



Case Report

Pneumothorax during Alectinib Treatment for a Uterine Inflammatory Myofibroblastic Tumor with Lung Metastasis

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Abstract

An inflammatory myofibroblastic tumor (IMT) is an uncommon sarcoma subtype with histopathological features, including inflammatory infiltrates. Anaplastic lymphoma kinase (ALK) gene rearrangement has been reported in half of the patients with IMTs; therefore, crizotinib, an ALK inhibitor, may achieve a response rate of 50% in these patients. We present a case with an initial diagnosis of uterine sarcoma and multiple lung metastases. After the failure of doxorubicin-based chemotherapy, revised pathology from a palliative hysterectomy revealed an IMT with ALK gene rearrangement. Treatment with alectinib achieved an excellent tumor response. The accurate differential diagnosis of uncommon sarcoma subtypes is crucial because a specific targeted therapy may considerably alter treatment outcomes.

Keywords: Alectinib, inflammatory myofibroblastic tumor, pneumothorax

INTRODUCTION

Inflammatory myofibroblastic tumors (IMTs) were first described in 1937 by Gleason and Hornick as histologically distinct myofibroblastic spindle cell neoplasms with lymphocyte infiltration that primarily develop in the lungs and peritoneum.^[1] A recent study reported that half of the patients with IMT presented with anaplastic lymphoma kinase (ALK) gene rearrangement, a characteristic rarely seen in other types of sarcomas.^[2] Other studies have indicated that the ALK inhibitor crizotinib had a remarkable efficacy in treating ALK-rearranged IMTs, and that other ALK inhibitors also

demonstrated beneficial results.^[3-6] Herein, we present a case of a patient with an IMT who was successfully treated with alectinib.

CASE REPORT

A 36-year-old woman sought treatment at our hospital after receiving a diagnosis of a vast uterine mass during a sonography examination at an infertility clinic. She presented

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Submitted: 07-Nov-2022

Revised: 10-Feb-2023

Accepted: 13-Feb-2023

Published: 16-Jun-2023

Access this article online

Quick Response Code:



Website:
www.ejcrp.org

DOI:
10.4103/ejcrp.eJCRP-D-22-00031

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How to cite this article: Lin CT, Wu CH, Huang HY, Liu CT. Pneumothorax during alectinib treatment for a uterine inflammatory myofibroblastic tumor with lung metastasis. J Cancer Res Pract 2023;10:71-4.

to our gynecology ward with the insidious onset of cough and dyspnea for several months. Notably, she had no underlying systemic diseases, family history of cancer, habits of alcohol consumption, betel nut chewing, or smoking.

Chest radiography revealed multiple lung masses, and a tissue sample was obtained using a computed tomography-guided needle biopsy from the largest tumor in the right lower lung [Figure 1]. Pathology results revealed a spindle cell neoplasm with a smooth muscle phenotype, compatible with a metastatic tumor of the uterus. Immunohistochemical (IHC) staining was positive for desmin, estrogen receptor (60%), progesterone receptor (70%), and CD10, and was negative for Melan-A, S100, and CD34.

The patient received standard first-line systemic chemotherapy with doxorubicin and ifosfamide for five cycles under the impression of metastatic uterine sarcoma. A response evaluation of the lung masses demonstrated stable disease. However, she developed severe anemia due to abnormal uterine bleeding 6 months after the initial diagnosis. A total hysterectomy was performed owing to the failure of conservative treatment to staunch the bleeding.

A 19-cm intramural soft tissue tumor was sent for pathology review. The results revealed diffuse infiltration of neoplastic spindle cells with moderate nuclear atypia, increased mitotic activity, and abundant lymphocytes. IHC staining was positive for smooth muscle actin, desmin, CD10, and ALK (VENTANA D5F3 CDx Assay). Fluorescence *in situ* hybridization confirmed an ALK gene rearrangement [Figure 2]. Therefore, she received a final diagnosis of an aggressive uterine IMT.

The patient received alectinib (a second-generation ALK inhibitor) at a dose of 600 mg twice daily, which resulted in considerable amelioration of dyspnea within 2 weeks. However, the sudden onset of chest tightness and shortness of breath occurred on day 20 of treatment. Chest radiography revealed remarkable regression of bilateral lung tumors and new onset of a massive right pneumothorax. An indwelling pigtail catheter was placed, and the pneumothorax resolved under conservative treatment [Figure 3]. She remained in partial response after 6 months of treatment with alectinib, despite experiencing several episodes of recurrent pneumothorax and one of pleurodesis [Figure 4].

DISCUSSION

An IMT is a rare mesenchymal neoplasm occurring primarily in children and adolescents. A minority of patients with IMTs present with local invasion and distant metastasis; however, 90% of patients have benign IMTs, which led to their former name, “inflammatory pseudotumors.”^[2] IMTs frequently occur in the lungs and abdominopelvic region, although they may be found in any part of the human body. Patients develop local pain or obstructive symptoms associated with a mass lesion in specific organs. Constitutional syndrome, characterized by fever and weight loss, has been reported in one-third of patients.^[1]

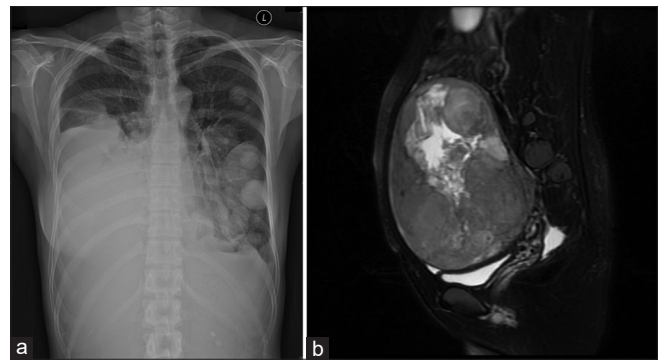


Figure 1: (a) Initial chest radiograph with multiple and bilateral lung tumors. (b) Heterogeneous soft tissue mass in the uterus on an MRI scan. MRI: Magnetic Resonance Imaging



Figure 2: (a) Total hysterectomy performed due to massive vaginal bleeding. (b) Firm, gelatinous tumor with focal necrosis and hemorrhage

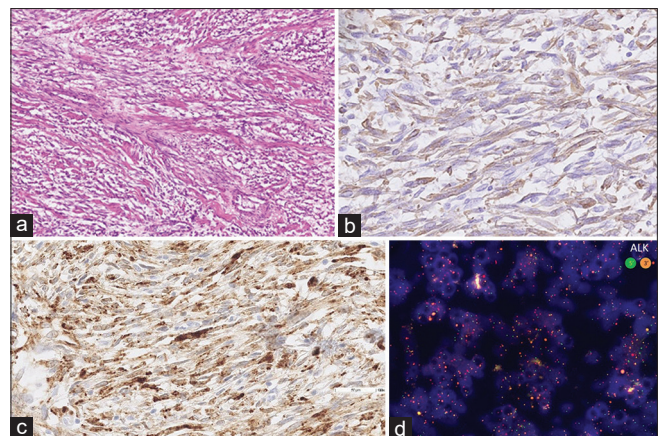


Figure 3: (a) Hematoxylin and eosin staining revealed myofibroblast proliferation with prominent lymphocyte infiltration. (b) IHC staining was positive for smooth muscle actin and (c) ALK (D5F3). (d) An ALK gene rearrangement was detected through fluorescence *in situ* hybridization. IHC: Immunohistochemical, ALK: Anaplastic lymphoma kinase

Our patient was a 36-year-old woman who developed symptoms in the lungs and pelvic region. We treated the uterus as the primary site due to its bulky presentation, and she also presented with bilateral pulmonary lesions. We biopsied the lung tumors because this method provided a safer alternative to take a biopsy of the transabdominal region; furthermore,

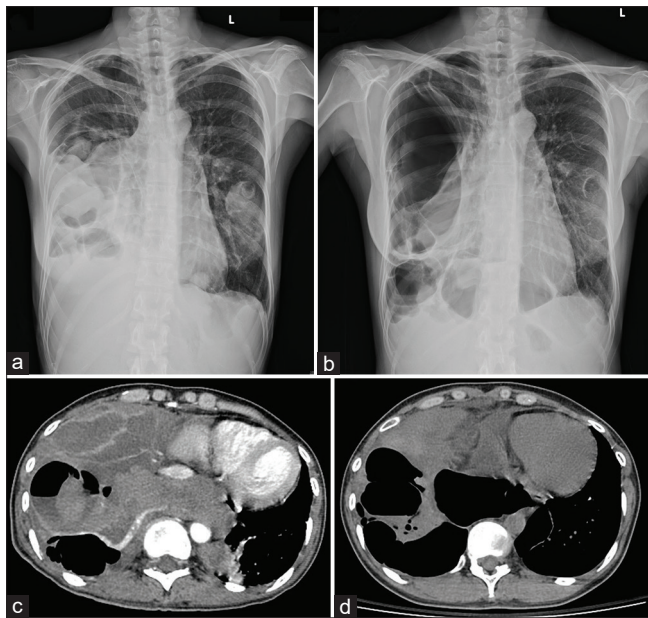


Figure 4: Right pneumothorax and multiple bleb formation after alectinib treatment; chest radiograph taken (a) before and (b) 5 months after treatment; CT scan taken (c) before and (d) 5 months after alectinib treatment. CT: Computed tomography

if proven malignant, the lung tumor stage would be more advanced. However, we were unable to correctly classify the sarcoma due to an insufficient amount of tissue and its atypical histological appearance; the tumor was more aggressive compared with typical IMTs.

The diagnosis of an IMT is challenging. Histologically, specimens generally consist of the proliferation of myofibroblastic spindle cells accompanied by inflammatory infiltrates rich in plasma cells and lymphocytes. The spindle cells may exhibit mild nuclear pleomorphism and generally have a low mitotic rate. Necrosis or vascular invasion is rare in patients with atypically aggressive disease.^[7] Our IHC staining results revealed approximately 50% positivity for ALK; this distinctive feature can thus be used to differentiate IMTs from other spindle cell neoplasms with inflammatory infiltrates. Although the fusion partner varies widely, ALK IHC staining constitutes a reliable marker of ALK gene rearrangement.^[8] In one study that included 24 patients with IMTs, researchers identified 12 patients with ALK gene fusions with 11 different partners using next-generation sequencing of DNA or RNA samples; these results differed from those of patients with lung cancers with ALK rearrangements.^[9]

Before the development of crizotinib, an ALK tyrosine kinase inhibitor, unresectable or metastatic IMTs were treated with systemic chemotherapy. A retrospective study demonstrated that anthracycline-based chemotherapy achieved a response rate of 47%–53%.^[10,11] Other active regimens include methotrexate with or without vinorelbine or vinblastine, gemcitabine, docetaxel, and trabectedin. In a 2018 nonrandomized, open-label phase II study, 20 patients with inoperable IMTs received crizotinib treatment;^[4] of 19

assessable patients, the objective response rate was 50% in the patients with ALK-positive IMTs (6/12) and 14% in those with ALK-negative IMTs (1/7). The results of these studies support the use of a biomarker-driven approach when treating patients with unresectable or metastatic IMTs. Furthermore, case reports have noted that second-generation ALK inhibitors, namely, ceritinib, brigatinib, and alectinib, and the third-generation ALK inhibitor, lorlatinib, yielded substantial treatment responses in ALK-positive IMTs.^[5,6,12,13]

Pneumothorax is a rare adverse event that occurs when ALK inhibitors are administered to patients with ALK-rearranged lung cancer. Postmarketing safety data on ALK inhibitors have reported a higher hazard ratio (HR) for pneumothorax (HR: 3.19 for crizotinib and 4.88 for alectinib) with more advanced generation ALK inhibitors.^[14] The corresponding mechanism remains poorly understood; however, it is possible that targeted therapy with a faster and deeper response may cause tumor necrosis and affect the integrity of the normal visceral pleura surface. Several case reports have also indicated that the successful treatment of primary or metastatic pulmonary malignancies, including osteogenic sarcoma, germ cell tumor, small-cell lung cancer, and lymphoma, may cause pneumothorax.^[15,16]

We present a case of a patient with an IMT treated successfully with alectinib. This case report highlights the importance of identifying the distinct histological and molecular features of IMTs. Treatment with ALK inhibitors can result in meaningful responses in a subset of patients with ALK gene rearrangements.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patient has granted consent for her images and other clinical information to be reported in this journal. The patient understands that her name and initials will not be published, and that although due efforts will be made to conceal her identity, anonymity cannot be guaranteed. This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (202201633B0).

Acknowledgment

This manuscript was edited by Wallace Academic Editing.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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