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Case Report

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Inflammatory Myofibroblastic Tumor Refractory to Three Lines of ALK Inhibitors and Combination Immunotherapy

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Abstract

Inflammatory myofibroblastic tumors (IMT) are spindle cell neoplasms with myofibroblastic differentiation and inflammatory infiltration that are typically benign in presentation but can present aggressively in rare circumstances. We herein report the case of a 17-year-old Jamaican female with metastatic IMT who initially presented to the emergency department in her hometown of Kingston, Jamaica with severe chest tightness. Due to severe hemoptysis in the emergency department, the patient underwent emergent right upper and middle lobectomy after initial radiological work-up showing a mixed density mass within the right upper lobe. Initial pathology done by a general pathologist interpreted immunohistochemical findings to be suggestive of histiocytic sarcoma. However, follow-up analysis by a sarcoma-specialized pathologist at our institution resulted in an interpretation of inflammatory myofibroblastic tumor. While typical treatment consists of surgical removal and chemotherapy, the aggressive presentation of this patient's disease necessitated combinations of targeted therapies such as ALK inhibitors with immunotherapy.

Article Highlights

- Inflammatory myofibroblastic tumor metastatic to brain
- Combination immunotherapy with ALK inhibitors for treatment of aggressive IMT
- Molecular profiling and next-generation sequencing may aid in therapies to circumvent resistance

Keywords

Inflammatory myofibroblastic tumor, ALK inhibitor, Immunotherapy, Sarcoma, Next-generation sequencing, Metastasis

Introduction

Inflammatory myofibroblastic tumor (IMT) is a spindle cell neoplasm showing myofibroblastic differentiation accompanied by an inflammatory infiltrate, that most commonly arises in the peritoneum and mesentery, although essentially all anatomic locations are known[1-4].

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IMTs usually behave indolently and mostly affect children and young adults, but tumors can arise in patients of all ages and occasionally display an aggressive clinical course [5-7]. Approximately half of IMTs possess rearrangements of the anaplastic lymphoma kinase (*ALK*) gene locus on chromosome 2p23 resulting in dysregulation of the receptor tyrosine kinase ALK, leading to loss of cell growth regulation[8,9]. Treatment typically requires combinations of surgical removal, chemotherapy, and targeted therapies such as ALK inhibitors [3,10].

Case Report

A 17-year-old Jamaican female presented with acute severe chest tightness to the emergency department in Kingston, Jamaica. Routine radiologic evaluation demonstrated a well-circumscribed hypodense lesion in the right lung adjacent to the right hilum, with a subsequent chest computed tomography (CT) scan showing a mixed density mass within the right upper lobe. The mass was initially considered to be a hamartoma, whereby she underwent an emergency upper and middle right lobectomy after a bout of severe hemoptysis. Initial pathology of the right lung mass tissue was conducted by a general pathologist. At this time, a panel of immunohistochemical stains was performed and reported to demonstrate expression of CD45, CD68, and CD138, and with negative cytokeratin, CD1a, S100 protein, CD21, and CD35. The findings were interpreted as suggestive of histiocytic sarcoma. Subsequent analysis by a sarcoma-specialized pathologist at our institution resulted in an interpretation ofinflammatory myofibroblastic sarcoma rather than histiocytic sarcoma.

Post-lobectomy follow-up CT imaging revealed two hypermetabolic foci along the surgical margins and at least one hypermetabolic right hepatic lobe focus, concerning for malignancy, as well as pleural based FDG-avid soft tissue lesions. Pelvis MRI with and without contrast also demonstrated multiple osseous enhancing lesions in the acetabulum bilaterally with extension to the right superior pubic ramus and left iliac wing concerning for metastatic disease. PET-CT four months later showed a hypermetabolic, 8 cm x 3 cm osseous lesion in the left scapula body and multiple smaller lesions in the pelvic region with osteolytic changes and cortical involvement, increasing risk for pathologic fractures. After confirmation of the diagnosis of inflammatory myofibroblastic sarcoma diagnosis of the right lung mass, next-generation sequencing (NGS) by Caris Life Sciences® and molecular analyses by Foundation One® revealed a *TPM3-ALK* positive fusion. Based on this finding, in January 2020, the patientbegan crizotinib 250 mg, twice daily, alongside denosumab due to the increased risk of pathologic fractures from skeletalinvolvement (Figure 1).

Chest, abdomen, and pelvis CT scan with contrast after six months of taking crizotinib displayed significant new changes in the right lower lobe with new scattered areas of ground-glass opacities, possibly reflecting novel inflammatory processes. Compared to prior PET, focal sclerotic areas in the T6 and T11 vertebral bodies showed low FDG uptake, reflecting potentially treated lesions. Bilateral lesions in the ovaries consistent with mature teratomas were also shown to be stable compared with prior CT scans. Developed symptoms of nausea and right hip pain improved with ondansetron and oxycodone as needed, as well as with ambulation support with a walker or cane.

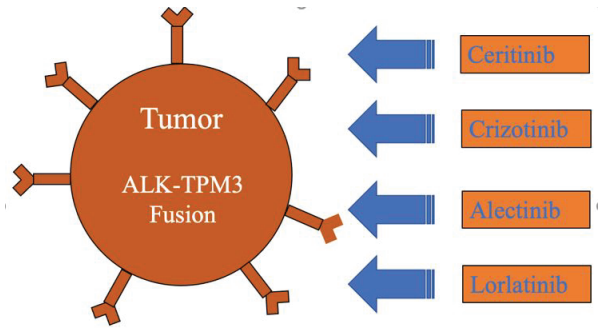

Figure 1: Potential beneficial ALK-inhibitor treatment options determined by next-generation sequencing and molecular profiling of inflammatory Myofibroblastic Tumor ALK-TPM3 fusion.

Due to the development of a new large mass centered in the right pelvic musculature and proximal thigh measuring 7.2 x 5.5 cm on a CT scan of September 2020, crizotinib was suspended nine months after initiation and replaced with ceritinib 150 mg three times daily (TID). Palliative radiation to the right pelvic/thigh mass was initiated. The patient tolerated ceritinib well, and chest, abdomen, and pelvis CT with contrast demonstrated unchanged osseous metastatic disease with decreases in size of the left scapular lesion and the right pelvis/hip mass. However, in June 2021, the patient presented to the ED with a new onset two-week history of fevers, decreased vision, unilateral left-sided weakness of the arm and leg, as well as chest heaviness and shortness of breath. A CT scan of the patient's head without contrast showed a large right temporal mass, attributed to metastatic disease. MRI with and without contrast demonstrated a 7.2 x 6.0 x 5.0 cm geographic ill-defined multilobulated tumefactive lesion within the right temporal lobe. As such, the patient underwent emergent right frontotemporal craniotomy for metastatic lesion resection.

With the development of new bone and brain metastasis, treatment was changed from ceritinib to alectinib 600 mg BID in July 2021. In conjunction with ALK inhibitor treatment, the patient continued to receive palliative radiation therapy to the left pelvis and whole brain with improvement of pain and symptoms. During an office visit in September 2021, she presented with new cough and fevers >102F, prompting a decision to add an immunotherapy regimen of nivolumab and ipilimumab. PET/CT at this time showed new brain lesions, worsening osseous and soft tissue involvement in the pelvis, and new extensive mixed density and nodular opacities of the right lung. Subsequent bronchoscopy showed no malignancy, but there was evidence of pneumonia. The patient therefore received a course of amoxicillin/clavulanate with resolution of her pneumonia. Due to likely treatment failure with alectinib, the patient's treatment regimen was changed to next line ALK therapy, lorlatinib 100mg daily, with continued immunotherapy regimen.After completion of cycle four in November 2021, ipilimumab was discontinued with no associated deterioration of response. As of May 2022, the patient has completed an additional eight cycles of nivolumab and daily lorlatinib with no new adverse events or progression of disease seen on PET scan (Figure 2).

Discussion

Since initiation of immunotherapy-ALK inhibition, the patient has tolerated twelve cycles of this regimen. The first two cycles were a combination of nivolumab-ipilimumab and alectinib, the subsequent two cycles with nivolumab-ipilimumab and lorlatinib, and the most recent eight cycles with nivolumab and lorlatinib. The patient's main treatment-associated symptoms of diarrhea has been well-controlled with loperamide and presumed disease-associated bone changes have been managed with denosumab. The patient continues to do well on her current regimen of immunotherapy-ALK inhibition and her clinical course will continue to be observed for any new symptoms or disease changes.

Although most patients with IMT experience an indolent clinical course, a subset has highly aggressive disease. Confirmation of the *ALK-TPM3* fusion once the diagnosis was clarified at a center with key pathology expertise via molecular profiling proved invaluable

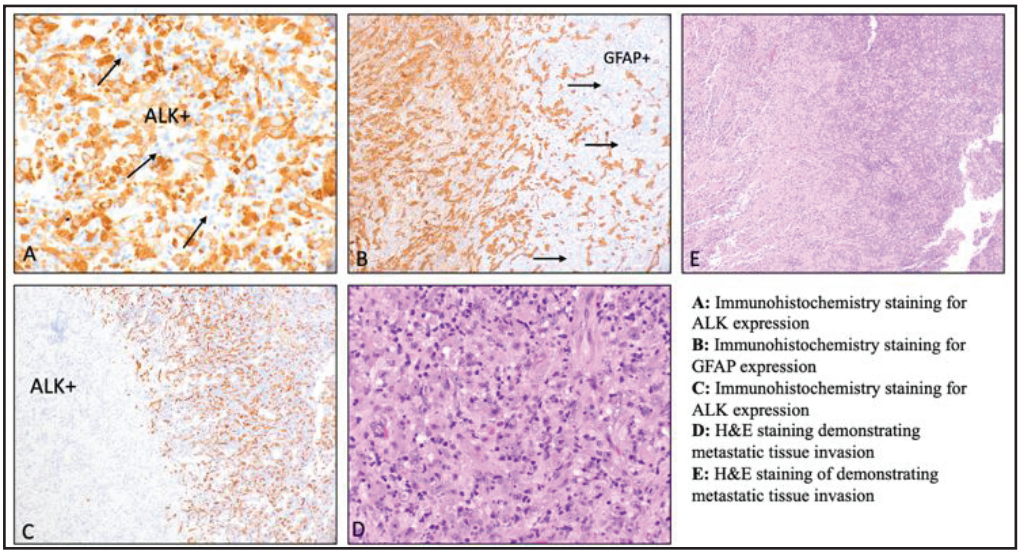

Figure 2: Brain metastasis lesion samples stained using immunohistochemistry and hematoxylin and Eosin (H&E) for evidence of ALK expression and disease presence.

in developing a treatment plan of targeted therapies that included crizotinib and ceritinib. Despite initial improvement with crizotinib treatment, the inflammatory myofibroblastic tumor and subsequent metastatic lesions would likely not have responded without the use of multiple targeted therapies, as seen in the evolution of treatment from crizotinib to ceritinib with radiation to alectinib and ultimately to lorlatinib with immunotherapy. Further research into tyrosine kinase drug development is necessary to better understand such targeted therapies and their efficacies against specific treatment-resistant tumors.

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