

## Case Report

# Malignant Inflammatory Myofibroblastic Tumor of the Lung with IgG4-Positive Plasma Cells

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- Lung
- ALK
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## Abstract

Inflammatory myofibroblastic tumor (IMT) is a rare lesion, described in numerous organ systems. The morphologic diagnosis relies on the presence of a fascicular arrangement of myofibroblasts with admixed lymphoplasmacytic infiltrate and slit-like vessels. We report a case of malignant IMT of the lung with rapid progression and features of IgG4-related disease in a 20 year-old woman. The patient presented with cough and hemoptysis. A chest imaging showed a 6-cm nodular-appearing right upper lobe mass. The lobectomy specimen demonstrated a well-circumscribed mass with a yellow-white fibrous and mucoid cut surface. Microscopic examination revealed storiform fibrosis with foci of atypical spindle cells in the lymphoplasmacytic well-vascularized background. Atypical foci also demonstrated necrosis and abnormal mitotic figures. One out of four regional lymph nodes was positive. The spindle cells showed cytoplasmic positivity with SMA and ALK-1 and no reactivity with AE1/AE3, S-100, CD34, and desmin. FISH study detected rearrangement of the ALK gene at locus p23.2. The lymphoplasmacytic infiltrate showed abundant IgG4 plasma cells with a ratio of IgG4 to IgG of 49%, satisfying minimal histopathologic criteria of IgG4-related disease. Two months post resection, the patient returned with multiple pulmonary nodules and mediastinal lymphadenopathy. Her disease was chemotherapy-resistant and soon spread distantly causing death 4 months after diagnosis. Identification of malignant features in inflammatory myofibroblastic tumors should alert physicians of dismal prognosis and guide toward aggressive therapy. Further studies necessary to address the link between malignant IMT infiltrated with predominantly IgG4-secreting plasma cells.

## ABBREVIATIONS

IMT: Inflammatory Myofibroblastic Tumor; IgG4RD: Immunoglobulin G4-related disease; SMA: Smooth Muscle Actin; ALK-1: Anaplastic Lymphoma Kinase-1; FISH: Fluorescent *In Situ* Hybridization

## INTRODUCTION

Myofibroblastic tumors represent a very large subset of mesenchymal neoplasms with various morphological features and biological behaviors, ranging from benign to rarely malignant. IMT, also referred to as pseudosarcomatous myofibroblastic proliferation or plasma cell granuloma, is a rare lesion that can arise in many organ systems and is characterized by a fascicular arrangement of myofibroblasts with admixed inflammatory cells and slit-like vessels and harbors an anaplastic lymphoma kinase (ALK) gene rearrangement in the majority of cases [1,2].

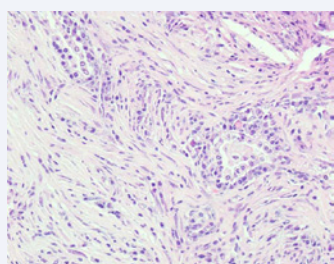
The etiology of IMT remains unknown [3]. It is recognized as a borderline tumor with the possibility to recur, undergo malignant transformation, and metastasize [4]. Malignant lesions in the differential diagnosis include sarcomatoid carcinoma, leiomyosarcoma, follicular dendritic cell sarcoma and rhabdomyosarcoma.

Search of current literature revealed disagreement among authors about association of IgG4RD and IMT. In addition to histomorphological features of IgG4RD that include dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis, a consensus statement introduced a requirement to fulfil an IgG4: IgG plasma cell ratio of >0.4 (40%) at any site [5]. Saab et al and Zen et al state that IgG4RD has a histological appearance and IgG4 to IgG ratio of plasma cells similar to IMT [2,6]. Here, we also describe a case of malignant IMT of the lung with features of IgG4-related disease.

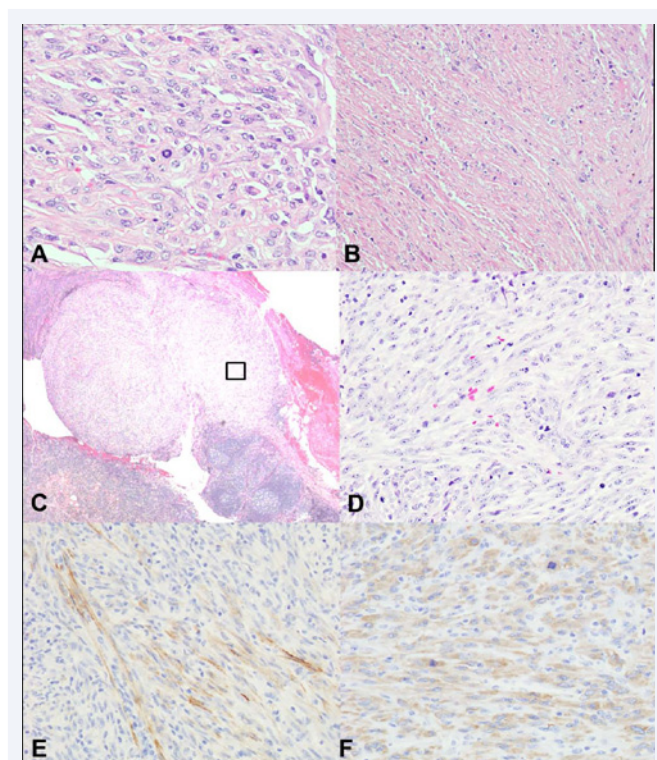
## CASE PRESENTATION

A 20-year old Chinese woman, an exchange college student, with no significant medical history presented with productive cough and hemoptysis without fever or night sweats. Her symptoms persisted over three months. A 9-mm induration was found on purified protein derivative skin test with history of Bacillus Calmette-Gurin vaccine in childhood. A chest radiograph showed a 6 cm nodular-appearing right upper lobe mass. A remote (taken in 2009) chest radiograph also reported some density in the right upper lobe. The patient underwent right upper lobectomy with regional lymph node dissection. Intraoperative diagnostic consult rendered diagnosis of spindle cell tumor. Gross examination of the right upper lobectomy specimen demonstrated a 7 x 6 x 5 cm yellow-white well demarcated firm to soft mass with fibrous to mucoid and partially hemorrhagic cut surface. One of two peritracheal lymph nodes contained a small yellow-white focus of fibrous tissue in subcapsular area resembling primary mass. Microscopic study revealed a spindle cell neoplasm with rich plasmacytic infiltrate and occasional Russel bodies (Figure 1). The neoplasm demonstrated storiform pattern and dual morphology: zones of spindle cells with bland nuclear chromatin, pale eosinophilic cytoplasm and long processes without increase in mitotic figures and other zones of spindle cells with nuclear pleomorphism, coarse chromatin and atypical mitotic figures admixed with readily apparent necrosis and hemorrhage (Figure 2A&B). One paratracheal lymph node demonstrated metastatic tumor with atypical spindle cells and increased mitosis (Figure 2C&D). A small focus of tumor was present at one of the margins. Immunohistochemical studies showed that the spindle cells had cytoplasmic reaction with SMA and ALK-1 (Figure 2E&F). Pancytokeratin stain revealed entrapment of pneumocytes by fascicles of non-reactive spindle cells. In addition, tumor cells were negative for S100, CD34, CD21, desmin, and c-kit. Plasma cells showed increased expression of IgG4 with ratio of IgG4 to IgG of 49% and polyclonal kappa lambda light chain expression (Figure 3). Final diagnosis was inflammatory myofibroblastic tumor with malignant features.

The tumor board reviewed the final pathologic report and agreed to defer chemotherapy due to rarity of the condition. Two months later, the patient returned with worsening dry cough and anorexia. The radiological study of the chest revealed heterogeneously attenuating masses in the posterior-lateral right chest wall, anterior right chest, and the anterior aspect of the left sixth rib suggestive of metastatic disease. In addition, it showed two mediastinal masses with central hypoattenuation favored to represent necrotic metastatic lymph nodes. The paraffin-



**Figure 1** Inflammatory myofibroblastic tumor demonstrating spindle cell proliferation with storiform pattern and rich plasmacytic infiltrate. Note a Russel body (central right), H&E, magnification 600x.



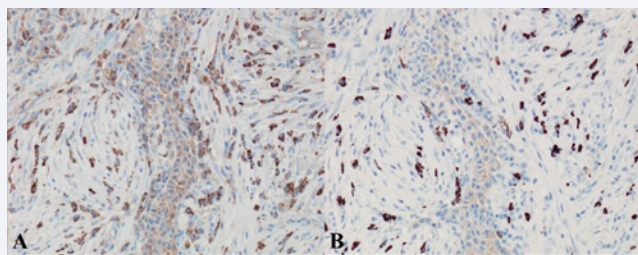
**Figure 2** Additional morphologic and Immunohistochemical findings. Zones with atypical plump cells remarkable for increased nuclear to cytoplasmic ratio, vesicular nuclei, prominent nucleoli (A) and necrotic regions (B). One paratracheal lymph node with a 3mm metastasis in lymph node sinus (C) and a magnified area insert (D) demonstrating similar malignant cells seen in primary lesion. Immunohistochemical studies highlight cytoplasmic expression of actin (E) and ALK-1 (F). Note atypical mitotic figure in F in the right upper quadrant. Panels A-D, hematoxylin-eosin, original magnifications 600x for A, 400x for B and D, 40x for C. Panels E and F, 3, 3'- diaminobenzidine, original magnification 600x.

embedded tissue was sent for FISH study to evaluate the possibility of rearrangement of the ALK gene locus at 2p23 in order to allow targeted therapy with crizotinib. FISH demonstrated a positive signal in 78% of nuclei. Generalized systemic chemotherapy was switched to crizotinib with worsening of the patient's symptoms and imaging studies suggesting rapid advancement of metastatic disease now involving cervical, thoracic and lumbar spine and central nervous system. The patient agreed to palliative radiation therapy and succumbed to her illness shortly afterwards.

## DISCUSSION

IMT is a very rare neoplasm with an incidence of approximately 0.04-1% of all the pulmonary neoplasms [7]. Malignant pulmonary IMT represent only a small fraction of these cases. In general, IMT can occur at any age, most commonly in the second decade of life. Patients present with cough, fever, and hemoptysis [7]. Our patient, a 20-year old woman, presented with chronic cough and hemoptysis without fever or night sweats.

Malignant IMT of the lung can be differentiated from their benign counterparts by larger polymorphic neoplastic cells, nuclear pleomorphism, the presence of atypical giant cells and increased mitotic activity [8]. In our case, grossly apparent foci



**Figure 3** One of three representative fields utilized for counting of IgG4 to IgG ratio. A highlights IgG positive plasma cells while B shows IgG4 expressing plasma cells. Average ratio was 49%, i.e. satisfactory for suggestion of IgG4-related disease. Original magnifications 400x, 3, 3'- diaminobenzidine.

of hemorrhage and necrosis were helpful features to hint toward malignancy. Microscopic examination supported these gross observations and, in addition, demonstrated readily apparent abnormal mitotic figures.

Differential diagnosis of a malignant IMT should include epithelioid inflammatory myofibroblastic sarcoma, a recently described entity, which is now accepted variant of IMT in WHO classification of soft tissue tumors (4<sup>th</sup> edition of WHO, 2013) [9,10]. This entity is differentiated on histomorphologic basis from conventional IMT by plump epithelioid cells in the myxoid background with mixed inflammatory infiltrate wherelesional cells resemblesoft part alveolar sarcoma. In our case, IMT did not show these features. One case of primary pulmonary epithelioid myofibroblastic sarcoma has been recently described, interestingly, in a 21-year-old Chinese man with a short clinical course due to fast spread and a fatal outcome similarly to our case [11]. Considering rarity of the malignant variant, the mentioned reported case and our case, both presenting in young Chinese patients, bring out a possibility of environmental or cultural factorsplaying a role in malignant transformation.

The IMT are generally regarded as a soft tissue tumor with low malignant potential, which is a somewhat indefinite but realistic prognostic category [10]. Mainstay treatment of solitary mass remains surgical resection with negative margins. Due to overall low probability of metastasis the malignant potential of IMT, except epithelioid variant, can be easily underestimated. Lu et al proposes, in retrospect, an imaging finding of abundant peritumoral vascularity suggestive of high metabolic demand of the tumor as a clue to potential malignant change [12]. ALK reactivity may be a favorable prognostic indicator [13]. Presence ALK gene rearrangement confirmed our morphologic diagnosis, but it did not result in favorable outcome for our patient.

Previous study showed that lung IMT cases demonstrate predominant infiltration of IgG4-positive plasma cells and a higher proportion of IgG4-positive plasma cells among the IgG-positive lesions of other organs.<sup>2,6</sup> There is no utility yet in evaluation of the IgG4/IgG ratio in such cases if the lesion fulfills the characteristic features of IMTbecause pathogenic association

between these entities is unclear. To our knowledge, there are no previously reported cases of malignant IMT of the lung with increased IgG4/IgG ratio.

In summary, our case demonstrates malignant IMT of the lung with a short clinical course and an unfavorable outcome. Pathologists should carefully evaluate cases of IMT for the presence of malignant features since such cases carry dismal prognosis and progress rapidly if left untreated. Further studies are necessary to address association of malignant IMT of the lungs and IgG4RD.

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