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Case Report

An Anaplastic Lymphoma Kinase-positive Inflammatory Myofibroblastic Tumor with Rapidly Acquired Resistance to First-line Anaplastic Lymphoma Kinase Inhibitor: A Case and Literature Review

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Abstract

Inflammatory myofibroblastic tumors (IMTs) are soft-tissue neoplasms with rare metastatic potential. Approximately half of IMTs are positive for an anaplastic lymphoma kinase (ALK) gene rearrangement which causes aberrant expression. Early phase clinical trials have demonstrated the efficacy of ALK inhibitors in the treatment of IMTs. However, there is no definite conclusion on which ALK inhibitor performs best, and data regarding subsequent therapy after first-line ALK inhibitor failure are scarce. Here, we report a case of ALK+ metastatic IMT that demonstrated a dramatic response to first-line alectinib but resulted in rapidly acquired resistance. Repeated biopsy and next-generation sequencing (NGS) showed ALK:c.3604G>A; p.(Gly1202Arg), which is a common mechanism of drug resistance in ALK fusion-positive non-small cell lung cancer. We also report subsequent treatment choices and responses in this patient and perform a literature review regarding similar cases as this rare tumor.

Keywords: Anaplastic lymphoma kinase inhibitor, inflammatory myofibroblastic tumor, sarcoma

Introduction

Inflammatory myofibroblastic tumor (IMT) is a specific and distinct medical condition diagnosed through pathological examinations according to the WHO criteria.[1] It is categorized as an intermediate neoplastic lesion with a tendency to be aggressive and sometimes capable of metastasis. IMTs can manifest in various locations within the body, although it is more commonly found in the lungs, retroperitoneum, and gastrointestinal tract.[2,3]

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Around 50% of IMTs exhibit a positive gene arrangement involving the anaplastic lymphoma kinase (ALK) gene located on chromosome 2p23, resulting in an oncogenic fusion gene. This genetic alteration is linked to several fusion partners, including TPM3, TPM4, CLTC, CARS, RANBP2, ATIC, SEC31L1, and PPFIBP1, which is likely to contribute a strong promoter to the fusion transcript.[4,5]

Multiple methods are used to identify ALK alterations, including immunohistochemical (IHC) staining for ALK expression, fluorescence *in situ* hybridization (FISH) for ALK rearrangements, and reverse transcription-polymerase chain reaction for ALK fusion transcripts. Next-generation sequencing (NGS) also plays a crucial role, enhancing our understanding of resistance mechanisms in ALK fusion-positive malignancies. This enables personalized treatments based on the tumor's genomic profile, leading to more effective therapies.[4]

It is well established that ALK inhibitors are effective in treating IMTs with ALK fusions, as demonstrated in early phase clinical trials.[6,7] However, there is currently no consensus on which specific ALK inhibitor is the most advantageous. The potential for later generation ALK inhibitors to produce deeper and more long-lasting responses remains uncertain. In addition, there is a lack of data concerning the resistance mechanisms to ALK inhibitors. IMTs are known to be sensitive to chemotherapy, but the optimal treatment regimen remains unclear.[8] Here, we present our experience with a patient suffering from a metastatic IMT who underwent a series of ALK inhibitor therapies and chemotherapy, resulting in noticeable clinical benefits.

Case Report

This 52-year-old female patient had been in good health except for hyperthyroidism until December 2021 when she started experiencing hypermenorrhea. There was no dyspnea, chest tightness, weight loss, fever, night sweats, or change in bowel habits. Subsequent diagnosis revealed ALK-positive uterine sarcoma. Chest computed tomography (CT) revealed bilateral lung metastases, and distant metastasis was impressed clinically. Debulking surgery with R2 resection was performed, but residual lung, pleural metastasis, and mediastinal lymphadenopathy were found. The final pathology report indicated the presence of spindle or epithelioid cells with solid sheets and fascicular patterns, and some tumors exhibited abundant myxoid stroma and numerous curvilinear vessels. IHC analysis confirmed ALK positivity. In addition, NGS with FoundationOne CDx showed ALK rearrangement, FAM179A fusion, IGFBP5 fusion, and KIDINS220 rearrangement.

The patient was initially treated with alectinib as first-line therapy starting in March 2022, and follow-up imaging in April 2022 showed a dramatic response [Figure 1]. Unfortunately, in August 2022, hemoptysis and desaturation developed. Chest CT revealed disease progression in the left pleura [Figure 2]. NGS of an echo-guided left lower lobe biopsy disclosed ALK:c.3604G>A; p.(Gly1202Arg). Lorlatinib was administered for 10 days, but a chest plain

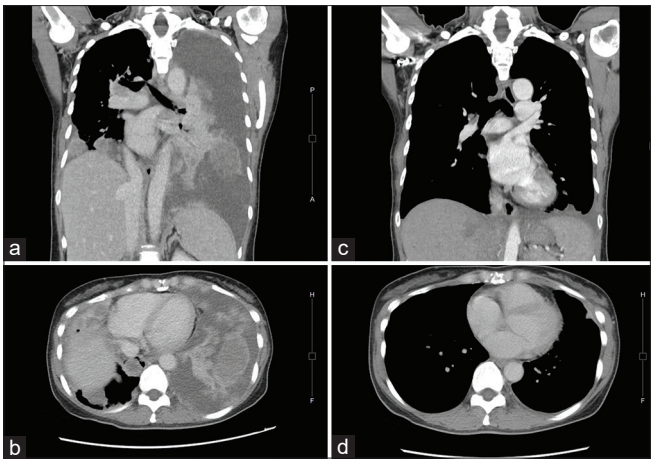

Figure 1: (a and b) Computed tomography (CT) scan before treatment in March 2022. (c and d) CT scan after 1 month of alectinib therapy in April 2022. The pleural tumor size significantly decreased

film indicated increased left pleural effusion. Her condition rapidly deteriorated, leading to impending respiratory failure. As salvage treatment, chemotherapy with ifosfamide (3 g/m^2 on day 1 and day 2) and etoposide (75 mg/m^2 on day 1 and day 2) was initiated, resulting in significant improvement. After that, her condition remained stable for the next 7 months, and she was able to live a fulfilling life.

In March 2023, the patient presented with a rapidly progressive cough and chest wall pain. Initially, methotrexate (30 mg/m^2 on day 1) in combination with vinorelbine (20 mg/m^2 on day 1 and day 7) was administered for one cycle. However, this treatment resulted in desaturation and acute respiratory failure, necessitating intubation and mechanical ventilator support. Subsequently, in the intensive care unit, she received cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2), which led to a transient and excellent response. After 4 days of drug administration, she was successfully extubated.

Unfortunately, her condition gradually deteriorated upon returning to the general ward, and within 2 weeks, respiratory failure recurred. Due to the short-lived response of the cisplatin-pemetrexed combination regimen, the decision was made to shift chemotherapy to epirubicin (90 mg/m^2) plus cyclophosphamide (600 mg/m^2) every 14 to 21 days. The tumor showed a minor response to this chemotherapy, with a schedule-dependent pattern. Currently, she has completed 6 cycles of this treatment and remains in a stable or stationary condition. She underwent a tracheostomy and is presently undergoing weaning training.

To investigate the efficacy of alectinib as a first-line treatment for IMTs, we conducted a PubMed search using the keywords "inflammatory myofibroblastic tumor" AND "alectinib." After a meticulous review of the titles, abstracts, and, when necessary, the full texts, we identified 10 patients with IMTs from 9 publications who received first-line systemic therapy with alectinib.[9-17]

To evaluate the effectiveness of subsequent therapies for IMTs, we performed an additional comprehensive literature search on

PubMed using the terms "inflammatory myofibroblastic tumor" AND "([second-line therapy] OR [subsequent therapy])." Initially, 98 articles were retrieved. From these articles, we identified 9 cases across 6 publications that reported the efficacy of second or later lines of systemic therapy for IMTs.[18-23]

Table 1 provides a concise summary of the reported cases of IMTs receiving first-line alectinib. In certain cases, ALK aberrancy was detected by IHC, so the fusion partners were not known. Notably, durable complete responses were reported, although some patients experienced only transient responses.[9-17]

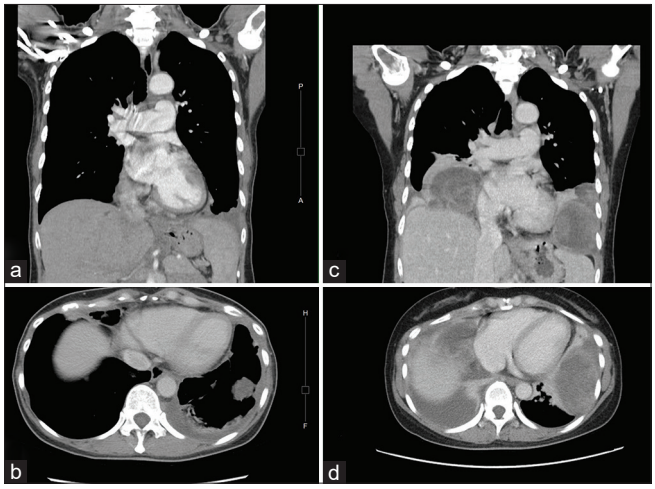

Figure 2: (a and b) Computed tomography (CT) scan at best response in April 2022. (c and d) CT scan showed progressive disease and increased pleural tumor size at 5 months after starting alectinib

Table 2 summarizes the reported cases of the efficacy of subsequent therapies for IMTs. All of the 5 cases that received crizotinib as first-line therapy switched to later generations of ALK inhibitors after the emergence of drug resistance. Among the four cases evaluable for the response to subsequent therapy, two cases achieved a partial response, and the other two cases achieved stable disease. Notably, no reports were available on the efficacy of subsequent ALK inhibitor rotation when a third- or fourth-generation ALK inhibitor was used first.[18-23]

Discussion

The treatment of ALK fusion-positive non-small cell lung cancer (NSCLC) has evolved rapidly in the past decade, with the development and approval of several ALK inhibitors that target aberrant ALK signaling pathways. These agents have shown superior efficacy and tolerability compared to chemotherapy in first-line and subsequent-line settings, and they have improved the survival and quality of life of patients with ALK-positive NSCLC.[24] In a phase 3 trial of alectinib, the median progression-free survival was as long as 34.8 months.[25] While the efficacy of ALK inhibitors has been established in IMTs, conducting a large-scale clinical trial to

Table 1: Summary of the reported cases of inflammatory myofibroblastic tumor receiving first-line alectinib

Case	Primary site	ALK fusion partner	Best response	PFS	Reference
1	Uterus	TNS1	CR	Ongoing after 36 months	[9]
2	Mesentery	SQSTM1	PR	Ongoing after 3 years	[10]
3	Mediastinum	Not reported	PR	8 months	[11]
4	Bladder	FN1	PR	Not evaluable	[12]
5	Lung	EML4	PR	Ongoing after 16 months	[13]
6	Lung	EML4	PR	Ongoing after 4 months	[14]
7	Lung	SQSTM1	PR	Ongoing after 17 months	[15]
8	Lung	EML4	PR	5.5 months	[16]
9	Peritoneum	Not reported	CR	44 months	[17]
10	Peritoneum	CTCL	PR	6.9 months	

ALK: Anaplastic lymphoma kinase, PR: Partial response, CR: Complete response, PFS: Progression free survival

Table 2: Available data of patients with inflammatory myofibroblastic tumor that receiving >2 lines of systemic therapy

Case	Primary site	Testing for ALK	First-line	Outcome	Second line	Outcome	Reference
1	Gall bladder	Negative	Steroid and NSAID	PD	Methotrexate and navelbine	PR	[18]
2	Pleural cavity	Positive	ASP3062	PR	Ceritinib	PR	[19]
3	Uterine	Positive	Crizotinib	SD for 4 months	Ceritinib	SD for 6 months	[20]
4	Uterine	Positive	Crizotinib	PR	Alectinib	PR	
5	Uterine	Positive	Crizotinib	SD for 30 months	Ceritinib	SD for 6 months*	
6	Uterine	Positive	3 lines of chemotherapy	PD	Ceritinib	PR	
7	Lung	Positive	Celecoxib	PD	Apatinib	PR	[21]
8	Omentum	Positive	Crizotinib	PR for 5 months	Alectinib	PR for 5.5 months	[22]
9	Lung	Positive	Crizotinib	PR for 8 months	Alectinib	Not evaluable	[23]

*Subsequent therapy with lorlatinib and dramatic response again. PD: Progressive disease, PR: Partial response, SD: Stable disease, NSAID: Nonsteroidal anti-inflammatory drug, ALK: Anaplastic lymphoma kinase

compare treatment outcomes between different ALK inhibitors or chemotherapy is not feasible due to the limited number of patients available for such a study.

The literature review showed that some patients achieved prolonged disease control, similar to that seen in lung cancer clinical trials. However, it is important to note that in some cases, the patients rapidly acquired resistance to the treatment. In our case, alectinib resistance developed only 7 months after starting the treatment, suggesting that the treatment efficacy in IMTs may not be as favorable as in lung cancer.

Some studies have investigated the underlying causes of discrepancies in the responses observed in ALK-positive IMTs and lung cancer. In a notable case report involving an IMT patient with an EML4-ALK rearrangement and EGFR activation (pEGFRY1068) who initially exhibited a positive response to first-line alectinib treatment but subsequently experienced disease progression, a secondary ALK I1171N mutation was found. In addition, reverse phase protein microarray results indicated that the ALK signaling pathway (ALKY1604) was not activated in the recurrent tumor. This shift in signaling suggests a reduced reliance on the ALK pathway, ultimately leading to alectinib resistance.[16] In another case report, a patient who had disease progression while receiving an ALK inhibitor displayed no evidence of secondary mutations but demonstrated compensatory upregulation of alternative pathways.[26] In the context of ALK-positive lung cancer, the rapid development of resistance to alectinib may be linked to a high tumor mutation burden and heterogeneous tumor evolution.[27] Further advanced multi-omic studies involving a larger number of IMT cases hold the potential to significantly enhance our comprehension of the resistance mechanisms specific to ALK-positive IMTs and facilitate improvements in treatment selection and sequencing strategies.

After developing drug resistance to alectinib, our patient acquired the ALK:c.3604G>A; p.(Gly1202Arg) mutation, which is the most common secondary mutation seen after resistance to second-generation ALK inhibitors in NSCLC.

In NSCLC, This genomic alteration has shown sensitivity to the third-generation ALK inhibitor lorlatinib.[28] However, in our case, rapid disease progression occurred despite treatment with lorlatinib. This discrepancy in response could potentially be influenced by tissue-specific epigenetic architecture, which might differentially determine the responsiveness to targeted therapy.[29]

ALK fusion-positive lung cancer has shown an excellent response to the cisplatin-pemetrexed combination regimen. However, in our patient, the response was short-lived, and rapid disease progression occurred thereafter. Interestingly, chemotherapy protocols typically used for soft-tissue sarcoma, such as ifosfamide-etoposide and anthracycline-based regimens, resulted in more durable disease control in our case. This discrepancy in treatment response again suggests that tissue-specific epigenetic architecture might play a more critical role in determining the sensitivity of chemotherapy rather than solely relying on oncogenic genetic alterations.[29]

The prevalence of IMT is relatively low, and there is a paucity of data on patients receiving multiple lines of systemic therapy in the metastatic setting. In this report, we share our experience with a patient who underwent up to 5 lines of systemic therapy and the treatment responses observed. While ALK inhibitors remain a viable and solid choice for treatment, it is worth noting that the response in patients with IMTs may not be as favorable as observed in ALK fusion-positive NSCLC. In addition, chemotherapy protocols designed for sarcomas showed potential in achieving disease control in our case.

Considering the advancements in treatment for ALK fusion-positive NSCLC, the use of novel ALK inhibitors may also hold promise in enhancing disease control for ALK-positive IMTs. Further exploration of such treatment options could potentially improve the outcomes for these patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflict of interest

There are no conflicts of interest.

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