



Metastasised Sarcomatoid Carcinoma Component with a Rare BRAF K601E Point Mutation and High PD-L1 Expression

Yusuke Sugita¹, Noriaki Sakakura¹, Yasushi Yatabe² and Hiroaki Kuroda^{1*}

¹Department of Thoracic Surgery, Aichi Cancer Center Hospital, Japan

²Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Japan

Abstract

We experienced the case of a 74-year-old male with difficulty in preoperative diagnosis, but the definitive diagnosis was explicitly obtained with genetic analyses and immuno staining of programmed death-ligand 1. Chest computed tomography revealed a tumour with a maximum diameter of 30 mm in the left upper lobe adjacent to the chest wall, with osteolytic changes of the second rib. The following two clinical possibilities were considered based on the chest wall biopsy: 1) Heterogeneous lung malignancy and its direct invasion and 2) Double primary lung cancer and the chest wall sarcoma. The patient underwent left upper division segmentectomy and combined costectomy of the second and third ribs. Contrary to our expectations, the histopathological diagnosis was metastasis of the sarcomatoid component in adenocarcinoma harbouring programmed death-ligand 1 expression positivity and an extremely rare BRAF K601E point mutation. Therefore, genetic analyses and immuno staining can be helpful in determining a definitive histopathological diagnosis.

Keywords: BRAF; K601E; NSCLC; PD-L1; Costectomy

Introduction

Recently, with the identification of oncogenic driver mutations, Non-Small-Cell Lung Cancer (NSCLC) therapy has undergone a revolutionary change. By comprehensive gene analyses, it is possible to detect detailed genetic mutations and make a diagnosis for disease states that was previously difficult based on histopathological or immuno histo chemical findings. Here, we describe a case that an extremely rare BRAF K601E point mutation and the immunostaining of programmed death-ligand-1 (PD-L1) lead to a definitive diagnosis of the Chest Wall (CW) haematogenous metastasis of heterogeneous adenocarcinoma.

Case Presentation

A 74-year-old male complaining of left chest pain was referred to our hospital for consultation. Chest computed tomography revealed a tumour with a maximum diameter of 30 mm in the left upper lobe adjacent to CW, with osteolytic changes of the second rib, appearing as a lump of tumour (Figure 1A). On biopsy, CW tumour was suspected to be a sarcoma or Sarcomatoid Carcinoma (SC); however, definitive diagnosis could not be made. Two clinical possibilities were discussed postoperatively: (a) heterogeneous lung malignancy and its direct invasion of CW (clinical T3N0M0, stage IIIB) and (b) double primary NSCLC and CW sarcoma. The possibility of radical resection by surgery was investigated. During thoracotomy using a hook approach, NSCLC did not have any adjacent structures, which implicated the former possibility. Subsequently, left upper division segmentectomy with lymphadenectomy and combined costectomy of the second and third ribs was performed. Contrary to our expectations, the final pathological diagnosis was adenocarcinoma, pT2aN0M1b stage IV, and including 10% of SC, which had independently metastasised to the second rib (Figure 1B, 1C, Table 1). The diagnosis was finally confirmed by immuno staining and genomic analyses (Table 1). In immunostaining, the proportion of PD-L1 using 22C3 pharm-Dx KIT (Dako, Carpinteria, CA) was <1% (negative) for adenocarcinoma, 80% for SC for primary (Figure 1D) and 90% for CW metastasis (Figure 1E). In the genomic analyses after RNA extraction, a rare point mutation of BRAF K601E was determined in primary and metastasis (Figure 1F). Consequently, adjuvant chemotherapy with S-1 was administered, and the patient had no recurrence for 2 years after initial pulmonary resection.

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*Correspondence:

Hiroaki Kuroda, Department of Thoracic Surgery, Aichi Cancer Center Hospital, Japan, Tel: +81-052-762-6111; E-mail: h-kuroda@aichi-cc.jp

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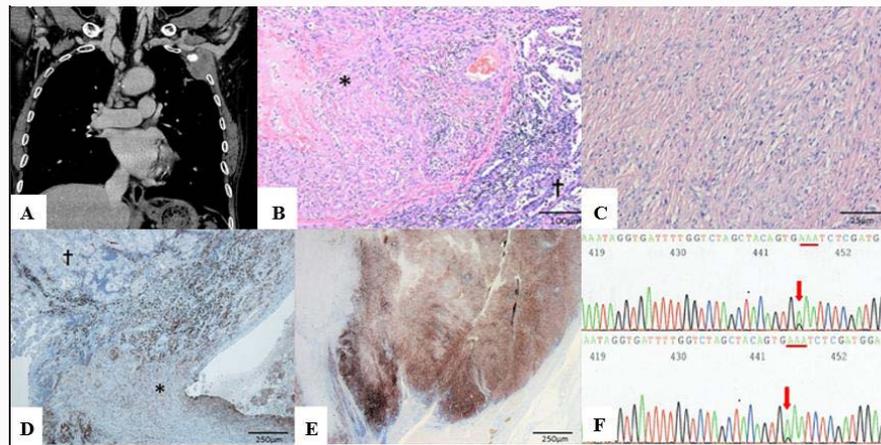


Figure 1: (A) Computed Tomography in mediastinal window of coronal showed lung malignancy was adjacent to the chest wall. (B) The primary adenocarcinoma (+) contains a small sarcomatoid component (*). (C) Metastasis consisted of only spindle-shaped pleomorphic cells. (D) PD-L1 expression of primary adenocarcinoma (+) and sarcomatoid component (*). (E) PD-L1 expression of chest wall metastasis. (F) BRAF variant at codon 601 Genetic of both primary (upper) and metastasis (bottom).

Table 1: Characteristics.

Variables	Primary NSCLC	Chest wall metastasis
Histology		
Adenocarcinoma	90%	none
Sarcomatoid	10%	100%
Genetic mutation	BRAF K601E	BRAF 601E
The proportion of PD-L1		
Adenocarcinoma	<1%	none
Sarcomatoid	80%	90%

NSCLC: Non-Small-Cell Lung Cancer; PD-L1: Programmed Dead-Ligand-1

Discussion

In this case, contrary to our preoperative expectations, the final diagnosis of haematogenous metastasis to CW of the small SC components in primary adenocarcinoma was proven histo logically and was strongly confirmed by immuno staining of PD-L1 and detection of a rare genetic mutation in BRAF K601E. Although this is only one case report, survival for 2 years with no recurrence proves the importance of definitive diagnosis and precise treatment.

Primary SC is rare, accounting for up to 0.3% of lung malignancies aggressiveness of their biological behaviors and unfavorable prognosis compared with other NSCLCs [1]. It may be difficult to clinically diagnose a primary or metastatic sarcoma using only haematoxylin and eosin staining, particularly when an obvious carcinomatous component is lacking. In this case, contrast immuno staining of PD-L1 played a key role in determining a definitive diagnosis. One possible reason for this heterogeneity is that epithelial-mesenchymal transition could be associated with PD-L1 up-regulation in sarcomatous areas [2].

Although BRAF mutations have been identified in only 2% to 4 % of lung malignancies [3]. In the collection of Somatic Mutations in Cancer database, the V600E mutation accounts for approximately 50% of BRAF mutations, but K601E for only 3%. Originally, in addition to the rarity of NSCLC with sarcomatoid carcinoma component in this presented case, the somatic acquisition of BRAF K601E it resulted in an extremely rare observation, accounting for 0.00006% to 0.00012%.

In conclusion, we experienced a case of primary adenocarcinoma with SC component metastasised only to CW and harbouring a BRAF K601E point mutation. Our preoperative expectations were off wonderfully. Genetic analyses and PD-L1 immunostaining can be used in the case of a difficult histological diagnosis to determine a definitive diagnosis.

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