Carcinoma of Lung with Rhabdoid Phenotype: A Case Report with Literature Review

Qiang Wu, Jung Woo Choi, Nam Hee Won, Jong Sang Choi*

Department of Pathology, Anam Hospital of Korea University Medical Collage, Seoul, Korea 136-701

Abstract Lung carcinoma with rhabdoid phenotype is very rare. We present a 64-year-old woman with this uncommon tumor. Bronchoscopically, the neoplasm was located in the anterior segment of bronchus of right upper lobe as a protruding mass. Histological examination showed rhaboid cells: neoplastic cells with abundant cytoplasm, an eccentric nucleus with a macronucleolus, and a round eosinophilic cytoplasmic inclusion. These cells constituted about 30% of the tumor, in which the "parent" neoplasm was a poorly differentiated carcinoma. The stains for mucus were negative. Immunohistochemistry revealed diffuse vimentin and p63 strongly positive. Pan-cytokeratin, CAM5.2, TTF-1 and synaptophysin were focally positive and eosinophilic cytoplasmic inclusions were found positive for CAM5.2. But CEA, chromogranin A, SCLC, myoglobin and desmin immunostains were negative. We concluded that lung carcinomas with rhaboid phenotype are rare variants, of which the "parent" neoplasm may present a poorly differentiated carcinoma with focal neuroendocine differentiation.

Key words Lung neoplasms; Rhabdoid phenotype; Immunohistochemistry

Malignant rhabdoid tumors were first reported in kidney by Beckwith and Palmer [1]. Since then tumors containing rhabdoid cells have been described in many extrarenal sites. However, carcinoma with rhabdoid features in the lung is very rare. Current literature review shows that less than 40 cases of this tumor have been compiled in the American and English literature [2]. In this article, we report on one case of carcinoma with rhabdoid phenotype in the lung and review the literatures about this tumor.

PATIENTS AND METHODS

Clinical data

A 64-year-old woman complaining dry cough lasting for 3 weeks was admitted to Anam Hospital of Korea University. She was non-smoker. And she had a history of diabetes mellitus and took Sulfonylurea orally. Positron emission tomography(PET) revealed conglomerated hypermetabolic lesions in the right upper lobe, mediastinum and right hilum. Chest computerized tomographic scan (CT) also showed an infiltrating associated narrowing in the right upper lobe anterior segment and multiple conglomerated lymph nodes with a diameter of 2.7cm. The above examinations of her chest implied a malignant lesion in the right lobe with lymph node involvement. Brain MRI and abdomen SONO did not find any evidence of tumor metastasis. Laboratory examination showed a high level of serum glucose (135mg/dl), a fast erythrocyte sedimentation rate (ESR, 43mm/hr) and hypoglobulia (3.76×104/μl), but haemaglobin level was normal (12.1g/dl). Bronchoscopic examination revealed an obstructive protruding mass with necrotic materials into the bronchus of anterior segment of right upper lobe, where washing and biopsy were done. Unfortunately, the washing and sputum smears gave a negative result.

Reagents and methods

For the patient did not undergo an operation, only specimens composed of several tiny grey-white tissues from brochoscopic biopsy were obtained, and they were all embedded in a paraffin block, of which the pathologic number was coded as S05-14123A. Parallel tissue sections were cut for the stains of hematoxylin-eosin (HE), Alcian blue (PH 2.5), PAS (with and without di-

Correspondence to: Jong Sang Choi
Tel: +82-2-920-6145
Emails: jongchoi0404@naver.com

astase) and immunohistochemical stains, for which EnVision two-step method and a DakoCytomatin autostainer were used. Mouse monoclonal antibodies against p63, TTF-1, CEA, chromograinin and desmin, rabbit multiclonal antibodies against synaptophysin and myoglobin, and EnVision immuno-detection kit were from Dako, USA. Mouse monoclonal antibodies against vimentin, pan-cytokeratin (panCK), SCLC (CD56) were from Zymed Laboratories, USA.

RESULTS

Histological findings

The HE staining sections showed that the cancer cells grew in nests, cords, sheets and in some areas the cancer cells were lack of cohesiveness (Fig. 1A). A tendency of glandular differentiation was found (Fig. 1B), but keratinization was not evident. Foci of tumor necrosis were seen. The tumor cells were pleomorphic, which varied in size and shape. Mitosis was not active. Approximately 30% cell showed a rhabdoid phenotype (Fig. 1C). These cells were ovoid, round and polygonal in shape with abundant eosinophilic cytoplasm and a large eosinophilic globular cytoplasmic inclusion. The nuclei were displaced toward the periphery given the impression of rhabdomyoblasts. Prominent nucleoli were present in some cells.

Histochemical and immunohistochemical findings

The tumor tissue was negatively stained by Alcian blue, and was focally positive for PAS staining in the area of nonrhabdoid component, but was negative for diastase-digested periodic acid-Schiff (d-PAS) staining.

Vimentin and p63 were diffusely and intensely positive in the cytoplasms and in the nuclei respectively (Fig. 1D, 2A). The tumor cells were focally positive for

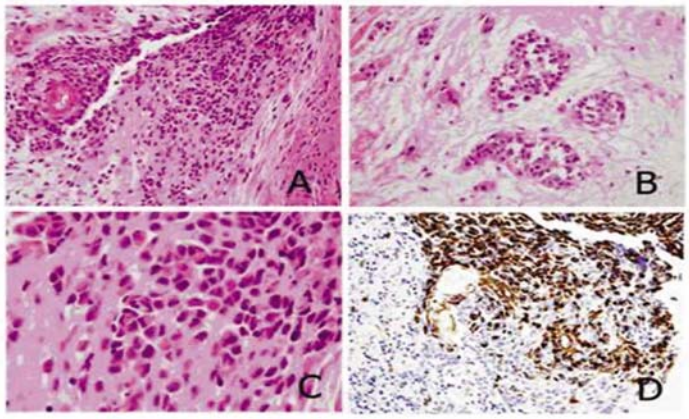

Fig. 1 A. Histopathologic section, stained with HE (×400); B. Histopathologic section, stained with HE (×400); C. Histopathologic section, stained with HE (×1000); D. Histopathologic section, stained with anti-vimentin and horseradish peroxidase (×400)

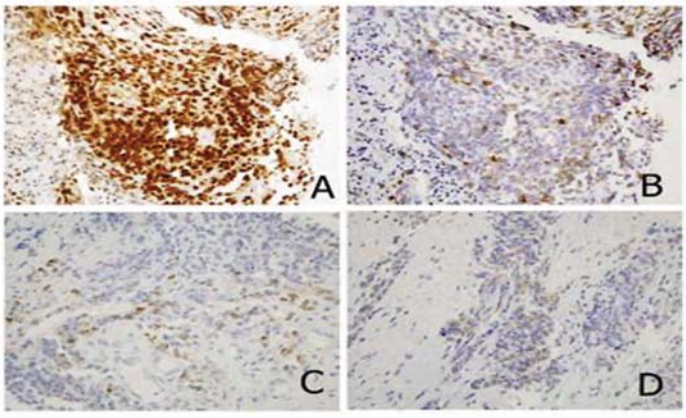

Fig. 2 A. Histopathologic section, stained with anti-p63 and horseradish peroxidase (×400); B. Histopathologic section, stained with anti-cytokeratin and horseradish peroxidase (×400); C. Histopathologic section, stained with anti-synaptophysin and horseradish peroxidase (×400); D. Histopathologic section, stained with anti-CAM5.2 and horseradish peroxidase (×400)

panCK (Fig. 2B), synaptophysin (Fig. 2C), CAM5.2 (Fig. 2D), and TTF−1. Vimentin and CAM5.2 were also found positive in the cytoplasmic inclusions. CEA, chromogranin A, SCLC, myoglobin and desmin were negative.

Final diagnosis

As a result of histologic, histochemical and immunihistochemical study, this case was diagnosed as a non−small cell carcinoma, poor differentiated, with rhadoid feature and with neuroendocrine differentiation.

DISCUSSION

Tumors morphologically resembling rhabdoid tumors of the kidney have been described in many extrarenal sites, such as alimentary tract, liver, uterus, vulva, prostatic region, blader, nasopharynx, tongue, orbit, soft tissue, central nervous system, breast and intrathoracic region including lung, thymus, mediastinum and heart etc [2~9]. However, they are not the same as renal rhabdoid tumor, for rhabdoid cells may be discerned focally in various tumors. Lung carcinomas composed of rhabdoid phenotype are very rare, which was first described by Colby *et al* [10] in 1995, as neuroendocrine carcinoma with rhabdoid phenotype. Additional cases have since been reported[2], and it has been included as a variant of large cell carcinoma in the 1999 WHO classification of lung tumors. In 2004 WHO classification of lung tumors, this variant is also decribed as follows, " Large cell carcinomas with a rhabdoid phenotype are very rare", "Small foci of adenocarcinoma and positive neuroendocrine markers may be seen", and "Cells with rhabdoid features may be seen focally in other poorly differentiated NSCLC"[11]. Up to now, only two cases of lung carcinoma with a pure rhabdoid phenotype without foci of any other carcinomatous components were repoted [3, 6].

There are some different appearances between extrarenal rhabdoid tumors and rhabdoid tumors of the kidney. Extrarenal rhabdoid tumors are observed in a broad range of age groups, although renal rhabdoid tumors are tumors of childhood. Renal rhabdoid tumors have pure rhabdoid morphology highlighted by the proliferation of typical monotonous rhabdoid cells, while most extrarenal rhabdoid tumors show a combined morphology with an epithelial or mesenchymal component and the rhabdoid component comprising 10%~90% of the tumor cells.

Lung cancers with a rhabdoid phenotype range from 1.3cm to 8.0cm in diameter. They are grossly solid and grayish white. Hemorrhage and necrosis are often found. The typical pathologic features of the lung rhabdoid tumors are showed as follows[2~7, 9, 11]: (1) The rhabdoid component is characterized by the presence of large cells with a large eccentric nucleus with a central macronucleolus, and with abundant cytoplasm and a rounded eosinophilic cytoplasmic inclusion; (2) Almost all tumors have non−rhabdoid component, which is usually poor differentiated with neuroendocrine fifferentiation, and the rhabdoid component composes 10%~90% of the tumor cells. A tumor containing less than 10% rhabdoid cells is decribed as lung carcinoma with a small number of rhabdoid cells instead of the diagnosis of lung carcinoma with a rhabdoid phenotype for the different prognosis of the two tumors; (3) In most cases the rhabdoid cells and the eosinophilic inclusions are negative for Alcian blue staining, and are negative or weekly positive for PAS staining with a diastase sensitive pattern; (4) Immunohistochemical stains demonstrate that all cases are consistently positive for vimentin, and that epithelial and neuroendocrine markers are at least focally positive, suggesting a neuroendocrine differentiation; (5) Electron microscopically, the rhabdoid cells have abundant collections of paranuclear intermediate filaments either as interlacing bundles or whorl−like arrays.

For this case, both histopathology and immunohistochemistry indicate that it is a poor differentiated non−small cell carcinoma with rhabdoid phenotype of which neuroendocrine differentiation is suggested by synaptophysin positivity.

To date, there are no reports on p63 expression in lung carcinomas with rhabdoid feature. p63 is a homolog of p53 which is consistently expressed by basal/stem cells of stratified epithelium, as well as benign basal cells of some nonsquamous epithelia, such as bronchial reserve cells, and are increasingly utilized as immuno-

histochemical markers in surgical pathology as a marker of carcinomas with squamous differentiation or squamous potential. p63 expression may also used a useful auxiliary marker for differentiation of primary non－small cell carcinoma and secondary tumors of the lung[12, 13]. In this case, p63 positivity implies a primary non－small cell carcinoma of the lung with squamous potential.

In the cases having been described, the "parent tumors" of lung cancers with rabdoid phenotype were not confined to large cell carcinomas, poor differentiated carcinomas seemed to be more frequently seen, and they showed neuroendocrine differentiation and adenocarcinoma differentiation. A transition between the adenocarcinoma component and the rhbdoid component was not found in the cases of Cavazza´s report, in which a small series of 6 cases was described, and there was a case that the non－rhabdoid component was sarcoma[7].

The histological differentiation diagnosis of lung tumors with rhabdoid features, which may be difficult on pure morphologic grounds, includes a variety of malignant primary and metastatic neoplasms, such as malignant melanoma, rhabdomyosarcoma, leiomyosarcoma, epithelioid angiosarcoma and plasmacytoma etc. The judicious use of a limited antibody panel may suffice for reliably segregating these lesions and singling out those that may benefit from specific treatments. Mucinous adenocarcinama with signet－ring cells, primary of the lung or metastatic, can simulate a rhabdoid phenotype. However the absence of a significant amount of intracellular and extracellular mucin in this case rules out the former diagnosis.

Lung cancers with rhabdoid phenotype may be considered to be aggressive, as the majority present with high－stage disease. The prognosis for the disease is poor. Follow－up showed that most patients died in 2 to 19 months after lobectomy, and metastasis was evident in most survived cases [2~8]. The proportion of rhabdoid cells is a significant indicator for prognosis. Shimazaki *et al* [9] found that tumors with>10% rhabdoid cells behaved more aggressively than did those with<10% rhabdoid cells. Those investigators also found that tumors with<5% rhabdoid cells behaved similarly to large cell carcinoma without rhabdoid cells [9]. Therefore, it is clinically significant to recognize such a disease.

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