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CASE REPORT

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Peripheral papillary tumor of type-II pneumocytes: a rare neoplasm of undetermined malignant potential

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Abstract Peripheral papillary adenomas of the lung are uncommon neoplasms (only ten cases have been described so far in the English literature) composed predominantly of type-II pneumocytes and generally considered benign. We describe here two additional cases of this lung tumor. In both cases histological examination revealed an encapsulated papillary neoplasm with invasion of the capsule and, in one case, invasion of the adjacent alveoli and visceral pleura too. The proliferative index (Ki67) was less than 2% and the epithelial cells were positive for cytokeratins, surfactant apoproteins (SP), and nuclear thyroid transcription factor-1 (TTF-1). Ultrastructurally, the epithelial cells showed the characteristic surface microvilli and cytoplasmic lamellar inclusions of type-II cells. Review of the literature has revealed two other cases of peripheral papillary adenoma of type-II pneumocytes with infiltrative features. Thus, we propose replacing the term peripheral papillary adenoma with peripheral papillary tumor of undetermined malignant potential.

Key words Unusual lung tumors · Papillary adenoma · Surfactant proteins · Immunohistochemistry

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Introduction

Peripheral papillary tumors of the lung are rare neoplasms of uncertain malignant potential and histogenesis. In a study of non-invasive bronchial papillary tumors, Spencer et al. [17] described two peripheral papillary tumors of probable Clara cell origin. Since then, eight additional cases have been reported in the English literature showing immunohistochemical and ultrastructural evidence of differentiation toward type-II pneumocytes [2, 3, 6, 10, 12, 13, 19]. Most of these reports and the AFIP atlas on tumors of the lower respiratory tract [1] consider papillary adenoma of type-II pneumocytes a benign lesion distinct from alveolar adenoma, another rare entity also composed of type-II pneumocytes [9, 20]. However, Mori et al. [12] have challenged this dominant view on the basis of a case that showed histological and cytological features of a low-grade malignancy. In this study, we report two additional cases of peripheral papillary adenoma of the lung which exhibited microinvasive characteristics and provide further evidence for a malignant potential of this tumor.

Case report

Clinical data

Case 1

A 15-year-old boy was admitted to the hospital for the evaluation of a solitary peripheral nodule in the left upper lobe, which had been discovered during a routine chest roentgenogram. On admission, the patient was asymptomatic; physical examination and routine laboratory studies were unremarkable. An inflammatory process was ruled out and a diagnostic thoracotomy was performed. A well-circumscribed subpleuric round mass in the left upper lobe was removed, with a narrow rim of healthy lung margined by a wedge resection. The postoperative course was uneventful; the patient was sent home without any further therapy to be followed up with annual chest X-rays. He is free of disease 9 years after resection.

Table 1 Source and immunoreactivity of the antibodies

Antibody to	Clone	Source	Dilution	Reactivity
Monoclonal surfactant Protein -A[a]	PE-10	Courtesy of Dr.T.Akino, Sapporo Medical College, Sapporo, Japan	1:500	Cytopl. strong >60% neoplastic cells
Surfactant protein A (SP-A)[b]	Poly	Chemicon Int. Inc., Calif., USA	1:500[c]	Cytopl. strong >60% neoplastic cells Nuclear, strong, inclusions neoplastic cells
Surfactant protein B (SP-B)	Poly	Chemicon Int. Inc., Calif., USA	1:500[c]	Cytopl. strong >60% neoplastic cells
Pro-surfactant protein C (NPRO-SP-C)	Poly	Courtesy of Dr.MF.Beers,.Univ.of Pennsylvania,Philadelphia, PA, USA	1:1000[c]	Cytopl. strong >60% neoplastic cells
Surfactant protein D (SP-D)	II E 11	BMA, Switzerland	1:50	Cytopl. strong >60% neoplastic cells
Thyroid transcription factor-1 (TTF-1)	8 G7G3/1	Neo Markers, Calif., USA	1:50	Nuclear strong >60% neoplastic cells in case 2, focal in case 1
Urine protein (UP1)	Poly	Dako, Denmark	1:800	Negative
Ki 67	MIB-1	Immunotech, France	1:50	Nuclear strong <2% neoplastic cells
Cytokeratin pool	AE 1/AE 3	Bio Genex, Calif., USA	1:100	Cytopl. strong >60% neoplastic cells
Cytokeratin 8, 18	CAM5.2	Becton-Dickinson, CA, USA	1:20	Cytopl. strong >60% neoplastic cells
Pulmonary adenocarcinoma	44-3A6	Affinity BioReagents Inc.,CO, USA	Undiluted	Cytopl. strong <10% neoplastic cells
Carcinoembryonic antigen (CEA)	Poly	Dako, Denmark	1:16000	Cytopl. strong <10% neoplastic cells
Chromogranin A	LK2H10	Bio Genex, Calif., USA	1:400	Negative
Neuron-specific enolase (NSE)	H 14	Dako, Denmark	1:400	Negative
Synaptophysin	SY 38	Dako, Denmark	1:50	Negative

[a] Tested only on case 1
[b] Tested only on case 2
[c] Dilution on semi-thin epoxy embedded sections: SP-A: 1:500; SP-B: 1:50; Pro-SP-C: 1:1000

Case 2

An asymptomatic 27-year-old man was admitted to the hospital to clarify the nature of a peripheral coin lesion in the right lower lobe, which had been detected during a routine chest roentgenogram. He had been a half-pack cigarette smoker for the previous 5 years. Physical examination and routine laboratory data were within normal values. Bronchoscopy was negative for endobronchial lesions and bronchial washing was negative for malignant cells. He underwent diagnostic thoracotomy and resection of a subpleural, nearly-spherical, mass in the right lower lobe. Frozen sections of the mass revealed a partially encapsulated papillary tumor infiltrating the contiguous lung parenchyma and visceral pleura. As a consequence, a lower lobectomy with a regional lymph-node dissection was performed. Postoperative course was uneventful and he is free of disease 2 years later.

Materials and methods

The resected lung specimens were totally sectioned into 2- to 3-mm thick slices, fixed in 10% buffered formalin and processed for routine histology. Sequential 5-µm sections of the masses were stained with hematoxylin–eosin (HE), periodic-acid Schiff (PAS) before and after diastase digestion, Alcian blue (pH 2.5), Masson trichromic, toluidine blue, and orcein.

For ultrastructural investigation, small samples of the tumors were obtained from formalin-fixed tissue. Part of samples were post-fixed in 2.5% buffered glutaraldehyde and in buffered 1% osmium tetroxyde (OsO_4), dehydrated in ethanol and embedded in epoxy resin. Another part of them was processed avoiding post-fixation and was embedded in epoxy resin.

The avidin–biotin complex immunoperoxidase technique was used both on paraffin-embedded sections and on non-osmicated epoxy-embedded semi-thin sections on case 2. Source and dilution of primary antibodies are shown in Table 1. Negative and positive controls were added in each test.

Results

In both cases the lesions had a similar appearance. The tumors were firm, nearly spherical masses, 2.5 cm and 2.4 cm, respectively, in greatest dimension; in case 2, there was slight puckering of the overlying visceral pleura. The cut surface of the nodules was gray–white solid; in case 1, there was a small central hemorrhagic area.

Histologically, the tumors were composed of epithelial cells nested in solid areas (Fig. 1A) or lining papillary structures (Fig. 1B), with a fibrovascular stroma containing lymphocytes, plasma cells, eosinophils and scattered mast cells in case 2. The neoplastic epithelial cells, particularly those lining the papillary structures, were cuboidal, with central round-to-oval nuclei. They often appeared microvacuolated, but the vacuoles were negative for mucin with PAS and Alcian-blue stains. In case 2, several nuclei contained eosinophilic inclusions. No mitotic figures were seen. The epithelial proliferation was associated with a desmoplastic reaction, particularly intense in case 1. Pre-existing elastic fibers of alveolar walls were not present within the fibrous areas. The tumors were delimited by a fibrous capsule, focally infiltrated by neoplastic cells in case 1 (Fig. 1A, *arrow*). In

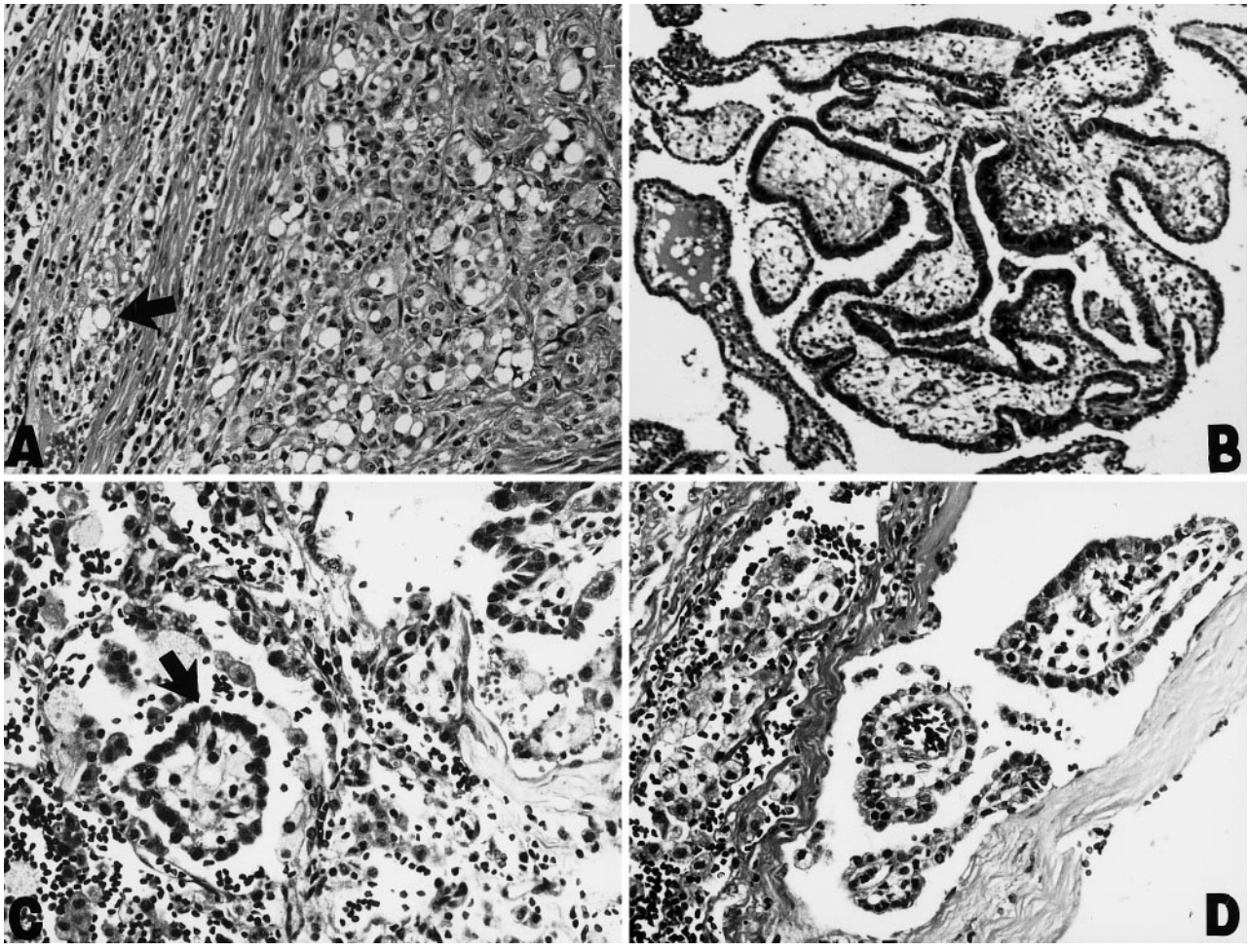

Fig. 1A –D. Histological features of peripheral papillary tumors of the lung (Hematoxylin–eosin). **A** Representative view of the tumor of case 1 showing solid epithelial component with a nest of tumor cells within the fibrous capsule (*arrow*) ×100. **B** Case 2: low-power view of papillary structures lined by cuboidal epithelial cells ×40. **C** Case 2: a nest of tumor cells arranged in a papillary structure within an alveolar space lined by hyperplastic type-II cells (*arrow*) ×100. **D** Case 2: invasion of a subpleural lymphatic by papillary neoplastic structures ×100

case 2, the capsule was incomplete and infiltrated by neoplastic cells, which were present in the adjacent alveoli (Fig. 1C, *arrow*) and in lymphatics of the overlying visceral pleura (Fig. 1D) either singly or in small papillary formations. Ciliated cells were not present.

Ultrastructurally, most of the epithelial neoplastic cells revealed morphological features of type-II pneumocytes: short surface microvilli, numerous cytoplasmic lamellar bodies (Fig. 2, *arrows*) and rare 60-nm diameter intranuclear tubular inclusions (Fig. 2, *arrowhead*). Few cells showed electron-dense granules characteristic of bronchiolar Clara cells; ciliated cells were not seen.

The results of the immunohistochemical studies are summarized in Table 1. The neoplastic cells were strongly decorated with anticytokeratins and with anti-surfactant apoproteins (anti-SP). Scattered cells were stained with the antibodies anti-carcinoembryonic antigen and 44-3A6. They were not immunoreactive for urine protein 1 (UP1) or neuroendocrine markers. Nuclear immunoreactivity for thyroid transcription factor-1 (TTF-1) was positive; less than 2% nuclei were decorated with Ki67. On semi-thin epoxy-embedded sections, SP-A strongly decorated the free luminal surface of neoplastic cells (Fig. 3A) as well as intranuclear inclusions (Fig. 3A, *arrows*). SP-B and Pro-SP-C revealed a dotty cytoplasmic immunoreactivity (more intense with the latter) in most neoplastic cells; nuclear inclusions were unstained with SP-B and weakly immunoreactive with Pro-SP-C (Fig. 3B,C, *arrows*).

Discussion

Peripheral papillary adenoma of the lung is a rare neoplasm, which is considered a benign lesion in the new edition of the AFIP fascicle on tumors of the lower respiratory tract [1]. Table 2 lists the cases reported in the English literature. As seen in Table 2, the tumor may occur at any age. Its presentation is that of a single pulmonary nodule, discovered incidentally in asymptomatic patients. However, Kurotaki et al. recently described a multicentric bilateral papillary tumor in a 13-year-old boy with von Recklinghausen's disease; the lesions re-

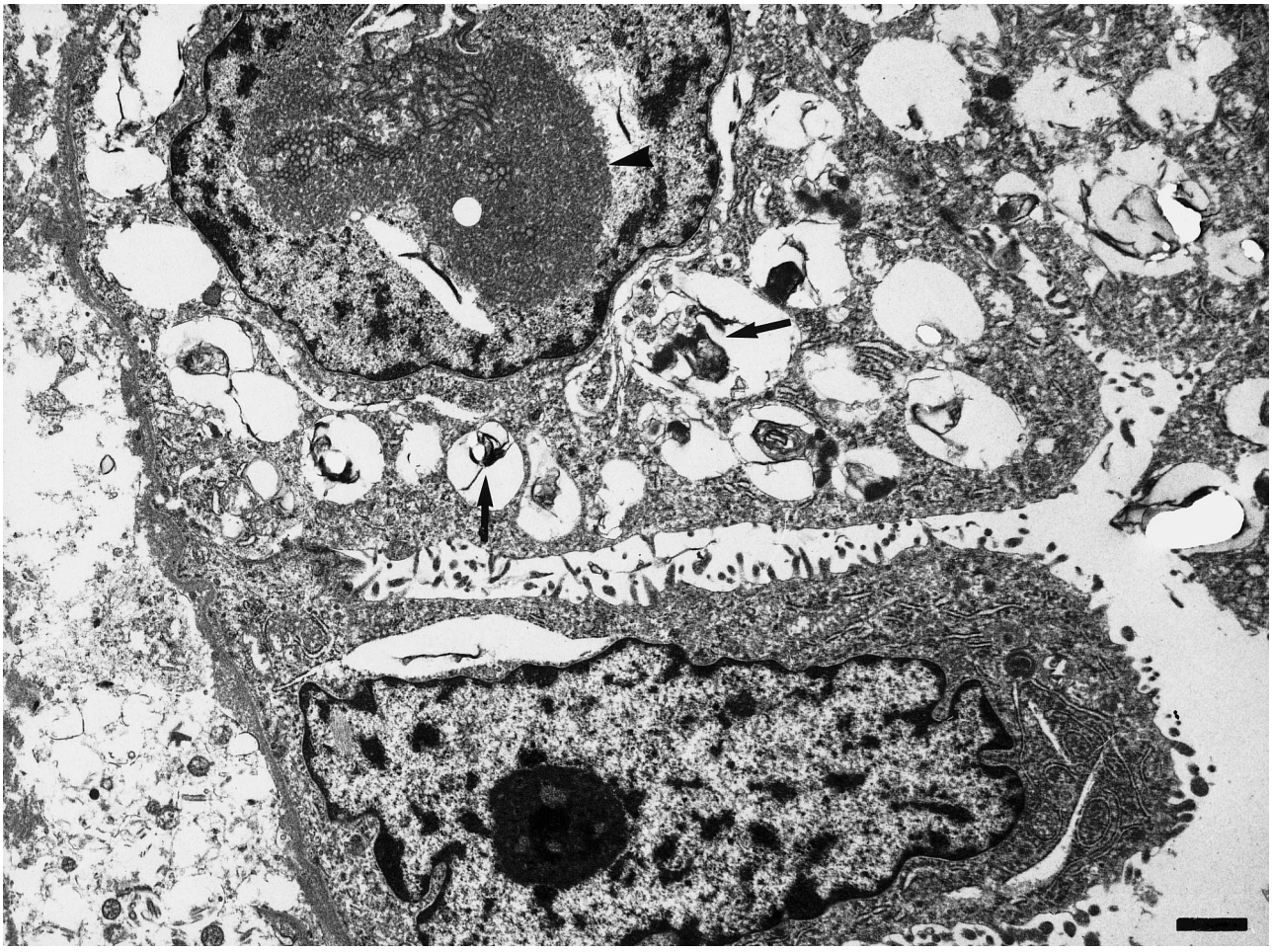

Fig. 2 Ultrastructural features of neoplastic type-II pneumocytes of case 2. Surface microvilli, lamellar bodies (*arrows*) and intranuclear tubular inclusions (*arrowhead*). ×9000; *Scale bar* 1 µm

mained stable and the boy was asymptomatic 6 years after diagnosis by lung biopsy [10].

Peripheral papillary adenomas are thought to arise from a multipotential stem cell that can differentiate into type-II pneumocytes and Clara cells. Our immunohistochemical observations confirm the differentiation toward type-II pneumocytes. The derivation of the tumor from type-II pneumocytes, supported by many authors [3, 9, 10, 12, 13, 19], is confirmed by us for the following reasons:

a. The neoplastic cells were decorated in their cytoplasms with SPs and presented lamellar bodies typical of normal and neoplastic type-II pneumocytes [2, 3, 6, 10, 12, 13, 19]. They were negative for UP1, a marker of differentiation for Clara cells [12].
b. All four SPs, normally expressed all together only in type-II pneumocytes, were present in the cytoplasms of the neoplastic cells.
c. Intranuclear tubular inclusions seen in case 2 and characteristic of reactive [5, 8] and neoplastic type-II cells [11, 15] appeared positive for SP A.
d. TTF-1, fundamental for the stimulation of SP-B and SP-C gene transcription [7, 18], was positive in the nuclei of the neoplastic cells.

Some of the reported cases were encapsulated, but in most cases the tumor was not encapsulated and compressed the surrounding lung parenchyma. Although generally considered benign, among ten cases of peripheral papillary adenomas reported in the English literature, two exhibited microscopic invasive properties suggesting a malignant potential [12, 17]. Thus, including the present two cases, in 4 of the 12 cases reported, infiltration into the capsule (our case 1), into the adjacent lung parenchyma [16], into lung parenchyma and venules [11], into lung parenchyma and visceral pleura (our case 2) was noted. We agree with Mori et al. [12] who considered peripheral papillary adenoma a neoplasm closely related to adenocarcinomas. Whether or not histological evidence of invasiveness indicates also a biologically aggressive behavior cannot be determined from the literature. None of the cases recurred or metastasized. The absence of mitotic figures and the low cellular replicative activity (Ki67<2%) in both our cases suggest that these tumors may have a relatively slow rate of growth. Therefore, longer follow-up periods may be necessary before ruling out malignancy.

Table 2 Cases of peripheral papillary adenomas of the lung in the English literature. *(SP* surfactant protein, *ChrA* chromogranin-A, *ND* not done, *IR* immunoreactivity, *Syn* synaptophysin, *NED* no evidence of disease, *TTF-1* thyroid transcription factor-1, *NSE* neuron-specific enolase, *UP1* urine protein 1)

Case	Author/reference	Gender	Age (years)	Immunohistochemistry	Ultrastructural features	Infiltration	Outcome
1	Spencer et al. [17]	Female	26	ND	ND		ND
2	Spencer et al. [17]	Male	7	ND	ND	Adjacent alveoli	ND
3	Fantone et al. [2]	Female	25	No IR for SP-A and Clara cell protein	Microvilli, lamellar and electrondense granules		NED 9 years
4	Noguchi et al. [13]	Male	57	Intense cytoplasmic IR for SP-A in almost all neoplastic cells, and in some nuclear inclusions	Short microvilli. Lamellar bodies and electrondense granules. Nuclear tubular inclusions		NED 8 years
5	Fine and Chang [3]	Female	28	Granular, cytoplasm. IR for SP-A. No IR for Clara cell protein	Short microvilli. Scattered lamellar bodies. Granular material and tubular myelin in extracellular areas	Incidental finding at necroscopy	
6	Hegg et al. [6]	Male	60	No IR for SP-A nor for Clara cell protein	ND		NED 2 years
7	Hegg et al. [6]	Female	52	IR for Clara cell protein.No IR for SP-A	Surface microvilli. Not found lamellar and electrondense granules into the cytoplasm		NED 11 months
8	Kurotaki et al. [10]	Male	13	Intense reaction for EMA, AE1/AE3, SP not specified in neoplastic cells. Few nuclei PCNA positive random	Short surface microvilli. Lamellar bodies and rare membrane-bound secretory granules		NED 6 years
9	Yamamoto et al. [19]	Male	26	IR for monoclonal SP-A. NSE and ChrA: negative	Numerous surface microvilli. Lamellar bodies. Scattered cells with electrondense granules		NED 16 months
10	Mori et al. [12]	Male	35	IR for SP-A,SP-B and P-450. Polar IR for CEA No IR for thyroglobulin and UP-1	Short surface microvilli. Lamellar bodies. Scattered cells with electrondense granules. Rare cells with nuclear tubular inclusions	NED 3 years Lung parenchyma and venules	
11	Our case 1	Male	15	Strong cytoplasmic IR for monoclonal SP-A, SP-B, Pro-SP-C, SP-D, CAM 5.2, AE1/AE3. Focal nuclear IR for TTF-1. Scattered cells IR for CEA and 44-3A6. Ki 67<2% of nuclei. UP1, NSE, ChrA, Syn: neg	Surface microvilli. Numerous lamellar bodies	Capsule	NED 9 years
12	Our case 2	Male	27	Strong cytopl.IR for SP-A, SP-B, Pro-SP-C, SP-D,CAM 5.2, AE1/AE3 Scattered cells IR for CEA and 44-3A6 Nuclear IR for TTF-1 in most cells. Ki 67<2%. UP1, NSE, ChrA, Syn: neg.	Surface microvilli. Numerous lamellar bodies Tubular nuclear inclusions. Rare cells with electron-dense granules	Adjacent alveoli and visceral pleura	NED 2 years

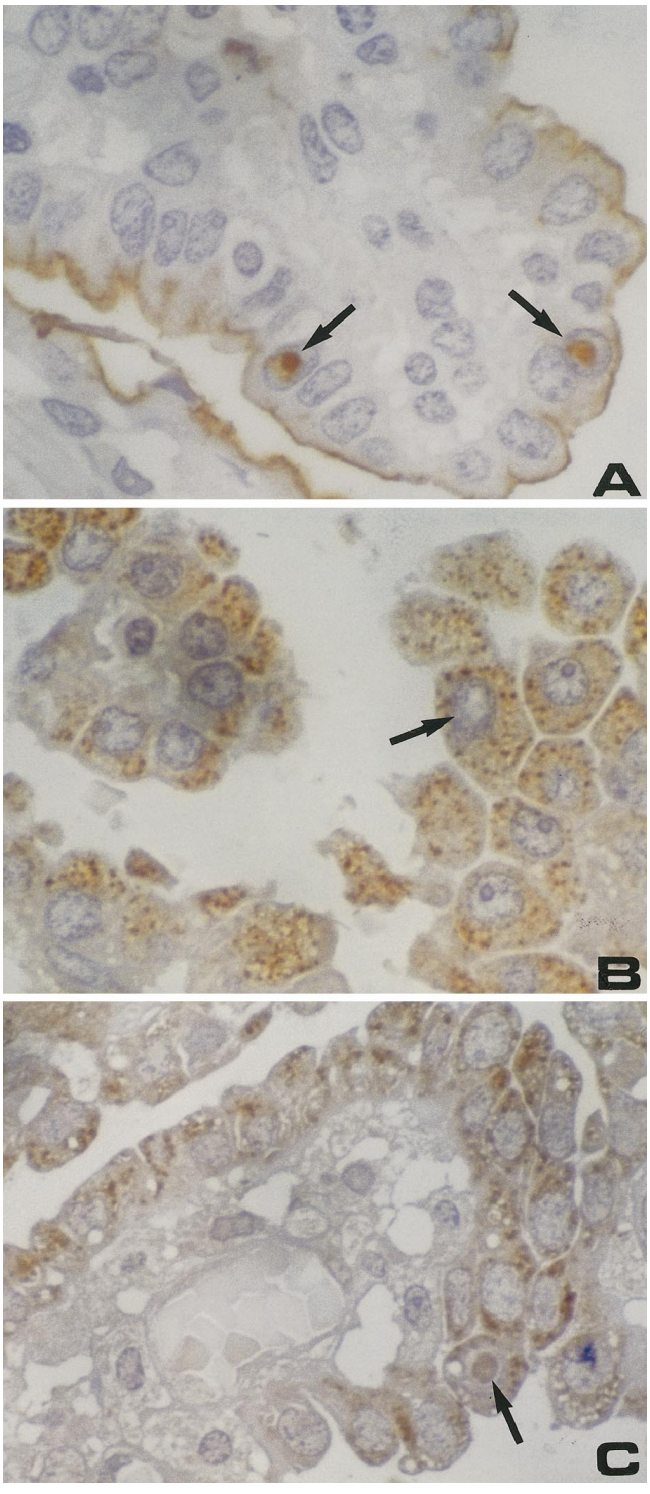

Fig. 3A –C. Immunoreactivity with anti-surfactant apoprotein antibodies of case 2. Semi-thin (0.5 µm) epoxy-embedded sections with avidin–biotin complex method, ×1000. **A** Anti-surfactant protein (SP)-A antibody strongly decorates luminal surface and nuclear inclusions of neoplastic cells (*arrows*). **B** Anti SP-B antibody reveals a dotty cytoplasmic positivity in tumor cells; a nuclear inclusion is unstained (*arrow*). **C** Anti-NPRO-SP-C antibody reveals a strong coarse granular cytoplasmic positivity and weakly reacts with a nuclear inclusion (*arrow*)

The diagnosis can be difficult, especially on frozen sections in which a careful examination of the capsule and of the contiguous lung parenchyma should be made in order to evaluate an infiltration by neoplastic cells, as in our cases. The differential diagnosis includes entities such as alveolar adenoma, solitary bronchioloalveolar adenocarcinoma, atypical adenomatous hyperplasia, micronodular pneumocyte hyperplasia, sclerosing hemangioma, and the "pulmonary tumor resembling fetal lung". The presence of a fibrous capsule and the absence of a cystic or cribriform pattern distinguishes it from the alveolar adenoma [9] first described by Yousem and Hochholzer [20]. The absence of marked nuclear atypia with fairly uniform round nuclei lining the papillary formations, the presence of a complete or partial fibrous capsule, and the expansive nodular growth with compression of the surrounding lung parenchyma distinguish the papillary tumor from the solitary bronchioloalveolar adenocarcinoma, which is characterized by a lepidic pattern of growth. The presence of broad papillary structures and solid tumor nests distinguish the papillary tumor from atypical adenomatous hyperplasia (AAH), which is characterized by the lepidic pattern of growth of type-II pneumocytes with variable grades of atypia; moreover, AAH is usually an incidental finding in lungs removed for other pathological lesions [8]. Similarly, micronodular pneumocyte hyperplasia, is a rare lesion in patients with tuberous sclerosis, characterized by small nonencapsulated nodules composed of thickened, fibrotic alveolar septa lined by atypical type-II pneumocytes [4]. The encapsulation of the tumors and the absence of angiomatous proliferation, sclerosis, hemorrhage, and neuroendocrine differentiation distinguish the peripheral papillary adenoma from a sclerosing hemangioma [14]. The absence of solid "morules", necrosis, neuroendocrine differentiation and mitotic activity separates the papillary adenoma from the "pulmonary tumor resembling fetal lung" [16].

In summary, our cases and the review of the literature suggests that the term "adenoma" should be replaced by peripheral papillary tumor of undetermined malignant potential, and, in view of its possible invasiveness, surgical treatment should be that of a potential malignant lesion.

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