

Case study

An Immunohistochemistry Proved Extensive Inflammatory Myofibroblastic Tumour of Lung: Being Treated with Crizotinib

Abstract

Inflammatory Myofibroblastic Tumour (IMT) is a rare entity which constitutes 0.04–1.2% of all lung tumours. Though IMT was first described as an 'Interesting Benign Lung Tumour', recurrence, discovery of cytogenetic aberrations, clonal population of cells and oncogenic protein over expression establish it as a malignant entity. Because of similar morphology of a number of tumours comprising of spindle cells with inflammatory background only immunohistochemical investigations can conclude the correct final diagnoses. Interestingly, half of IMTs carry rearrangements of the anaplastic lymphoma kinase (ALK) locus. Though, complete resection is the treatment of choice, ALK positivity opens the door for Crizotinib for the treatment of invasive, unresectable, recurrent IMTs.

We report a case of an aggressive, large IMT of Left Lung with contralateral multiple nodular lung metastasis in a 50 years old male patient. On the basis of ALK locus rearrangement this case is being treated with Crizotinib and patient has improved symptomatically after a period of 8 weeks of treatment.

Introduction

Inflammatory Myofibroblastic Tumour (IMT) represents 0.04–1.2% of all lung tumours. [4] Though, the pulmonary variant occurs more commonly in children and young individuals and has a more benign clinical course,[3,7] this case of an aggressive, large IMT of Left Lung with contralateral multiple lung metastasis took place in a 50 years old male patient who is being treated with Crizotinib on the basis of ALK locus rearrangement.

Case Report

A 50 years old gentleman normotensive, euglycaemic with addiction history of smoking (70 pack-years), oral tobacco and alcohol who was apparently well before 6 months, presented in out-patient department on 10th November, 2017 with chief complaints of three episodes of

haemoptysis with gradually exaggerated dry cough for 6 months, shortness of breath for 4 months and intermittent low-grade fever for 3 months as the present history of illness. Past history and family history were insignificant. Along with symptomatic treatment patient was advised a Plain and Contrast Enhanced Computed Tomography (CECT) Scan of Thorax. Performed on 14th November, 2017 it revealed a left basal large heterogeneous mass with peripheral nodular enhancement with collapsed left lower lobe and left encysted effusion. [Figure 1] Right lung also involved with multiple nodular space occupying lesions (SOL) suggestive of metastases though there was no hilar or mediastinal lymphnodal enlargement. [Figure 2] A digital Chest Roentgenogram (Postero-Anterior view) done on the same day also showed bilateral lung lesions.



Figure 1: CECT Scan showing A left basal large heterogeneous mass with peripheral nodular enhancement

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66 Figure 2: Right lung involved with multiple nodular space occupying
67 lesions (SOL) suggestive of metastases

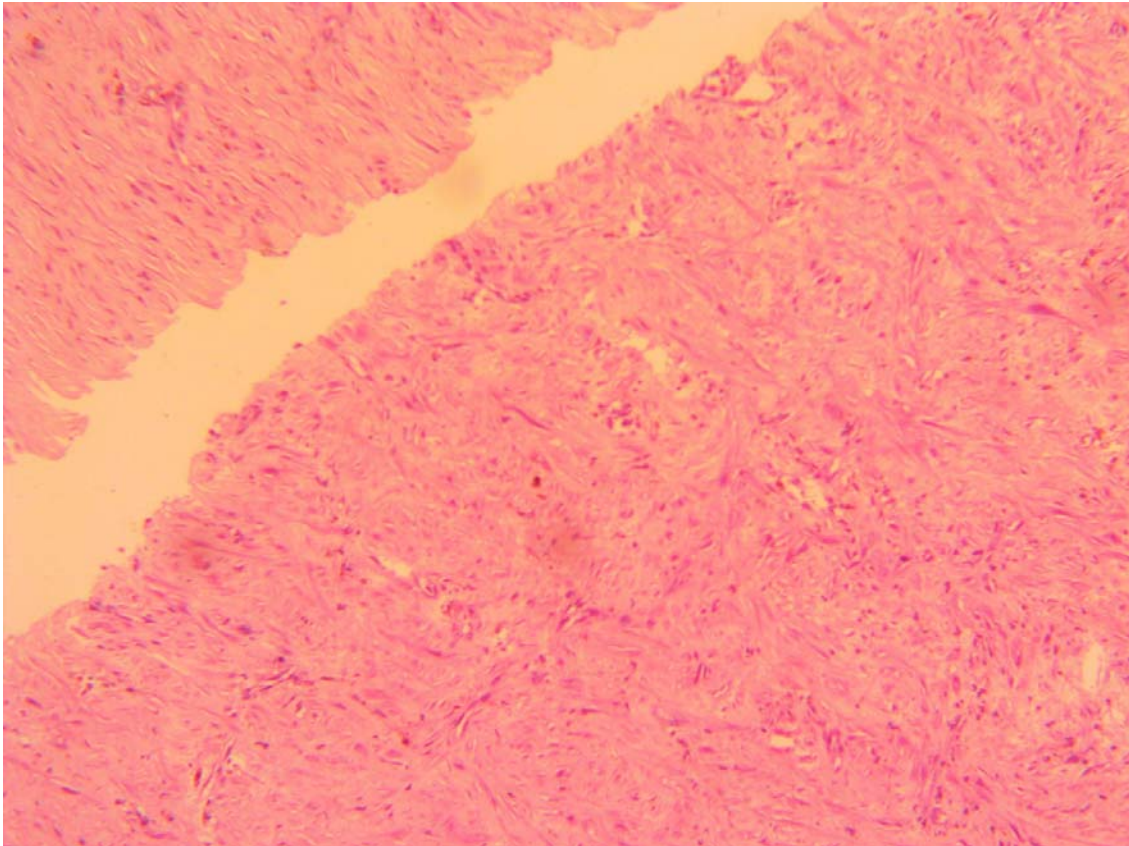
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70 On 16th November, 2017, a CT guided Tru Cut Biopsy was done from
71 the left lung SOL. Microscopic examination suggested few scattered as
72 well as clusters of oval to spindle tumour cells with mild and focal
73 nuclear pleomorphism and chromatin clumping in a hyaline background.
74 Slides were reviewed and the depicted picture was cores of tissue
75 showing spindle shaped cells with interspersed collagenised stroma
76 along with focal areas of inflammatory infiltrate of neutrophils and
77 lymphocytes. Areas of fibrinous material and necrosis surrounded by
78 neutrophils were seen. [Figure 3 & 4] It also suggested differential
79 diagnosis of spindle cell tumour or solitary fibrous tumour which leded
80 us to perform an Immunohistochemistry(IHC) profile from the paraffin
81 blocks. Finally, on 20th November IHC profile [Table no.1] clinched the
82 final diagnosis of IMT.

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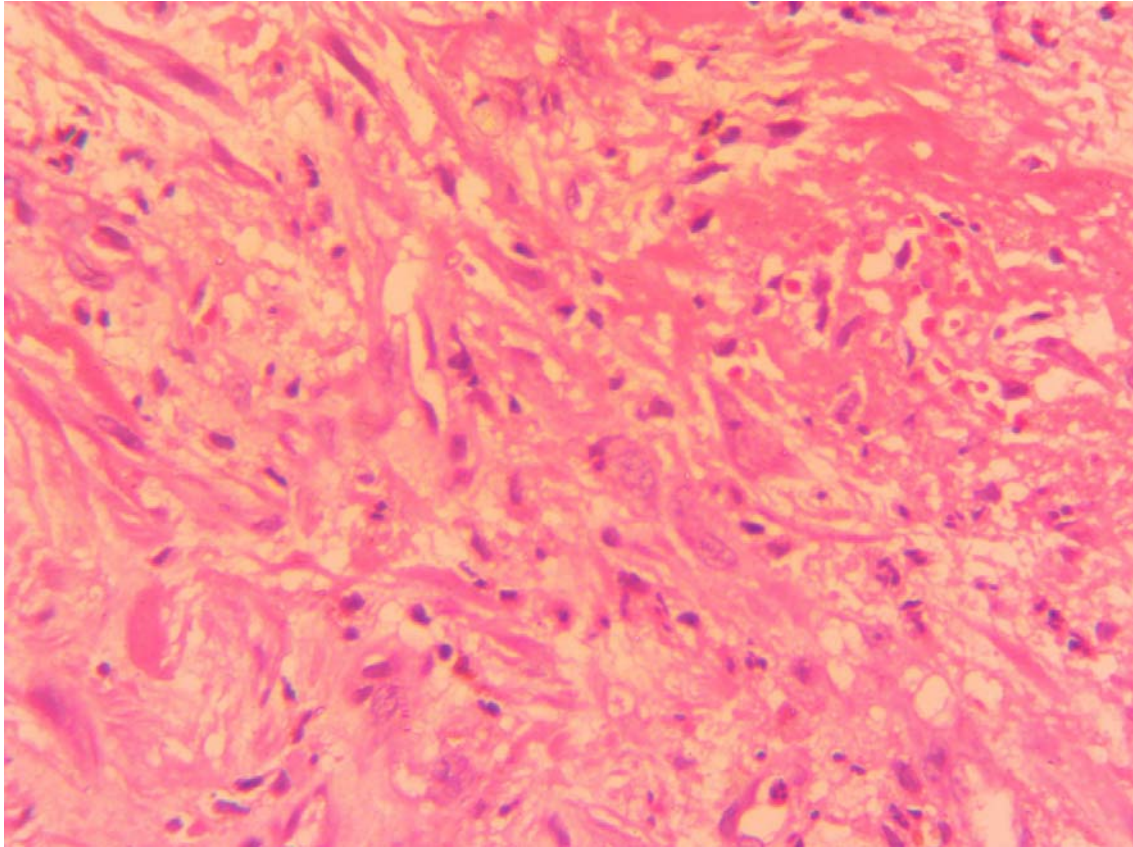
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87 Figure 3: Spindle cells in sheets with interspersed collagenised stroma in
88 low power view (10x X 10; Haematoxylin and Eosin)
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92 Figure 4: Individual spindle cells show slender nuclei; moderate
93 mixed inflammatory infiltrate is present in high power view (40x
94 X 10; Haematoxylin and Eosin)

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Table no. 1

IHC MARKERS	RESULT
CK	Focal positive in spindle cells
S100	Negative in spindle cells
SMA	Diffusely positive in spindle cells
CD34	Negative in spindle cells, vascular endothelium is positive
Ki-67	3%
Desmin	Positive in spindle cells
MyoD1	Negative in lesional cells
Myogenin	Negative in lesional cells
Alk1	Negative
B catenin	Cytoplasmic positivity
HMB45	Negative

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Subsequently FISH was done on 22nd November, 2017 and on the basis of detected rearrangements of the anaplastic lymphoma kinase (ALK) locus on chromosome 2p23 Crizotinib Tablet (250 mg twice daily) was started and continued for 6 weeks with no interruption. Except mild elevation of liver transaminase enzymes, no other toxicities made the treatment period uneventful. After eight weeks patient has improved symptomatically and we have planned to continue Crizotinib till disease progression.

Discussion

While looking back, the Inflammatory Myofibroblastic Tumour (IMT) was first described as an 'Interesting Benign Lung Tumour' by Brunn and his colleagues in 1939. [1] Later it was proved that, the IMT has an uncertain pathogenesis, a wide range of clinical and histological presentations and a potential for recurrence. While, clinical 'reactive' nature of the lesion and histological presence of a large number of inflammatory cells represent its benign face, features like up to 37% recurrence, discovery of cytogenetic aberrations e.g. anaplastic lymphoma tyrosine kinase (ALK) gene rearrangements, clonal population of cells and oncogenic protein over expression (ALK, p53, bcl-2, Ki 67) establish it as a malignant entity.[2,6] However, in 1994, the WHO coined Inflammatory Myofibroblastic Tumour (IMT) as the universal terminology to address this lesion and defined it as an intermediate soft tissue tumour comprising of spindle cells that exhibit myofibroblast differentiation and numerous inflammatory cells, plasma cells and/or lymphocytes.[3] The differential diagnosis of IMT includes low-grade myofibroblastic sarcoma (LGMS) and a list of benign or malignant spindle-cell tumours such as leiomyoma, solitary fibrous tumour, spindle-cell carcinoma, nodular fasciitis and peripheral nerve sheath tumour.[4] As myofibroma is a close entity, Bajpai et al.[5] suggested smooth muscle actin as a confirmatory immunohistochemical marker to clearly differentiate it from IMT.

Representing 0.04–1.2% of all lung tumours, IMT is a rare lesion [6]. While it usually occurs in the lungs, there are also reports of cases with extrapulmonary sites such as spleen, breast, maxillary sinus, epididymis, central nervous system, and soft tissues [7,8]. Though the pulmonary variant occurs more commonly in children and young individuals and has a more benign clinical course and the extra pulmonary variant affects older individuals [after the 2nd decade] and has a more aggressive clinical course, [3,9] this patient with an aggressive and metastatic IMT is diagnosed in fifth decade of life. The pathogenesis of this lesion remains uncertain. Several hypotheses suggest that it may be associated with autoimmune or infectious mechanisms. ALK gene

rearrangements is positive for more than half of all IMTs. It has been reported that in 30% of patients, IMT was related with recurrent infections caused by mycoplasma, nocardia, actinomycetes, and Epstein–Barr virus. [10,11] Nonspecific symptoms such as cough, shortness of breath, haemoptysis, chest pain, fever, and fatigue may be observed in cases with IMT. However, such lesions may also be identified during routine screening or by a radiograph taken for other reasons in asymptomatics. [8,12] Because of its diversified radiologic manifestations and because it can be difficult to distinguish from malignant tumours on small tissue samples obtained from bronchoscopic examination or needle biopsy, only 6.3% of IMT cases are diagnosed based on analysis of biopsy specimens alone. [13] IMT is characterized histologically by spindle cell proliferation. The tumour is referred to by different names in the literature depending on the predominant cell type encountered in the lesion: plasma cell granuloma or tumour, xanthogranuloma, plasma cell/histiocytoma complex, or post inflammatory pseudotumour. [14] Radiological findings are variable and nonspecific. In 87% of patients, there is a mass or nodular lesion with regular margins, ranging from 1 to 6 cm in diameter. Nodules are usually solitary, but multiple nodules may develop occasionally. Calcification and cavitation are very uncommon. Ten percent of patients may have pleural effusion, while atelectasis may develop in 8% of patients. PET scan always shows a positive FDG uptake like a malignant tumour. [15] Computed tomography shows the presence of a heterogeneous nodule or mass with variable contrast enhancement. It specifies the tissue or cystic nature of the tumour, its vascular behaviour and it assesses the locoregional extension. Calcifications and cavitations are rare. Pleural effusion is seen in less than 10% and atelectasis in 8% of cases. Sometimes the tumour can extend towards the hilum, mediastinum, pleura or diaphragm. [16,17] Because of similar morphology of these lesions, only immunohistochemical profile for IMT [CK, S100, SMA, CD34, Ki67, Desmin, MyoD1, Myogenin, Alk1, B catenin, HMB45] are allowed to conclude the correct final diagnoses. [18]

Complete resection is the treatment of choice for diagnostic and therapeutic purposes. The risk of recurrence is high in incomplete resections. The rate of local recurrence has been reported as 6.6–13% following the resection. [19,20] Radiation, chemotherapy [cyclosporine, azathioprine, methotrexate and cyclophosphamide], ALK molecular targeted therapeutic drugs [Crizotinib] and steroid therapy are used when the tumours are invasive, non-resectable, recurrent, show signs of malignancy/metastasis or when surgical margins are positive. [21] Recommended dose of Crizotinib is 250 mg twice daily till disease

progression. Approximately half of IMTs carry rearrangements of the anaplastic lymphoma kinase (*ALK*) locus on chromosome 2p23, causing aberrant *ALK* expression. [22] However, the most often reported adverse events are visual changes, nausea, diarrhoea, vomiting, oedema, constipation, and elevated transaminases. [23]

Conclusion

Immunohistochemistry profile is mandatory for the diagnosis of IMT, but FISH should always be performed to detect rearrangements of the anaplastic lymphoma kinase (*ALK*) locus on chromosome 2p23 as an independent predictive factor. Though complete resection is the treatment of choice in IMT, *ALK* molecular targeted therapeutic drugs [Crizotinib] can be used when the tumours are invasive, non-resectable, recurrent, or when surgical margins are positive on the basis of this predictor with the hope for a favourable outcome.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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