CASE REPORT

Blastomatoid pulmonary carcinosarcoma: A rare case report and review of the literature

Tadashi Sakane¹, Katsuhiro Okuda¹, Hideo Hattori², Takuya Watanabe¹, Risa Oda¹, Tsutomu Tatematsu¹, Keisuke Yokota¹, Hiroshi Haneda¹, Hiroshi Inagaki² & Ryoichi Nakanishi¹

¹ Department of Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
² Department of Pathology and Molecular Diagnostics, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Keywords
Beta catenin; carcinosarcoma; lung neoplasms; pulmonary blastoma.

Correspondence
Katsuhiro Okuda, Department of Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan.
Tel: +81 52 853 8231
Fax: +81 52 853 6440
Email: kokuda@med.nagoya-cu.ac.jp

Received: 14 June 2018;
Accepted: 10 July 2018.
doi: 10.1111/1759-7714.12831
Thoracic Cancer 9 (2018) 1323–1326

Abstract
A 65-year-old never-smoking woman presented to a local hospital, because an abnormal shadow was detected at the right lower lung field by annual chest X-ray. Computed tomography (CT) revealed a 5-cm tumor in segment 6 of her right lung and an enlarged subcarinal lymph node, suggesting metastasis. The lung tumor was diagnosed as adenocarcinoma by a CT-guided percutaneous needle biopsy. She was referred to our hospital and underwent right lower lobectomy with lymph node dissection (ND2a-2). A histopathological examination of the tumor showed a biphasic proliferation made of carcinomatous and sarcomatous components. The carcinomatous component consisted of glandular structures of atypical cells that possessed chromatin-rich nuclear and clear cytoplasm, confirming high-grade fetal adenocarcinoma. The sarcomatous component consisted of immature spindle cells that differentiated into chondrosarcoma. Immunohistochemically, the glandular structures expressed membranous beta-catenin, and the ultimate diagnosis was blastomatoid variant of pulmonary carcinosarcoma. She received four courses of cisplatin plus vinorelbine as adjuvant chemotherapy and remained alive with neither recurrence nor distant metastasis at two and a half years after the operation. We experienced a rare case of blastomatoid pulmonary carcinosarcoma.

Introduction
Blastomatoid pulmonary carcinosarcoma is one of the rarest histologic types of carcinosarcoma of the lung.¹ Although there have been only a few reports on this histologic type so far, there might be some cases in which a definitive diagnosis of blastomatoid pulmonary carcinosarcoma was not obtained.²⁻⁴ Advances have been made in recent years in ancillary diagnostic techniques for this histologic type, such as immunohistochemistry and gene mutation analyses.²,³

We herein report a case of blastomatoid pulmonary carcinosarcoma.

Case report
A 65-year-old never-smoking woman presented to a local hospital, because an abnormal shadow was detected at the right lower lung field by annual chest X-ray. She had no subjective symptoms. Computed tomography (CT) revealed a 5-cm well-circumscribed tumor in segment 6 of her right lung, which was in wide contact with the parietal pleura (Fig 1a,b). An enlarged subcarinal lymph node was suspected of being metastasis (Fig 1c). A CT-guided percutaneous needle biopsy of the lung tumor was performed, and a diagnosis of adenocarcinoma was made. She was referred to our hospital for treatment. Since there was no evidence of distant metastases, we performed right lower lobectomy with lymph node dissection (ND2a-2), and combined resection of the parietal pleura with video-assisted thoracoscopic surgery.

Macroscopically, the lesion was a well-circumscribed tumor of 7.0 × 4.5 × 4.2 cm in size with a soft, fleshy, and pale tan-white cut surface. A histopathological examination showed biphasic proliferation with carcinomatous and sarcomatous components with a sharp border between both...
components (Fig 2). The carcinomatous component consisted of glandular structures of atypical cells that possessed chromatin-rich nuclear and clear cytoplasm, confirming high-grade fetal adenocarcinoma (H-FLAC) (Fig 2a,b). Morule formation was not seen in the carcinomatous components. In contrast, the sarcomatous component consisted of immature spindle cells that differentiated into chondrosarcoma (Fig 2c–e). Immunohistochemically, the glandular structures expressed membranous beta-catenin and focal alpha-fetoprotein (Fig 3). The expression of p53, murine double minute 2 (MDM2), cyclin-dependent kinase 4 (CDK4), and thyroid transcription factor 1 (TTF-1) were not confirmed. A diagnosis of the blastomatoid variant of pulmonary carcinosarcoma was thus established.

The tumor infiltrated the parietal pleura, but there was no invasion of tumor cells on the detached surface of the parietal pleura. As expected before surgery, the involvement of the subcarinal lymph node was confirmed, although no other lymph node metastases were confirmed. The tumor was ultimately staged at pT3, pN2, M0, G3, R0, UICC stage 3A by the UICC 7th classification. The mutations in epidermal growth factor receptor (EGFR) gene and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) gene, and the anaplastic lymphoma kinase (ALK) translocations were not detected. She received cisplatin (80 mg/m², Day 1) plus vinorelbine (25 mg/m², Day 1 and 8) every three weeks for four cycles as adjuvant chemotherapy six weeks after the operation and remained alive.
two and a half years after surgery with no evidence of local recurrence or distant metastasis.

Discussion

Sarcomatoid carcinomas are estimated to account for only 0.1–0.4% of all lung cancers, and of these, only 4% are pulmonary carcinosarcomas. According to the recent World Health Organization (WHO) classification of lung tumors, carcinosarcoma is defined as a malignant tumor that consists of an admixture of non-small cell lung carcinoma and sarcoma-containing heterologous elements. Koss et al. reported that 18% of 66 carcinosarcoma cases contained H-FLACs as epithelial components. These carcinosarcomas, including H-FLACs, are defined as blastomatoid pulmonary carcinosarcomas, but they are not yet recognized as a distinct entity by the WHO classification and are only obliquely referenced in the section on carcinosarcoma. H-FLACs are referred to by Nakatani et al. as a type of pulmonary adenocarcinoma of the fetal lung. Those authors divided pulmonary adenocarcinomas of the fetal lung into low- and high-grade forms, and low-grade adenocarcinomas of fetal lung type (L-FLACs) are also known as well-differentiated fetal adenocarcinomas (WDFAs) in the WHO classification at present. Currently, both L-FLACs/WDFAs and H-FLACs are included as a subtype of adenocarcinoma in the WHO classification. Although both groups show similar histological findings, H-FLACs show high nuclear atypia and typically lack morules. The pathogenesis of these two groups has been discussed, and the up-regulation of the Wnt signaling component, including gene mutations of beta catenin, is suggested to be important for L-FLACs/WDFAs but not for H-FLACs. Furthermore, immunohistochemical analyses have demonstrated aberrant nuclear and cytoplasmic staining of beta catenin in the epithelial cells of L-FLACs/WDFAs, while membranous staining in H-FLACs. These findings with ancillary techniques support our diagnosis in the present study. In addition, α-fetoprotein staining is often positive and TTF-1 staining negative in H-FLACs.

No valid therapy has yet been proposed for the treatment of carcinosarcomas, other than complete resection as for other types of sarcomatoid carcinomas, and the role of chemo- and radiation therapy remains controversial. At least seven cases of blastomatoid pulmonary carcinosarcoma have been reported (Table 1). All were advanced cases (stage 2 or more), reflecting the difficulty of early detection due to the disease’s rapid progression.

According to the previous reports, pulmonary carcinosarcomas occur seven to eight times more often in men than in women, particularly in elderly smokers predominantly in their 60s. The prognosis of carcinosarcoma is generally very poor. Indeed, most of the above-mentioned seven cases of blastomatoid pulmonary carcinosarcoma were males with smoking history, and they also showed a poor prognosis.

It is well known that smoking is one of the most important risk factors in the etiology of lung cancer including...
Blastomatoid pulmonary carcinosarcoma1,9,16 However, the present case was a never-smoking female, and she remained alive without recurrence for at least two and a half years after complete resection followed by adjuvant chemotherapy. Because there is no established chemotherapy for blastomatoid pulmonary carcinosarcoma, we used the regimen of cisplatin plus vinorelbine, which is used for non-small cell lung cancer as adjuvant therapy. Our selected chemotherapy regimen as adjuvant therapy after complete resection may be effective against blastomatoid pulmonary carcinosarcoma.

In summary, we herein described a particularly rare case of blastomatoid pulmonary carcinosarcoma. Due to the similarity in the histopathological findings between H-FLACs and L-FLACs/WDFAs, and the rarity of the disease, the exact behavior of blastomatoid pulmonary carcinosarcoma remains unclear. The accumulation of more cases and long-term follow-up data leading to a more objective assessment is needed.

Disclosure
The authors have no conflicts of interest to declare.

References
1 Koss MN, Nicholson AG, Travis WD et al. Carcinosarcoma. In: Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG (eds). WHO Classification of Tumours of Lung, Pleura, Thymus and Heart, 4th edn. IARC, Lyon 2015; 91–2.
2 Sekine S, Shibata T, Matsumo Y et al. β-Catenin mutations in pulmonary blastomas: Association with morule formation. J Pathol 2003; 200: 214–21.
3 Nakatani Y, Miyagi Y, Takemura T et al. Aberrant nuclear/cytoplasmic localization and gene mutation of β-catenin in classic pulmonary blastoma: β-catenin immunostaining is useful for distinguishing between classic pulmonary blastoma and a blastomatoid variant of carcinosarcoma. Am J Surg Pathol 2004; 28: 921–7.
4 Schaefer IM, Sahlmann CO, Overbeck T, Schweyer S, Menke J. Blastomatoid pulmonary carcinosarcoma: Report of a case with a review of the literature. BMC Cancer 2012; 12: 424.
5 Kawachi K, Murakami A, Sasaki T et al. Blastomatoid carcinosarcoma of the lung. Pathol Int 2013; 63: 377–9.
6 Sobin LH, Gospodarowicz MK, Wittekind C (eds). UICC International Union against Cancer. TNM Classification of Malignant Tumours. 7th edn. United Kingdom Wiley-Blackwell, Oxford; 2009.
7 Nakatani Y, Masudo K, Miyagi Y et al. Aberrant nuclear localization and gene mutation of β-catenin in low-grade adenocarcinoma of fetal lung type: Up-regulation of the Wnt signaling pathway may be a common denominator for the development of tumors that form morules. Mod Pathol 2002; 15: 617–24.
8 Travis WD, Brambilla E, Nicholson AG et al. The 2015 World Health Organization classification of lung tumors: Impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015; 10: 1243–60.
9 Koss MN, Hochholzer L, Frommelt RA. Carcinosarcomas of the lung: A clinicopathologic study of 66 patients. Am J Surg Pathol 1999; 23: 1514–26.
10 Nakatani Y, Kitamura H, Inayama Y et al. Pulmonary adenocarcinomas of the fetal lung type: A clinicopathologic study indicating differences in histology, epidemiology, and natural history of low-grade and high-grade forms. Am J Surg Pathol 1998; 22: 399–411.
11 Travis WD, Nakatani Y, Scagliotti G et al. Variants of adenocarcinoma. In: Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG (eds). WHO Classification of Tumours of Lung, Pleura, Thymus and Heart, 4th edn. IARC, Lyon 2015; 38–43.
12 Zhang J, Sun J, Liang XL, Lu JL, Luo YF, Liang ZY. Differences between low and high grade fetal adenocarcinoma of the lung: A clinicopathological and molecular study. J Thorac Dis 2017; 9: 2071–8.
13 Huang SY, Shen SJ, Li X. Pulmonary sarcomatoid carcinoma: A clinicopathologic study and prognostic analysis of 51 cases. World J Surg Oncol 2013; 11: 252.
14 Rahouma M, Kamel M, Narula N et al. Pulmonary sarcomatoid carcinoma: An analysis of a rare cancer from the surveillance, epidemiology, and end results database. Eur J Cardiothorac Surg 2018; 53: 828–34.
15 Brahm E, Ben Rejeb H, Aouadi S, Kilani T, El Mezni F. Pulmonary carcinosarcoma with heterologous component: Report of two cases with literature review. Ann Transl Med 2014; 2: 41.
16 Tonini G, D’Onofrio L, Dell’Aquila E, Pezzuto A. New molecular insights in tobacco-induced lung cancer. Future Oncol 2013; 9: 649–55.