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Case report

Multiple papillary adenomas of type II pneumocytes found in a 13-year-old boy with von Recklinghausen's disease

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Abstract. A case of multiple papillary adenomas of type II pneumocytes is reported. A 13-year-old boy with von Recklinghausen's disease had small nodular lesions in both lungs without symptoms. The biopsied lung contained greyish-white nodules ranging in size from 0.5 to 2 mm. Light microscopic examination revealed cuboidal to low columnar cells arranged in a papillary pattern. Elastic fibres were present in the tumour stroma. Electron microscopically, the cells had osmiophilic lamellar bodies in the cytoplasm and short microvilli along the free border. The tumour cells expressed immunoreactivity for epithelial membrane antigen and surfactant apoprotein antibodies. More than 6 years after open lung biopsy, the patient is well but small nodular shadows can still be identified.

Key words. Multiple papillary adenomas – Type II pneumocyte – Von Recklinghausen's disease – Immunohistochemistry – Electron microscopy

Introduction

Von Recklinghausen's disease (VR) is a disorder of neural crest cells that may be expressed by autosomal dominant inheritance or may occur spontaneously from new mutation. Abnormalities of almost every organ system have been described in VR patients (Riccardi 1981) and it is reported that approximately 10% of VR patients have pulmonary involvement (Massaro and Katz 1966) with neurofibromatous tumours within the lung or diffuse interstitial fibrosis and bullous lung disease, alone or in combination (Fishman 1980).

We encountered a rare case of multiple nodular lesions of the lung in a 13-year-old boy with VR. These nodules were considered to be multiple papillary adenomas after immunohistochemical and ultrastructural studies. Papillary adenoma of the lung is uncommon, and a few cases have been reported in the literature (Fantone et al. 1982; Fukuda et al. 1992; Hegg et al. 1992; Noguchi et al. 1986a; Spencer et al. 1980). The current case is possibly the first case associated with VR. The histopathology, immunohistochemistry and ultrastucture of this uncommon case are described and the pertinent literature is reviewed.

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Case report

A 13-year-old Japanese boy was found to have small nodules on chest radiography and was admitted to Hirosaki University Hospital on 5 August 1986 for further evaluation of the abnormal shadows. The patient was asymptomatic. The chest X-ray film showed a diffusely reticulo-nodular pattern in both lungs. Physical examination and all routine laboratory tests were unremarkable. Cultures of gastric juice yielded no growth of pathogenic organisms including mycobacteria. Open lung biopsy was performed on 8 August 1986 because of suspected pulmonary fibrosis. Multiple small nodules up to 2 mm in diameter, greyish-white in colour, were found, distributed throughout all lobes with no apparent predilection of localization. They were located both deeply within the parenchyma and subpleurally. There was no pleural indentation on the lung. A specimen containing small nodules was resected from the left lower lobe. The hilar lymph nodes were not enlarged. After an uneventful recovery the patient was discharged with no symptoms and more than 6 years after open lung biopsy, the patient is well and engaged in farming. However, multiple nodules of both lungs can still be identified radiographically, without any increase in their size or number.

The patient, with no family history of VR, had had multiple café-au-lait spots over the whole body since birth. Soft subcutaneous tumours of the forehead and back were noticed from the age of 7 years, on the basis of which a diagnosis of VR was made. Cutaneous lesions, such as sebaceous adenoma on the face, were not noted. The patient had been treated with several anti-epileptic drugs to control seizures classified as generalized tonoclonic epilepsy from the age of 1 year. No seizure has occurred for a few years but he is slightly mentally retarded.

Materials and methods

For light microscopy, the specimen was fixed in 10% buffered formalin, processed in a routine manner, and embedded in paraffin.

Sections were stained with haematoxylin and eosin, alcian blue, periodic acid-Schiff, silver impregnation, azan, Giemsa and elastica van Gieson. For immunostaining, the streptavidin-biotin method was used. Mouse antisera to keratin (AE1/AE3; diluted 1:200, Oxoid, UK), epithelial membrane antigen (EMA; diluted 1:500, Dakopatts, Denmark), carcinoembryonic antigen (CEA; diluted 1:50, ICN, USA), vimetin (diluted 1:100, Dakopatts) and proliferating cell nuclear antigen (PCNA; diluted 1:100, Novocastra, Newcastle-upon-Tyne, UK) were employed as primary antibodies. By the courtesy of Dr. Yukio Shimosato, Chief, Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan, immunostaining for surfactant apoprotein was performed.

A portion of the greyish-white nodules from the specimen was minced into tiny cubes, fixed in 2.5% glutaraldehyde with phosphate buffer at pH 7.4, postfixed in 1% osmium tetroxide, dehydrated in graded alcohol, and embedded in Epon 812. Ultrathin sections of selected areas were stained with uranyl acetate and lead citrate and observed by a JEOL TEM-2000EX electron microscope.

Results

The excised lung tissue measured $12 \times 12 \times 10$ mm and contained greyish-white nodules. The nodules ranged in size from 0.5 to 2 mm and were clearly demarcated from the adjacent parenchyma (Fig. 1). They exhibited mainly papillary proliferations, although more solid areas were present in larger nodules. The peripheral areas of the nodules merged imperceptibly with the adjacent lung parenchyma (Fig. 2A). The papillae contained fibrovascular cores with focal sclerosis (Fig. 2B). They were lined by cuboidal to low columnar cells with central nuclei. Intranuclear eosinophilic inclusion bodies were not present. Nuclear atypia and prominent nucleoli were occasionally noted in the cells of the larger nodules. Mitotic figures and ciliated cells were not identified. The cytoplasm was vesicular or amphophilic and it was negative for mucin. Elastic fibres were present in the tumour stroma (Fig. 2C). There was slight infiltration of lymphocytes, histiocytes and mast cells in the oedematous or fibrous stroma which stained with alcian blue. The adjacent lung parenchyma was unremarkable with no evidence of interstitial fibrosis, inflammation, or alveolar pneumocyte hyperplasia.

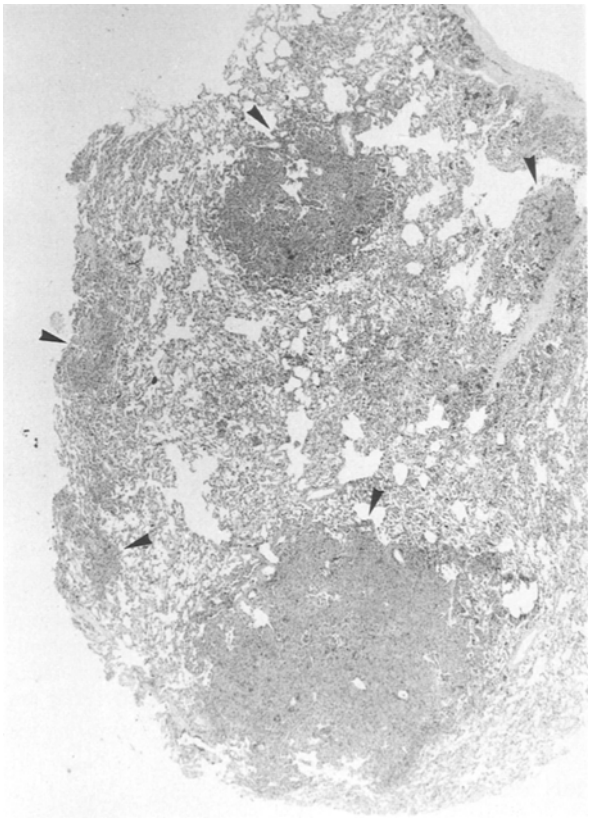

Fig. 1. Open lung biopsy specimen containing five nodular lesions ranging in size from 0.5 to 2 mm (*arrowheads*). H & E, ×20

Immunostaining for EMA showed an intensely positive reaction in the cytoplasmic membrane of cuboidal to low columnar cells (Fig. 3A). These cells also reacted for AE1/AE3 but CEA staining yielded negative results. Most of the cells lining papillae gave a positive reaction with anti-surfactant apoprotein. Some cells within solid areas showed only weakly positive staining (Fig. 3B). Only a small number of the nuclei of the tumour cells demonstrated PCNA positivity randomly.

Ultrastructurally cuboidal or low columnar cells contained round to oval nuclei with finely dispersed chromatin (Fig. 4). Short microvilli were observed along the free border; cilia or microvillous core rootlets were absent. Osmiophilic lamellar bodies were encountered in the cell cytoplasm, and their number varied from cell to cell. These features were similar to those of type II pneumocytes. A small number of these cells contained membrane-bound secretory granules.

Discussion

Diffuse interstitial fibrosis and bullous lung disease, either alone or in combination, have been reported in 10% of VR patients (Massaro and Katz 1966). However, it is known that pulmonary interstitial fibrosis in VR is not observed until the patient reaches adulthood (Webb and Goodman 1977). Neurofibromata can present intrathoracically, particularly in the posterior mediastinum. To our knowledge, there is no reported case of VR associated with multiple papillary adenomas of type II pneumocytes.

Papillary adenoma of the lung is rare, and only a few cases have been reported in the literature. Spencer et al. (1980) reported two non-invasive bronchial papillary tumours of Clara cell origin. Fantone et al. (1982) and Noguchi et al. (1986a) reported papillary adenomas showing differentiation toward both Clara cells and type II pneumocytes. Recently a case of papillary adenoma with the presence of ciliated cells was reported (Fukuda et al. 1992). According to the multidirectional differentiation of tumour cells, it is suggested that immature or stem cells in the bronchioloalveolar epithelium may be the origin of this rare tumour. In the present case, the lesions were composed of cuboidal to low columnar cells containing osmiophilic lamellar bodies, membrane-bound secretory granules and surfactant apoprotein in

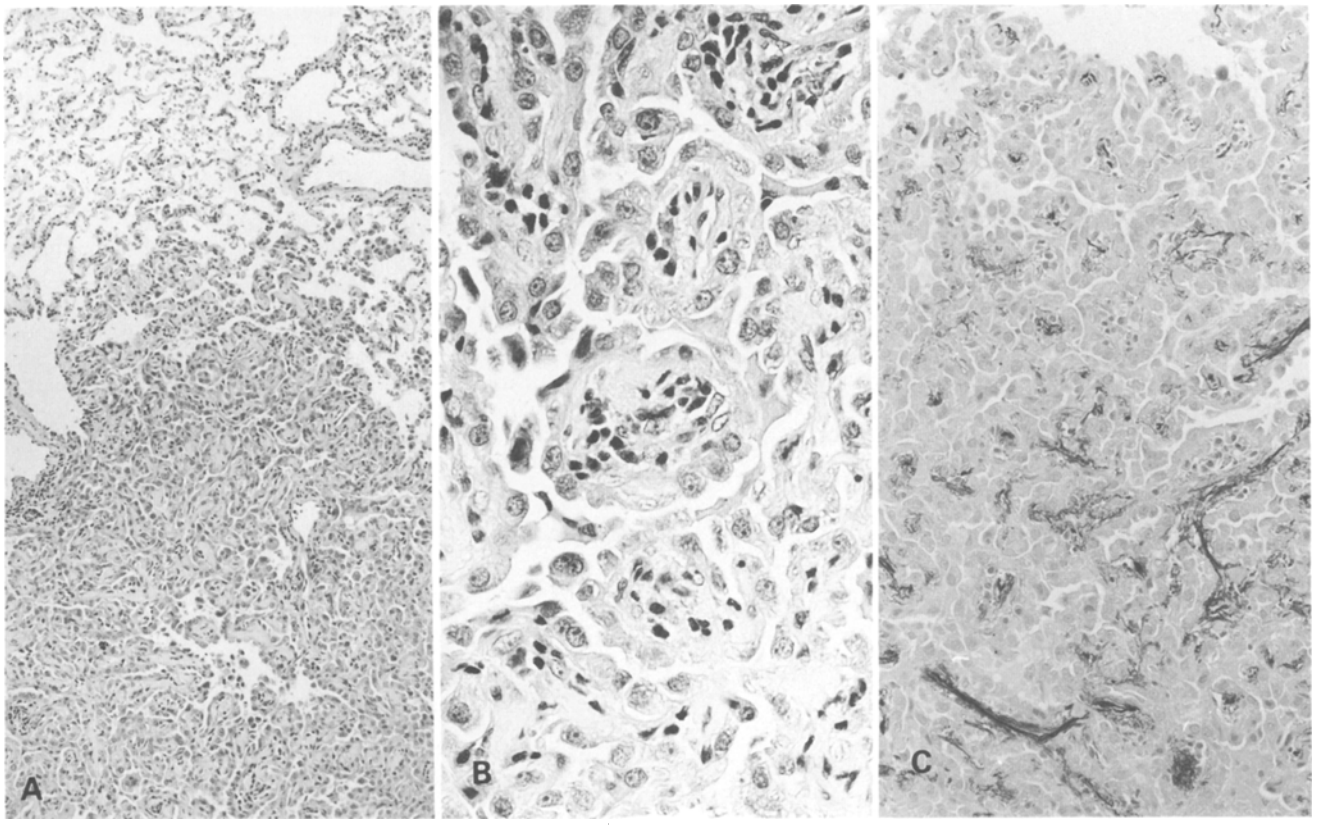

Fig. 2. **A** Cuboidal to low columnar cells arranged in a papillary pattern in the nodules. The peripheral areas of the nodule merge imperceptibly with the adjacent lung parenchyma. H & E, ×100. **B** The papillae contain fibrovascular cores with focal sclerosis and infiltration of lymphocytes, histiocytes and mast cells. H & E, ×400. **C** Elastic fibres are identified in the tumour stroma. Elastica van Gieson, ×200

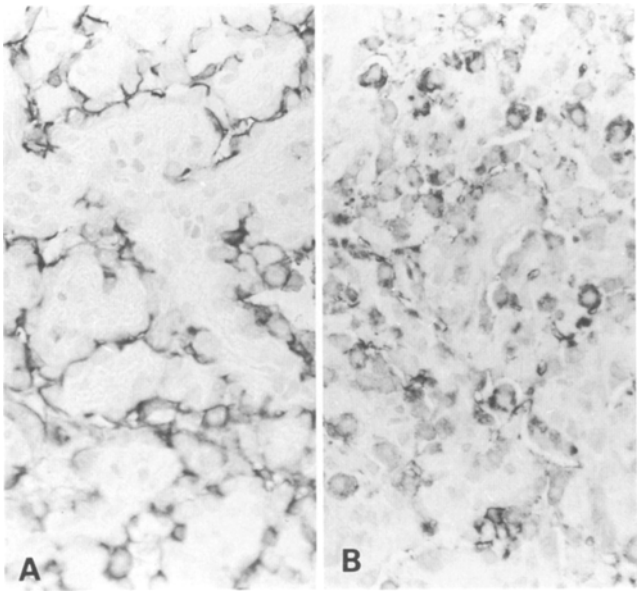

Fig. 3. Immunohistochemical positivity for EMA (**A**) and surfactant apoprotein (**B**) in the tumour cells. Streptavidin-biotin method, ×400

their cytoplasm, indicating differentiation toward both type II pneumocytes and Clara cells, as in the previous cases.

Within the differential diagnosis, other tumour lesions showing papillary pattern should be ruled out before establishing the diagnosis of papillary adenoma. Bronchioloalveolar carcinoma is the malignant counterpart of papillary adenoma and proliferates along the alveolar walls with preservation of the elastic fibres in the stroma (Delarue et al. 1972; Sherwin and Laforet 1963). Noguchi et al. (1986a) and Fukuda et al. (1992) presented cases of papillary adenoma with absence of elastic fibres in the stroma. According to these investigations, this finding is the feature that most distinguishes papillary adenomas from well-differentiated adenocarcinomas. The case reported here differs from those previously described in several respects. In our case, elastic fibres were clearly identified in the stroma of all pulmonary nodules and a few cells lining the papillae showed positive nuclear staining for PCNA. It is said that PCNA immunoreactivity is a marker of cell proliferation in fixed histological specimens (Robbins et al. 1987). The result of PCNA staining suggests that most of the tumour cells might not be in proliferative phase and seems to be corroborate by the absence of metastases in lymph nodes and distant organs. It should be pointed out that in the current case the patient is alive and well more

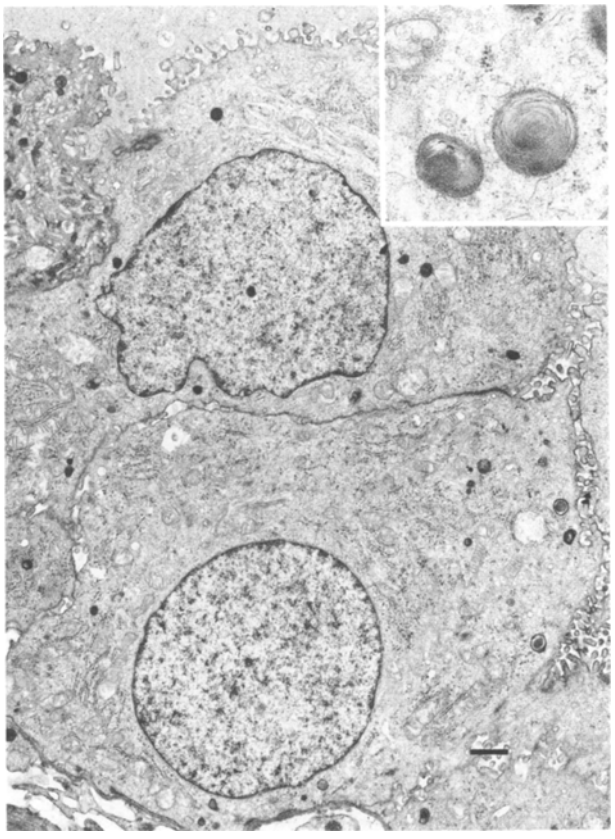

Fig. 4. Cuboidal cells attached to the basement membrane have osmoiphilic lamellar bodies in the cytoplasm and short microvilli along the free border. ×5000 (*bar*=1 μm). *Inset*, osmiophilic lamellar bodies. ×22000

than 6 years after open lung biopsy. In spite of the presence of elastic fibres within the stroma of the tumours, we diagnosed this case as benign papillary adenomas because of the absence of mitotic activity, infiltrative growth pattern and CEA reactivity as well as the clinical course.

Papillary adenoma also resembles so-called sclerosing haemangioma of the lung. However, the histological features of this tumour are characterized by solid, haemorrhagic, papillary, and sclerotic patterns (Katzenstein et al. 1980). Some reports suggest a close relationship between papillary adenoma and sclerosing haemangioma (Hegg et al. 1992; Noguchi et al. 1986b). In our case, the possibility that multiple papillary adenomas might be the early stage of sclerosing haemangioma cannot be ruled out.

From our studies on a single case, it is difficult to determine the histogenesis of this tumour. There is no evidence of association of multiple papillary adenomas with VR. The patient is alive and is being treated with several anti-epileptic drugs. One may contend that the present case was incidentally associated with VR, but the possibility remains that these papillary adenomas may be associated with the effect of the anti-epileptic drugs. We consider that re-biopsy is needed to elucidate the natural history of this uncommon tumour, but the patient and his family refused to permit such a examination.

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