

Sustained complete response on crizotinib in primary lung inflammatory myofibroblastic tumor - Case report and literature review

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Abstract

Inflammatory myofibroblastic tumors (IMT) are rare soft tissue tumors of intermediate malignant potential occurring usually in children and adolescents. Treatment options for advanced disease are limited. A 35-year-old lady presented to us with fever, cough and decreased appetite. On evaluation, she was diagnosed with left lung IMT. She underwent surgery and developed recurrence with pleural nodules after two years. Immunohistochemistry showed positivity for ALK (diffuse). Since recent evidence suggested that crizotinib is effective in advanced IMT with 50% response rates, she was treated with crizotinib 250mg BD with which she had a complete radiological response at three months. She has completed one year of treatment thus far and continues to be in complete remission. Treatment with ALK inhibitors like crizotinib has brought about a paradigm shift in the management

of advanced ALK-positive IMT's with excellent clinical responses which are durable in a majority of cases.

Highlights

1. Inflammatory Myofibroblastic Tumor is a rare soft tissue tumor of lung with intermediate malignant potential;
2. 50% of patients with unresectable tumors have ALK rearrangements;
3. Crizotinib provides durable responses in half of patients with excellent safety profile.

Introduction

Inflammatory myofibroblastic tumor (IMT), originally a member of the inflammatory pseudotumor family was first described in 1939 in the lung [1]. Since its first description, the understanding of biology and clinical features of IMT has undergone a paradigm change. They are now considered potentially malignant with a propensity for local recurrence and rarely metastasis [2]. Most often presenting as a mass in the abdomino-pelvic region of children and young adults, they have been described in almost all anatomical locations [3,4]. Histologically, IMTs are characterized by a variably cellular spindle cell proliferation in a myxoid to collagenous stroma with a prominent inflammatory infiltrate composed primarily of plasma cells and lymphocytes, with occasional admixed eosinophils and neutrophils. Three basic patterns namely myxoid/vascular, spindle cell and hypocellular fibrous were described by Coffin et al in 1995 and are still widely recognized [3]. Immunohistochemistry is often positive for smooth muscle actin in 80-90% of cases and desmin/calponin in 60-70% though they are often focal and diagnosis requires recognition of microscopic features by an experienced sarcoma pathologist [3]. Generally, pathological features do not correlate with outcome in IMT except epithelioid variant which is postulated to have an aggressive course and inferior prognosis. As far as Indian literature is concerned, largest single center case series of 6 cases of IMT has been described; three were abdominal, two arising from head and neck and one from cervix [5]. Surgery (open or minimally invasive) remains the treatment of choice for localized resectable disease as described in previous reports from India [6,7].

With the discovery of anaplastic lymphoma kinase (ALK) rearrangements in around 50% of cases of IMT's, potential for targeted therapy with ALK inhibitors and subsequent reports of effi-

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cacy of crizotinib with responses in around half of ALK positive patients; management of IMT has undergone a paradigm change. Here, we present one such case of young woman with recurrent lung IMT with sustained complete response to crizotinib. To the best of our knowledge, this is the first report from India.

Case Report

A 35-year-old lady presented in June 2017 with low grade fever, decreased appetite and dry cough for four months. On evaluation, contrast enhanced CT scan of the chest showed a 6.5*5*5.5 cm mass lesion in the left lingular segment abutting mediastinal pleura, left cardiac margin and costal pleural reaching up to hilum (Figure 1 a,b). There was no evidence of metastatic disease. Biopsy from the mass was suggestive of spindle cell tumor in a myxoid background with admixed lymphoplasmacytic cells. Tumor cells were positive for ALK (diffuse) and smooth muscle

actin (SMA) while being negative for cytokeratin (CK), CD34 and S100 (Figure 2 A-D). Overall it was suggestive of IMT of the Lung. She underwent surgery (minithoracotomy with left lingular mass excision with mesh repair of pericardium) and was kept on observation subsequently. She developed recurrence in February 2019 tiny irregular parenchymal nodule in right lung and two pleural based deposits in left lung (Figure 1c). There was no other site of disease. She was started on crizotinib 250 mg twice a day in March 2019 in view of unresectable metastatic disease. Repeat CT chest done in June 2019 showed a complete response (CR) with resolution of lung lesions (Figure 1d). She has completed one year of therapy and continues to be in CR.

Discussion

IMTs are uncommon lung neoplasms representing around 1% of all lung tumors [8]. Lung as the primary site has been described

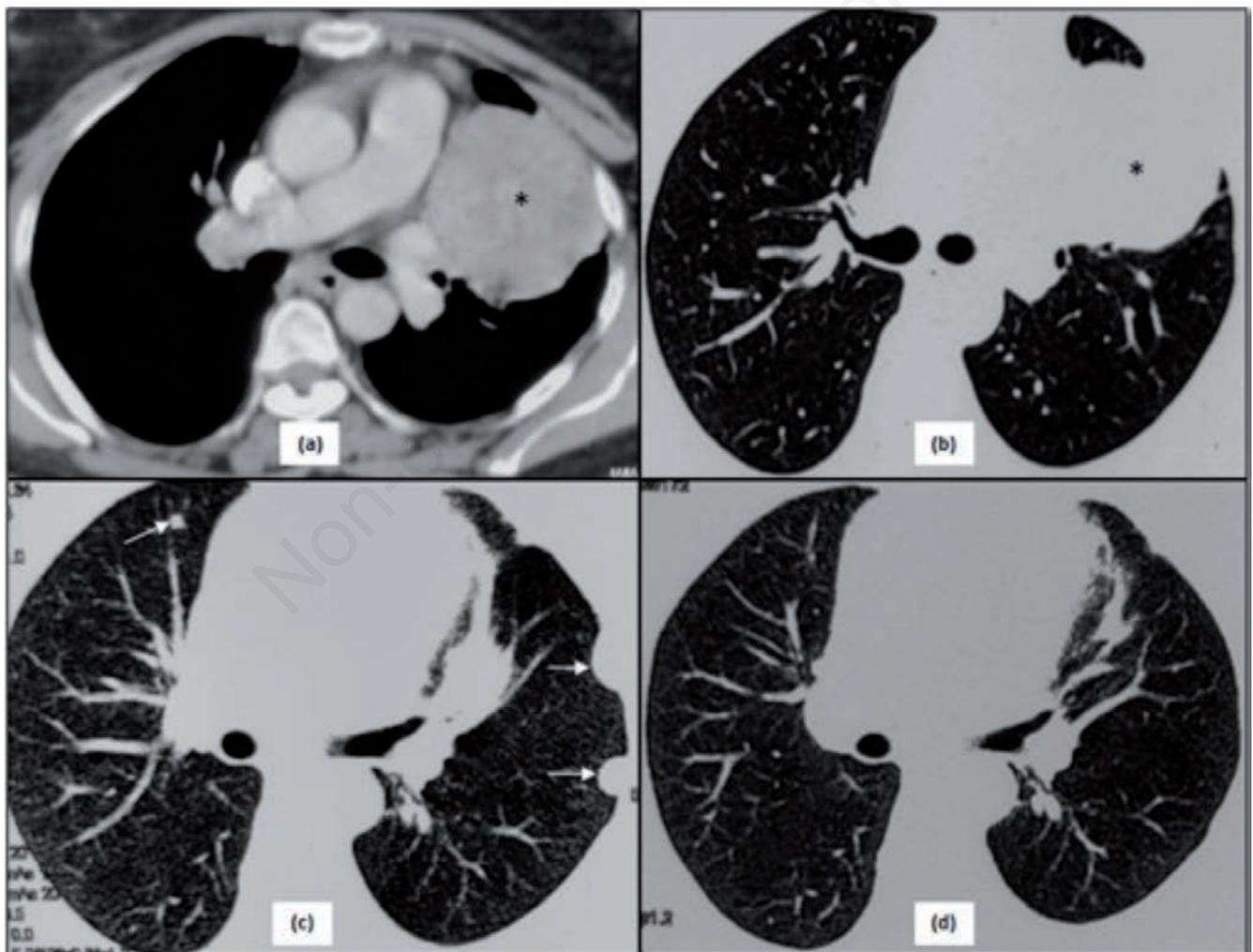


Figure 1. Axial CT scan at baseline (a) in 2017 show well defined heterogeneously enhancing mass in left upper lobe (asterisk) with no fat or calcification within. The mass shows maintained fat planes with main pulmonary artery trunk and there is no extra-thoracic extension. Lung window of same point CT reveals no lung parenchymal or pleural nodules (b). Follow up CT scan after 2 years (c) of surgical resection showed tiny irregular parenchymal nodule in right lung and two pleural based deposits (arrows) which show complete resolution after 3 months of Crizotinib (d).

almost as often as the abdomen and can present with constitutional symptoms in 15-30% with elevated proinflammatory markers. Our patient had history of low-grade fever and decreased appetite prior to developing cough. Fever is uncommon in primary lung carcinomas and hence may raise the suspicion of an alternate possibility [4]. IMTs of lung usually present as solitary pulmonary nodules (SPN) with lower lobe predilection without pleural or mediastinal invasion, however patterns at recurrence are less well defined [9]. Involvement of pleura is rare and has only been described in few case reports [10,11]. Our patient had lower lobe SPN initially but developed pleural nodules at recurrence which is rare.

Discovery of rearrangements in ALK gene on chromosome 2p23 has revolutionized the understanding and management of IMT.

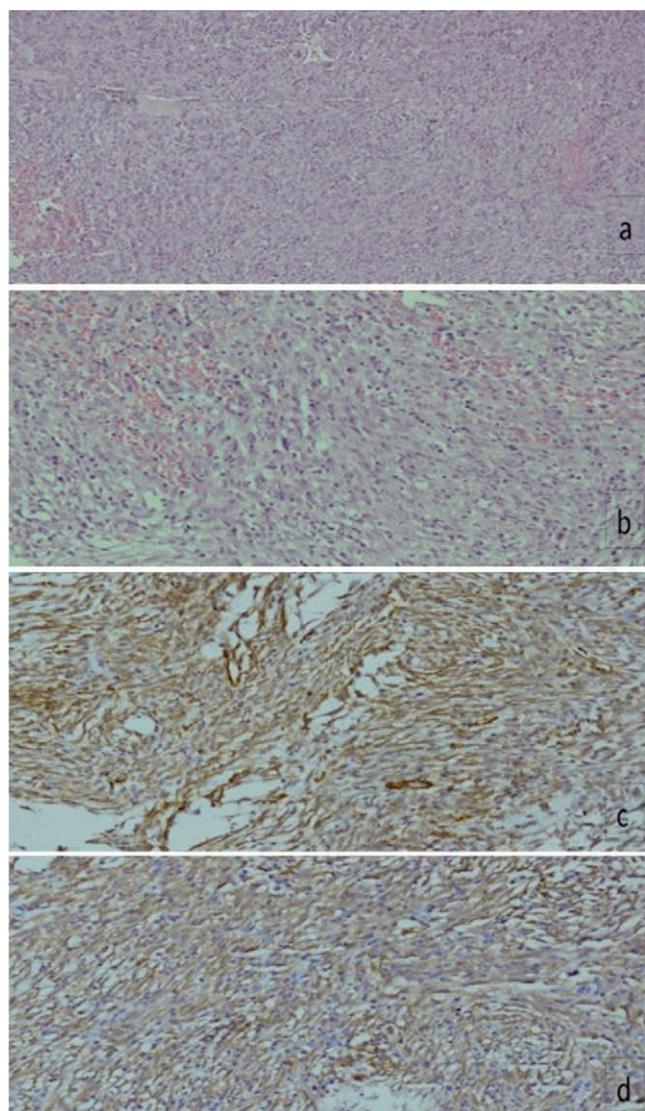


Figure 2. a) Low power photomicrograph of the tumor showing a spindle cell tumor with admixture of inflammatory cells. The tumor cells are arranged in short fascicles as well as haphazard pattern. b) High power photomicrograph showing tumor cells showing spindled morphology with finely dispersed chromatin and eosinophilic cytoplasm. There is abundant admixture of lymphocytes, plasma cells and few scattered eosinophils. c) Immunostain for smooth muscle actin showing cytoplasmic positivity. d) Immunostain for ALK-1 showing cytoplasmic positivity.

The ALK gene encodes a receptor tyrosine kinase which when constitutively activated owing to molecular rearrangement can give rise to tumorigenesis. Rearrangements in ALK can be detected in 50% of IMT by either fluorescence in-situ hybridization (FISH) or staining by IHC [12]. The prevalence of ALK positivity depends on primary tumor location (45% lung, 60% GI, 62-71% bladder, 100% in peritoneum) [13]. Our patient showed diffuse positivity of ALK on IHC and hence, was a candidate for treatment with ALK inhibitors. Owing to activity of ALK inhibitors like crizotinib in ALK rearranged non-small cell lung cancer (NSCLC), they were tested in IMT as well. In the first published case series, two patients (one ALK positive and one negative) with advanced abdominal IMT were treated with crizotinib. The ALK positive patient attained a sustained CR (no toxicity) with no response in ALK negative patient, thus providing early evidence of biomarker based therapeutic strategy [14]. On the basis of this data, a phase II trial was undertaken in Europe in which patients with unresectable/metastatic IMT were treated with crizotinib. ALK positivity was considered if >15% cells showed diffuse staining for ALK on IHC. Out of 12 ALK positive patients, 6 patients achieved a response (50% response rate) with two durable complete responses and four partial responses [15]. Among the ALK positive cohort, 73% patients were progression free at one year. Median duration of response was nine months with some patients achieving sustained remissions (35% on treatment at median follow up of 2.3 years). This trial established crizotinib as treatment of choice for unresectable IMT. We started our patient on 250 mg BD of crizotinib. She developed complete radiological response after three months of starting therapy and is maintaining that response after 12 months of therapy at last follow up (duration of response- not reached). In line with advancements in field of molecular pathology, additional abnormalities have now been characterized in IMTs including ROS1 and RET gene fusions. In a recent case series of 62 cases of IMT, 35 patients (56%) were positive for ALK, 6 patients (10%) positive for ROS1 and one patient had RET gene arrangement [16]. Authors noted that fusion positive cases were more often reported in children and lung and soft tissue IMT's were most often positive for ALK or ROS1 fusions (83% cases). Novel RET gene rearrangement was identified in pulmonary IMT. In a recent case report, Li *et al.* described partial response to ceritinib in a woman with ROS1 fusion positive IMT thus exploring yet another treatment paradigm in this extremely rare disease [17].

Conclusions

Precision oncology and targeted therapy has opened up novel avenues in the treatment of this extremely rare sarcoma. While crizotinib is now established as a standard of care for patients harboring ALK rearrangements, research into further molecular characterization holds promise for multiple other targeted therapies in future. However, literature on use of targeted agents in IMT from Indian subcontinent is scarce. This is the first report of complete response of ALK positive IMT to crizotinib from the Indian subcontinent and authors consider it as the first line of management in this disease.

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