b** ×160


3a
b
4a
b

type-II alveolar pneumocytes [2, 5, 6, 9], an hypothesis confirmed by investigations revealing common features in both cell types. First, the surfactant apoproteins B and C are immunohistochemically detectable in the cytoplasm [2]. Secondly, on the ultrastructural level, both cell types contain lamellar bodies in the cytoplasm and short microvilli on the cell surface [5, 6, 9]. By analogy with non-neoplastic alveoli, the alveolar spaces in AAL often contain macrophages in their lumina, which immunostain with CD68 and MAC 387 [2]. The loose septa-like mesenchyme surrounding the alveolar spaces in AAL shows no specific immunohistochemical reactions and stains negatively with cytokeratin and desmin [2, 9]. Although AAL are not truly encapsulated, their borders are sharply demarcated from the adjacent compressed lung tissue, which allows surgical enucleation of the lesions.

The present case differs from the descriptions in the literature only by the absence of a zonal pattern (larger cystic spaces in the centre, microcystic architecture on the periphery) within the tumour. Some authors [2, 6, 9] regard AAL as benign proliferations of both the alveolar epithelium (type II alveolar pneumocytes) and the septal mesenchyme, while others [1] speculate that the proliferating cells in AALs may be solely mesenchymal and that the cystic spaces may be incorporated alveoli. We agree with the former idea, since we were able to demonstrate that both the epithelial and the mesenchymal component of the tumour showed a similarly low MIB-1 proliferation rate. Until now all cases of AAL have shown a benign clinical course; there have never been metastases or recurrences after surgery.

Semeraro and Gibbs [5] have suggested that AAL represents a variant of the sclerosing haemangioma of the lung (SHL), but with a monophasic histological pattern in which pneumocytes predominate. Indeed, the two entities share common features (female predominance, age distribution, tumour location and clinical behaviour), but differ considerably in their histology (SHL: variegated histological patterns including papillary and solid areas, sclerosis and haemorrhage; inflammatory reaction). Reviewing the literature, Dail [1] remarks that SHL are non-endothelial lesions in which entrapped alveolar pneumocytes line cystic spaces but in which "the nature of the basic tumour cells remains elusive". We, therefore, conclude that further studies are needed to clarify the relationship between AAL and SHL. The differential diagnosis of AAL also includes benign lesions like lymphangiomas (cystic spaces with an endothelial lining), hamartomas (chondroid, bronchiolar and adipose tissue) and adenomatoid malformations as well as bronchioloalveolar carcinomas (infiltrative growth, cytological atypia) [1, 5, 6, 9]. Miller [4] and Kushihashi et al. [3] have used a similar term, "bronchioloalveolar (cell) adenoma (BAA) of the lung" for different lesions. BAA are described as unencapsulated nodules with an alveolar growth pattern, found in the neighbourhood of overt lung carcinomas. BAA measure only a few millimetres and are often multicentric; the cells lining the alveolar spaces always show nuclear atypia. The authors interpret BAA as precursor lesions for adenocarcinomas of the lung, and since BAA and AAL are neoplasms with different biological behaviour, a clear distinction must be made between the two terms.

In conclusion, alveolar adenomas of the lung represent a distinct benign tumour entity, which should be included in the differential diagnosis of solitary peripheral lung nodules.

Acknowledgements The authors thank Ms. Sabine Noll for her excellent technical assistance.

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Note added in proof After submission of the manuscript another new case of AAL was reported: Oliveira P, Nunes JFM, Clode AL, Duro da Costa J, Almeida MO (1996) Alveolar adenoma of the lung: further characterization of this uncommon tumour. Virchows Arch 429:101–108