

Boleslaw Papla<sup>1</sup>, Eugeniusz Malinowski<sup>2</sup>

## Alveolar Adenoma of the Lung - a Report of Two Cases

<sup>1</sup>Chair and Department of Clinical and Experimental Pathology, Collegium Medicum, Jagiellonian University Kraków,

<sup>2</sup>Thoracic Surgery Ward, Specialist Center of Lung Diseases, Bystra Śląska

**The authors present two cases of an extremely rare alveolar adenoma of the lung in a 64-year old female and a 45-year old male surgical patients. The report is the first description of such a tumor in the Polish literature.**

### Introduction

Alveolar adenoma of the lung was described for the first time by Yousem and Hochholzer [13] in 1986 based on the analysis of six cases seen at the U.S. Army Forces Institute of Pathology. The tumor is extremely rare and since that time mainly isolated reports on such cases have been published [1, 8, 10]. Alveolar adenoma of the lung has been included in the WHO classification of pulmonary tumors (1999) [11]. A more comprehensive description of 17 cases, including the original six patients presented by Yousem and Hochholzer and based on immunohistochemistry and electron microscopy [2] was also prepared at the U.S. Army Forces Institute of Pathology in 1999.

Most likely earlier authors considered the tumor a lymphangioma of the lung [12]. To the best of our knowledge, not a single case of alveolar adenoma has been presented in the Polish literature.

### Cases Description

**Case 1:** A 54-year old asymptomatic male, in whom a round mass situated in the peripheral zone of the right lung was accidentally detected radiologically in routine X-ray in November 1989. Preoperative tests failed to establish a diagnosis. In January 1990, a wedge resection of the lung, including a tumor, approximately 2.5cm in diameter, was performed. The postoperative course was uneventful; a follow-up examination performed in November 2002 revealed normal chest X-ray with resection-associated lesions. The patient presented with no complaints.

The intraoperative specimen No. 1110342 submitted for pathological analysis constituted a lung fragment with a gray-whitish mass 1cm in diameter. The material was fixed

in formalin and embedded in paraffin blocks and then routinely stained with HE and additionally with Mayer's mucicarmine, paS and paS following diastase, and also subjected to immunohistochemical staining: EMA, cytokeratin, chromogranin, actin, SP-A (surfactant), Ki-67 and HMB-45, alpha-1-antitrypsin, CD34 and TTF-1 applying sera manufactured by DAKO. The reactions were obtained using standard methods and the controls.

Histologically, the tumor was not encapsulated, yet it was clearly separated from the surrounding lung tissue (Fig. 1), which was slightly atelectatic. The mass consisted of numerous cystic spaces with the diameter ranging between that of an alveolus and a diameter almost twenty times greater. The spaces were layered with a single layer of cubic or hobnail cells that were at times flattened. The cysts were filled with protein contents, which was negative in the mucicarmine staining and positive for the SP-A surfactant. The stroma separating the cysts was scarce, similar to the interalveolar septa, or at times it was thicker, showing the presence of cells filled with clear, transparent cytoplasm and a round nucleus, or else revealing spindle cells with scant cytoplasm (Fig. 2). No mitotic figures were noted in the tumor specimen.

The cellular layer within the cysts was positive for the SP-A surfactant, similarly as type II pneumocytes. These cells were also EMA-positive (Fig. 3) and weakly positive in the cytokeratin reaction. Actin reacted with the small vessel walls within the stroma of the tumor, TTF-1 showed a weak positive reaction in the nuclei of some tumor cells, while the Ki-67 reaction was negative in all neoplastic cells.

**Case 2:** A 66-year old female, an ironworker by profession, who had been exposed to metallic dust over 25 years of her employment. She presented with signs of stable coronary disease and grade II hypertension (BP 170/90). Her routine chest X-ray (Fig. 4) showed a tumor-like lesion in the right lung. Sputum cytology was negative, similarly as *Mycobacterium tuberculosis* testing, but she was administered antituberculous therapy for six months, without any success. In May 2002, the middle lobe of the right lung was



Fig. 1. The tumor margin in case 1, clearly separated from the pulmonary parenchyma. HE.

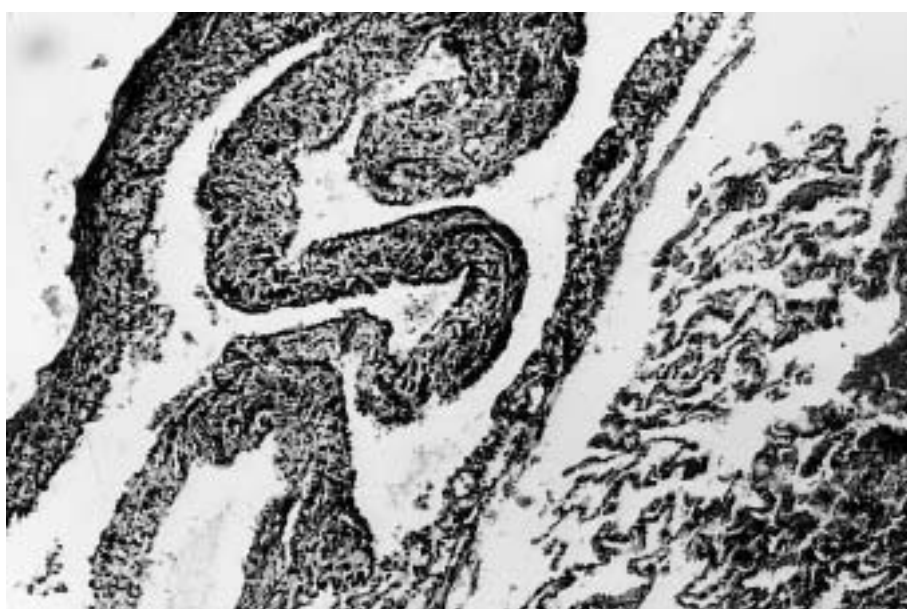


Fig 2. A tumor composed of numerous air spaces layered with a single-layer epithelium with a relatively thick stroma between the cysts (material from tumor margin). HE.

resected along with a tumor situated adjacent to the main bronchus. The postoperative course was uneventful.

The material submitted for histopathological analysis consisted of the middle lobe of the right lung with a round tumor, 14mm in diameter. The mass was grayish, somewhat harder than the surrounding pulmonary tissue, clearly separated from the lung and situated in the vicinity of the slightly stenotic main bronchus (specimen No. 1487184). The formalin-fixed material was embedded in paraffin and the sections were subjected to routine and immunohistochemical staining employing the same methods as these described in Case 1.

Histologically, the tumor was clearly separated from the surrounding normal pulmonary parenchyma, but it was not encapsulated and partially penetrated the bronchus, where it was layered with a normal mucosa (Fig. 5). The mass

consisted of numerous cysts whose size ranged from that of normal alveoli through several to less than 20 times greater. The cysts were layered with a single epithelial layer, without any papillary structures (Fig. 6). Within the relatively numerous intracystic spaces, granular protein contents was seen, sometimes showing whorled bodies (Fig. 7). The contents was mucicarmine and PAS-negative, while the cells layering the air spaces, whorled bodies and the contents within the cysts were surfactant (SP-A) positive (Fig. 8). At times, these spaces, especially those situated at the periphery of the tumor, showed macrophages or fresh blood. The cysts were layered by a single layer of hyperplastic type II pneumocytes, often cubic or hobnail in shape, with typical nuclei. The stroma of the cystic structures was very scarce, similar to that of normal interalveolar walls; only in a low number of fields was the stroma thicker and contained spindle cells. In ap-

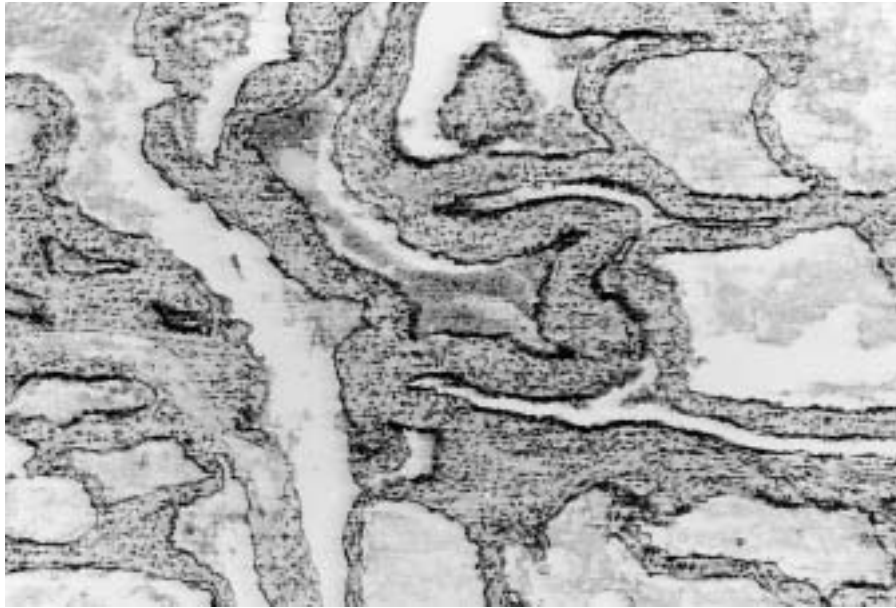


Fig. 3. Positive EMA reaction in cells layering the cyst-like structures.

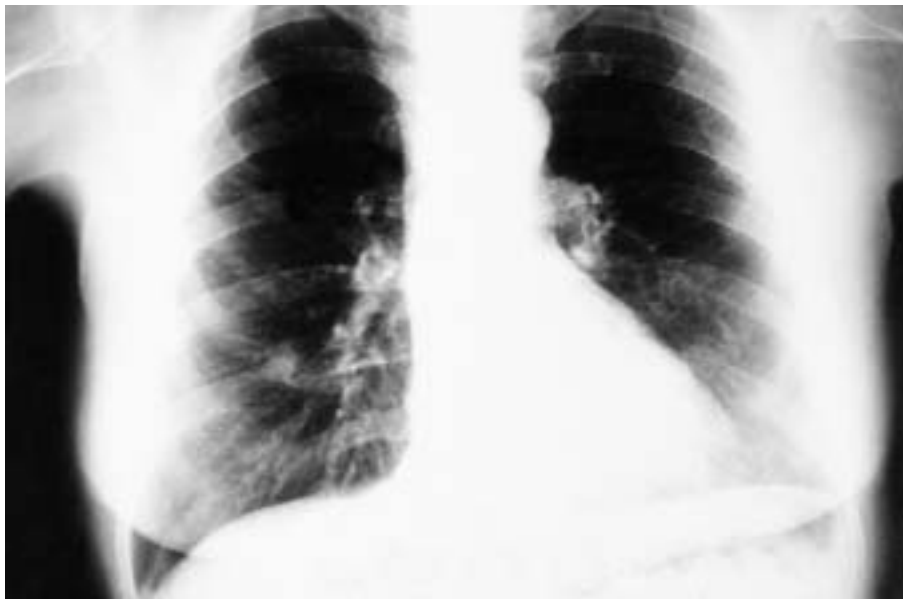


Fig.4. A-P chest X-ray of Patient 2 showing the tumor situated in the middle lobe of the right lung.

proximately one fourth of the tumor mass numerous cells with clear cytoplasm and round nuclei were seen forming small solid fields or showing cyst-like structures with the diameter smaller than that of a regular alveolus (Fig. 7). These cells demonstrated no paS-positive contents in the cytoplasm and were negative in the HMB-45 antigen and alpha-1-antitrypsin reactions, what is an element of the differential diagnosis of a sugar tumor. The tumor cells showed no atypia and mitotic figures.

In immunohistochemistry, all the tumor cells that layered the cysts were strongly EMA-positive and showed a weaker positivity for cytokeratin. Within the solid fields, at a distance from the cysts, only isolated cells showed positivity in the above reactions. Ki-67, which reacts with proliferating cells, was present only in isolated hobnail cells.

Actin reacted with the walls of small and larger vessels within the tumor. No S-100-positive or chromogranin-containing cells were found within the neoplastic cells. The TTF-1 reaction was positive in the nuclei of a large portion of tumor cells, especially in cells layering the lumen of the cyst-like structures.

## Discussion

Clinically, alveolar adenomas are usually asymptomatic and detected accidentally as isolated tumor lesions in routine chest X-ray [2]. The tumor is not malignant and all authors report no metastases in their patients, while long-term follow-up confirms recovery without relapses and metastases. In the course of preoperative follow-up ranging from two to ten years, only in four

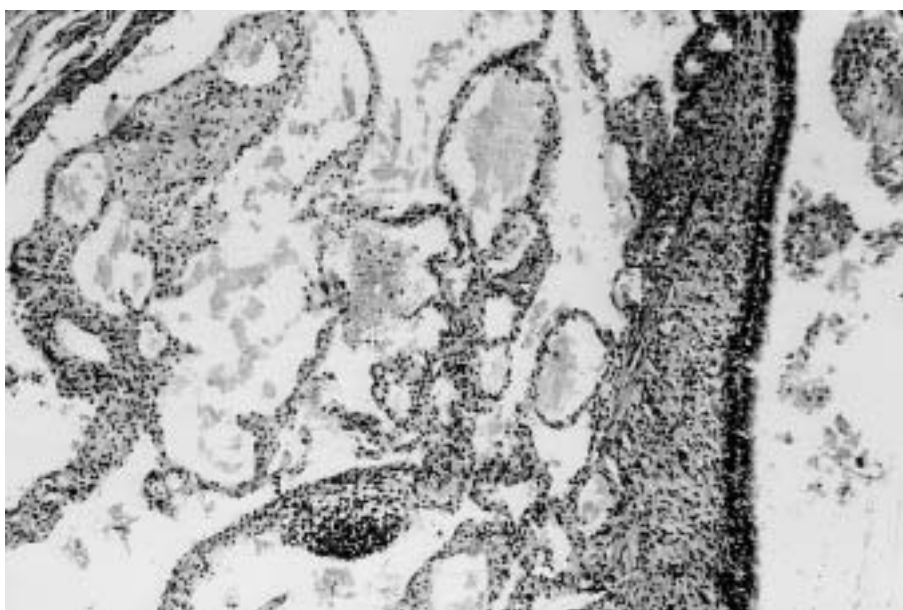


Fig. 5. The tumor partially penetrating the main bronchus wall. HE.

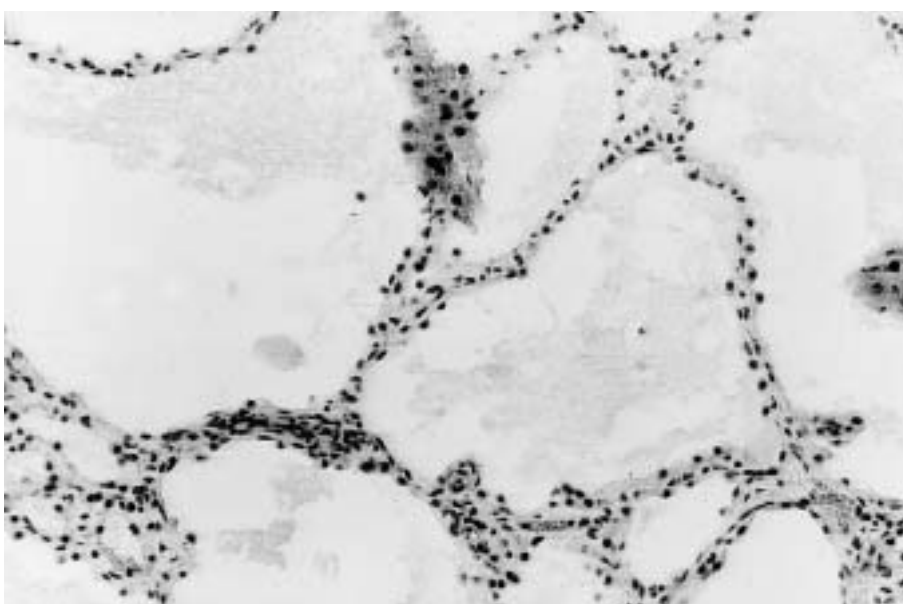


Fig. 6. The cyst-like spaces at times have very thin walls, while in other sites the walls are similar to those seen in Case 1. HE.

cases did the tumors grow, what supports the thesis of their slow development and non-malignant character [2]

While evaluating alveolar adenomas, three issues have been considered, namely whether the process represents neoplastic epithelial proliferation, or - as Dail [3] believed - primary proliferation involves the stroma, which is secondarily layered by type II pneumocytes, or else whether proliferation involves both these structures. More evidences point to the proliferation of epithelial structures, mostly type II pneumocytes, while mesenchymal proliferation is most likely secondary in character, being stimulated by the growth of epithelial cells, and it is seen in the central zones of the tumor and residual on its periphery.

The proliferation of tumor cells is slow, what is confirmed by the lack of mitoses and isolated Ki-67-positive cells in the peripheral zone of the tumor; thus we may regard

the mass as an adenoma. The issue whether this process should be classified as a neoplastic one has also been questioned, but the studies of Roque et al. [10] demonstrated the clonal translocation of  $der(16)t(10:16)(q23:24)$  in 19% of tumor cells, what may indicate the neoplastic character of the lesion. In tumors belonging to our series proliferation involved type II pneumocytes. In our cases, a large portion of the tumor mass was composed of type II pneumocytes, what is also confirmed by a strong staining of tumor cell nuclei in the anti-thyroid transcription factor (TTF-1) reaction. While in the first patient the tumor fully corresponded to a typical alveolar adenoma, in the second patient the mass differed slightly in that it contained a larger number of solid zones with cells with clear, empty cytoplasm, which slightly resembled the sugar tumor cells, but were HMB-45 and alpha-1-antitrypsin negative. These fragments of the mass

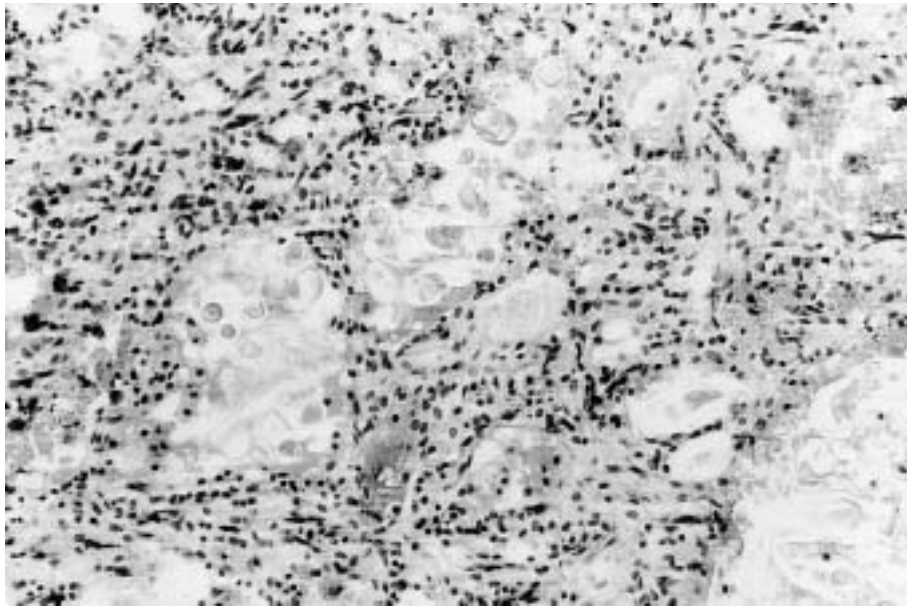


Fig. 7. Case 2: Whorled bodies seen in the air spaces situated in sites with a more solid structure. HE.

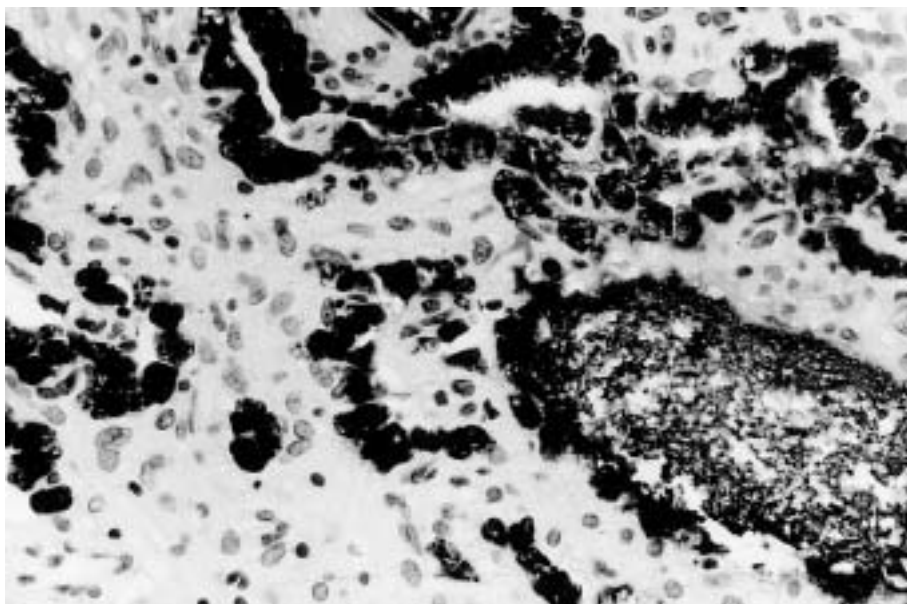


Fig. 8. Positive SP-A surfactant reaction in cells layering the cyst-like structures and in the protein contents.

resembled rather the so-called sclerosing hemangioma, which also originates from type II pneumocytes and their precursors. The feeling was augmented by the presence of whorled bodies inside the alveolar structures. The bodies are observed in approximately 25% of sclerosing hemangioma cells [4, 9]. This observation may indicate some degree of affinity between alveolar adenoma and sclerosing hemangioma. In alveolar adenoma the proliferation of pneumocytes is accompanied by the formation of alveolar structures or larger cysts, but with a similar structure, while in sclerosing hemangioma the degree of alveoli formation is low in the papillary type or entirely absent in the solid type. In this case one might also consider a mixed-type tumor composed of alveolar adenoma and sclerosing hemangioma. A similar case was described by Nicholson et al. [7] and the preliminary diagnosis was that of sclerosing hemangioma.

In preoperative differential diagnosis the tumor presents considerable problems, similarly as in intraoperative examinations. It may resemble other lesions, such as for example pulmonary hamartoma or adenomatous malformations. Sometimes local honeycomb fibrosis is taken into consideration, similarly as sclerosing hemangioma or bronchioloalveolar adenoma [6]. In particular, we need to remember about atypical adenomatous hyperplasia (AAH), from which alveolar adenoma differs mainly in the lack of atypia and the formation of alveolar structures, while AAH grows in lepidic form. Also, bronchioloalveolar carcinoma may be at times erroneously diagnosed in such cases. In bronchioloalveolar carcinoma and atypical adenomatous hyperplasia we also find carcinoembryonic antigen (CEA) [5].

## References

1. *Bohm J, Fellbaum C, Bautz W et al*: Pulmonary nodule caused by an alveolar adenoma of the lung. *Virch Arch* 1997, 430, 181-184.
2. *Burke LM, Rush WI, Khor A et al*: Alveolar adenoma: histochemical, immunohistochemical, and ultrastructural analysis of 17 cases. *Hum Pathol* 1999, 30, 158-167.
3. *Dail DH*: Uncommon tumors. "Alveolar adenoma". In: *Pulmonary Pathology of Tumors*. Dail HD, Hammar SP, Colby ThV, eds. Springer, New York 1995, 258.
4. *Katzenstein AA, Gmelich JT, Carrington SB*: Sclerosing haemangioma of the lung: a clinicopathological study of 51 cases. *Am J Surg Pathol* 1983, 7, 3-16.
5. *Kitamura H, Kameda Y, Nakamura N et al*: Atypical adenomatous hyperplasia and bronchioloalveolar carcinoma. Analysis by morphometry and the expressions of p53 and carcinoembryonic antigen. *Am J Surg Pathol* 1996, 20, 553-562.
6. *Miller RR*: Bronchioloalveolar cell adenomas. *Am J Surg Pathol* 1990, 14, 904-912.
7. *Nicholson AG, Magkou C, Snead D et al*: Unusual sclerosing haemangiomas and sclerosing haemangioma-like lesions, and the value of TTF-1 in making the diagnosis. *Histopathology* 2002, 41, 404-413.
8. *Oliveira P, Moura Nunes JF, Clode AL et al*: Alveolar adenoma of the lung: further characterisation of this uncommon tumour. *Virch Arch* 1996, 429, 101-108.
9. *Papla B*: Sclerosing haemangioma of the lung - benign sclerosing pneumocytoma. *Pol J Pathol* 1999, 50, 99-106.
10. *Roque L, Oliveira P, Martins C et al*: A non-balanced translocation (10;16), demonstrated by FISH analysis in case of alveolar adenoma of the lung. *Cancer Genet Cytogenet* 1996, 89, 34-37.
11. *Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E*: *Histological Typing of Lung and Pleural Tumours* (ed. 3). Springer, Berlin 1999, 26.
12. *Wada A, Tateishi R, Terazawa T et al*: Case report: lymphangioma of the lung. *Arch Pathol* 1974, 98, 211-213.
13. *Yousem SA, Hochholzer L*: Alveolar adenoma. *Hum Pathol* 1986, 17, 1066-1071.

### Address for correspondence and reprint requests to:

B. Papla M.D.  
 Chair and Department of Pathomorphology CMUJ  
 Grzegórzecka 16, 31-531 Kraków