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Inflammatory myofibroblastic tumor of the central airways: treatment and molecular analysis

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Short title: IMT bronchoscopic treatment and pathology

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Abbreviations:

ALK: Anaplastic lymphoma kinase

EML4: Echinoderm microtubule associated protein like 4

FISH: Fluorescence in situ hybridization

IHC: Immunohistochemistry

IMT: Inflammatory myofibroblastic tumour

PDGFRβ: Platelet derived growth factor receptor beta

RET: Rearranged during transfection

ROS1: c-ros oncogene 1

ETV6: ETS variant transcription factor 6

RANBP2: RAN binding protein 2

TPM3: Troopomyosin3

TPM4:Tropomyosin4

SMA: Smooth muscle actin

NTRK1: Neurotrophic receptor tyrosine kinase1

Abstract:

Inflammatory myofibroblastic tumors (IMT) are a rare cause of endobronchial masses in adults. Surgery has been the main stay of treatment of endobronchial IMTs, based on the potential for recurrence. Interventional pulmonology has emerged as a minimally invasive and lung function preserving modality in management of airway obstruction due to tumors. We present a series of 3 adult patients with IMT treated endo-bronchially with a short discussion on its potential role. We also discuss how molecular analysis of IMTs for mutations in genes such as ALK and ROS1 might provide insights into clinical behavior and potential targetable therapy in advanced, unresectable and metastatic cases.

Introduction:

Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal tumor that presents as a pulmonary or soft tissue mass, mostly in children and young adults with an intermediate potential for recurrence, rarely local invasion and metastasis [1]. It is a neoplastic proliferation of myofibroblasts always accompanied by non-neoplastic inflammatory cells such as lymphocytes, plasma cells or macrophages. Recent insights in the molecular genetics of these tumors allow for a more precise delineation from the non-malignant mimickers [2].

Endobronchial IMTs are rare in adults. Most available literature on bronchoscopic resection of IMTs pertains to tumors in the pediatric age group. We present three cases of endobronchial IMTs resected with bronchoscopic techniques along with a review of literature on the same. To the best of our knowledge, this is the first such series in adults. In addition, we discuss newer insights into the molecular genetics of the tumor and treatment modalities for advanced and metastatic lesions.

Case 1:

A 42-year-old man presented with increasing dyspnea, wheezing and hemoptysis. Patient presented with right testicular carcinoma 2 years before, that was treated with surgical resection and adjuvant chemotherapy. CT showed a mass in the right main bronchus and possibility of metastasis was considered.

Urgent rigid bronchoscopy revealed a globular tumor blocking 90% of the right main bronchus [Figure1A]. The tumor was completely resected with the diathermy snare and the tumor bed was treated with diathermy.

Histological examination showed spindle shaped cells with prominent nucleoli and eosinophilic cytoplasm arranged in short fascicles with occasional mitoses in the tumor cells [Figure2A,B]. The

stroma was infiltrated with lymphocytes, histiocytes and occasional eosinophilic granulocytes. On immunohistochemistry (IHC) tumor cells stained positive for ALK-p80 [Figure 2C]. ALK FISH was positive with split signals. Fluorescence in situ hybridization (FISH) revealed a rearrangement in ALK [Figure 2D], and Hybrid Capture based next generation sequencing (NEOselect) showed EML4-ALK1 fusion. Diagnosis of inflammatory myofibroblastic tumor was made.

Bronchoscopy after 1 month showed necrotic tissue at the tumor base. Follow-up with bronchoscopy and CT has revealed no recurrence in 38 months. [Figure 1B]

Case 2:

A 49-year-old man presented with hemoptysis and breathlessness of 1-month duration. CT chest showed a mass in the middle lobe bronchus with atelectasis of the middle lobe.

Urgent bronchoscopic intervention was planned due to increasing dyspnea. A flexible scope was passed through the channel of the rigid bronchoscope. A smooth rounded tumor covering the right middle and lower lobe bronchi was seen. [Figure 1C] The tumor was removed with the diathermy snare and the tumor base at middle lobe carina (RC2) was treated with diathermy. Bleeding was controlled with endobronchial instillation of epinephrine, tranexamic acid and use of a bronchial blocker.

Histology showed epitheloid cells with granular cytoplasm arranged in short fascicles with infiltration of lymphocytes. Tumor cells were negative for S100 on IHC, ruling out a granular cell tumor. Subsequent ALK-p80 was positive. FISH and Hybrid Capture based next generation sequencing confirmed the diagnosis of EML4-ALK1 fusion positive IMT.

Rigid bronchoscopy was repeated after a month. Abnormal mucosa on the roof of right middle lobe bronchus and RC2 was treated with diathermy and cryotherapy. Biopsies showed no residue. Bronchoscopy at 5 months showed an edematous right middle lobe opening, but biopsies were clear

of residual tumor. Follow-up with CT scan and bronchoscopy showed no recurrence in 40 months. [Figure 1D]

Case 3:

A 16-year-old girl presented with cough and was diagnosed as having pneumonia that was treated with antibiotics. One month later she presented with pneumo-mediastinum. CT scan showed a tumor in the distal left main bronchus with atelectasis of the left lower lobe.

Rigid bronchoscopy revealed a tumor in the distal left main bronchus, vascular and bleeding easily on touch. The surface of the tumor was coagulated with cautery and mechanical debulking with the rigid scope was done. [Figure 1 E, F] Bleeding from the tumor bed at the ventro-medial aspect of distal left main bronchus was controlled with diathermy and pressure with a bronchial blocker. The procedure was stopped at this point and the patient was advised a follow up.

Histology showed spindle shaped tumor cells with elongated nuclei, prominent nucleoli and eosinophilic cytoplasm arranged in a herring bone pattern, with infiltrates containing lymphocytes and occasional eosinophilic granulocytes. The cells stained positive forALK-P80 on IHC, FISH and Hybrid Capture based next generation sequencing showed an EML4-ALK1 fusion positive IMT.

After 2 months, repeat bronchoscopic treatment for residual tumor with application of diathermy was done. Biopsies after 4 months were clear of tumor. After 7 months, a recurrence was noted at the distal left main bronchus that was treated with cryotherapy and diathermy. Biopsies at 9 and 12 months were clear of tumor. After 18 months, CT showed recurrence in the distal left main bronchus and bronchoscopic biopsies confirmed ALK positive IMT. The patient was referred for sleeve resection of the distal left main bronchus and surgical resection was achieved with margins being clear of tumor. In the resected tumor the EML4-ALK1 fusion was confirmed. FISH for ROS1 and RET mutations were negative. The patient is asymptomatic and CT scan 30 months after surgery has shown no evidence of recurrence.

Discussion:

IMT is a soft tissue neoplasm of mesenchymal origin composed of spindle cell myofibroblasts accompanied by an inflammatory reaction. Nomenclature of IMT was ambiguous in the past. Terms such as inflammatory pseudotumor (IPT), plasma cell granuloma, pseudoxanthomatous tumors, were used interchangeably and it was considered to be benign. Subsequently, it was noted that a subset of these pseudo-tumors had clonal proliferation, harbored genetic mutations and showed potential for local recurrence and distant metastases. These tumors were recognized as IMTs and classified as an intermediate grade bone and soft tissue neoplasm by WHO [1,2,3]. Approximately 50-70% of IMTs harbor rearrangements of ALK-4, ROS1, PDGFRβ, RET and ETV6 genes, most of them members of the mitogen activated protein kinase pathway [4, 5]. These insights into the molecular genetics of IMT denote a malignant potential and delineate it from benign mimickers like IgG4 related plasma cell granulomas, inflammatory pseudotumor of the lymph node and spleen or mycobacterial pseudotumor. These genetic alterations result in activation of the tyrosine kinase receptor and may offer novel possibilities for treatment with receptor kinase inhibitors in unresectable and metastatic cases [6,7].

IMTs can involve many organs including abdomen, mesentery, lung, head, neck, extremities, genito-urinary tract and orbit. Local recurrence rates of 15- 37 % and metastases rates of 5- 11% have been reported. [2,3,8]

Incidence of pulmonary IMT in adults is around 0.04 – 1% of all lung tumors. Most tumors are found in patients less than 40 years of age with a reported mean range of 27-50 years. No gender predilection has been noted. Endobronchial growth of IMT is rare, with a prevalence of 0-12 %, although one study reported 22 %. [9]

Tracheo-bronchial IMTs may present with airway obstruction, respiratory distress or collapse of the distal lung. Rare presentations include pneumothorax [10] and pneumo-mediastinum as noted in one of our patients.

Surgery is often the first treatment choice but may result in significant loss of lung function especially if the location of the tumor renders it unsuitable for parenchyma sparing surgeries such as sleeve resection. Bronchoscopic removal is a minimally invasive technique and a valuable tool for preserving lung function especially if the tumor is purely endoluminal [11,12]. Bronchoscopic removal of IMTs has been well documented in the pediatric age group and recurrence was mainly noted following partial resection. In adults, data is largely restricted to case reports.

We conducted a review from PubMed, Embase and Medline database for case reports and series wherein bronchoscopic methods were used as an intervention for management of inflammatory myofibroblastic tumors. Studies with full text available in English were included in the analysis.

We reviewed 27 articles that included 22 case reports and 5 case series. [10-36]

Including the 3 patients from our series, 37 patients underwent resection of endobronchial IMT with the help of bronchoscopic techniques. 22 (69%) patients were over 16 years of age. The most common site of tumor involvement was the left main bronchus (17) followed by the trachea (14). 24/37 patients (64.86%) were successfully treated with bronchoscopic interventions. Modalities of therapy included use of the rigid bronchoscope with mechanical or forceps debulking (17), laser resection (10), use of diathermy (9), argon plasma coagulation, cryotherapy and electrocautery snare. Flexible bronchoscopic resection was undertaken in 1 patient.

5 patients had to undergo repeat bronchoscopic procedures, following which the tumor was completely removed. [12,26,29,30]

Surgery was done after primary bronchoscopic treatment in 12 patients. Indications for surgery were elective (3) [10,14,29], incomplete bronchoscopic resection (2) [15,21] extraluminal component (1)

[25] and recurrence (6) [18,23,27,28,32]. 1 patient was deemed too old and unfit for surgery due to severe COPD and hence endobronchial treatment was palliative. [19] Thus, only 8 of the 37 patients (21%) who underwent bronchoscopic resection as the primary treatment modality needed surgery for tumor recurrences or incomplete removal. Mean follow up period after successful resection was 22 months and mean time to recurrence, when noted was 14 months.

Considering the rare occurrence of this tumor, it is unlikely that a prospective study comparing success rates of surgery versus endoscopic removal will be conducted.

Endoscopic resection can also be a useful approach in conditions such as pregnancy where the risk of definitive surgery may be higher [37] or in patients who are unfit or unwilling for surgical resection [19,36]. Even with large tumors having extra-luminal components, it is useful in managing respiratory distress as a bridge till the patient is fit to undergo surgery. [14,21,25], This approach was used for 10 of the 11 pediatric patients with IMTs who subsequently underwent definitive surgery for submucosal components. [38]

When single step resection is not possible, a repeat procedure may also be successfully performed [12,26,29,30] as was the scenario in 5 cases including one from our series. Regular follow-up with CT scans and repeat bronchoscopy with biopsies when required is mandatory to assess response and recurrences.

Endoluminal location of the tumor may be confirmed with imaging with thin slice CT scan and endoscopic evaluation. Radial EBUS can be used to determine if the tumor is extending beyond the cartilage or is limited to submucosal layers and is superior to CT scan in this respect. For better approximation in proximal airways the central probes with balloon sheath may be used for airway assessment. The normal central airways have 7 layers visualized on radial EBUS. Inner most 2 are the mucosa and submucosa, 3rd ,4th and 5th correspond to the cartilage and external 2 to loose and dense fibroelastic tissue surrounding the airway. One of the first indications for use of EBUS was for

identifying extent of tumor extension prior to endobronchial treatment of tumors. In differentiating tumor compression and infiltration EBUS has an accuracy of 94 %. [39] Linear EBUS may be used to detect nodal involvement. IMTs may be FDG avid and PET CT may be a sensitive tool in determining pulmonary and mediastinal involvement, distant metastases, recurrences and residual disease. [40] Advances such as confocal laser endoscopy guided cellular imaging and biopsy may be an added asset in assessing adequate resection and possible recurrences in the future. [41]

An important aspect to be considered is the vascularity of the tumor and the potential for bleeding. Significant bleeding was noted in 2 of our cases requiring use of hemostatic measures including the use of a bronchial blocker. It is imperative that resections be undertaken at centers with the required expertise and facilities for hemorrhage control.

On histology, IMTs show the presence of spindle cells of myofibroblast origin with low mitotic activity, an inflammatory component of plasma cells, lymphocytes and histiocytes, and fibromyxoid stroma. The ratio of different components may vary. Some cases show a prominent number of inflammatory cells, while others may have a mild inflammatory component. The cytoplasm of the spindle cells may be homogeneously stained or sometimes appear granular. Histological spectrum is quite broad and 3 patterns have been described: [42].

1. Myxoid /vascular which resembles nodular fasciitis with loosely arranged plump spindle cells in a myxoid stroma and prominent vasculature. This variant may have more eosinophils or neutrophils and fewer plasma cells than the other types.
2. The compact spindle cell pattern with a cellular proliferation of spindle cells and a fascicular architecture in a collagenous stroma. These foci show numerous plasma cells and lymphocytes.
3. Fibromatosis type which is relatively hypocellular with elongated spindle cells in a densely collagenous background with lymphocytes, plasma cells and eosinophils.

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The differential diagnosis includes reactive lesions like granulation tissue and plasma cell granulomas [1,2,3]. Differentiation from reactive lesions can be difficult on morphology alone. High cellularity, and the fascicular, relatively monomorphic growth pattern of the IMT can be helpful in this matter. Standard immunohistochemistry is mostly of no specific help, SMA is positive as it is in the reactive myofibroblasts. However, molecular abnormalities, such as ALK, ROS1, RET and NTRK1 fusions are definite in the differentiation from reactive pseudotumours. If immunohistochemistry is used for fusion screening, a positive ALK/ROS1 should always be confirmed by an orthogonal technique, FISH or next generation sequencing as we presented in our cases.

In the second case of our series, a granular cell tumor was considered in the differential diagnosis due to prominent granular cytoplasm. The absence of S100 immunohistochemistry staining renders a granular cell tumor unlikely.

Nuclear pleomorphism and atypia are rare in the myofibroblasts of IMT, and when present should warrant that a differential of sarcoma should be ruled out.

Clonal cytogenetic rearrangements that activate the ALK receptor kinase gene in the chromosome band 2p23 emerged in recent years as genetic drivers in IMTs harboring different fusion partners. Immuno-histochemistry for ALK1 may be positive in 45 -50% of IMTs and shows a granular or perinuclear staining pattern. In ALK negative cases other rearrangements may be found. Its genetic profile closely resembles that of lung adenocarcinoma even when it arises in soft tissue and other organs. In 10% of IMTs, ROS1 rearrangement was found. Occasionally tumors harbored RET, PDGFRβ and ETV6 gene rearrangements [5,6]. These new findings imply that IMT is a kinase fusion-driven neoplasm [4]. Interestingly, circa 90% of pediatric IMTs are ALK fusion positive whereas only 10% of adult IMTs are ALK fusion positive tumors [5]. Roughly 30% of IMTs do not harbor any known mutations or genetic rearrangements, mostly in adults. Novel genes might still emerge as drivers of this neoplasm. The presence of ALK- RANBNP2 fusion has been associated with a distinct variant of IMT with round or epithelioid cells on morphology, a perinuclear staining pattern and an aggressive

clinical course. The term epithelioid inflammatory myofibroblastic sarcoma (EIMS) has been suggested to distinguish this aggressive variant [43].

In a previous study of 59 IMTs, analysis of a subset of tumors with histological atypia and aggressive clinical course had revealed that ALK negative tumors were associated with older age of presentation, greater nuclear pleomorphism, nuclear atypia and atypical mitosis with a tendency for distant metastasis [44]. In our series, 2 patients were adult males in the 40-50 age group, while the third was a 16-year-old female. All 3 had IMTs with IHC positive for ALK protein and FISH detected EML4-ALK1 re-arrangement. While the 2 older males could be treated with endobronchial resection, the female had a local recurrence. This series is too small to draw firm conclusions about tumor site, molecular profile, histological profile and prognosis.

The molecular genetics of IMT has opened up a potentially new therapeutic possibility in unresectable and refractory tumors. The ALK inhibitor crizotinib has been evaluated in patients with advanced or metastatic IMTs deemed incurable by surgery, radiotherapy or systemic therapy with response rates of 50 % by RECIST criteria in ALK+ve and 14 % in ALK-ve tumors, concluding that crizotinib should be considered standard of care in the subset of patients with ALK +ve IMTs who do not qualify for curative surgery[7]. However, amongst ALK negative tumors the presence of other oncogenic drivers such as ROS1 gene rearrangements may render them amenable to treatment with crizotinib [6]. Ceritinib has been used with a significant and sustained partial response in an IMT that had progressed despite crizotinib [45]. A future perspective may be to study the efficacy of combined modalities including bronchoscopic resection and ALK1 inhibitors, especially in refractory or recurrent tumors.

In conclusion, interventional bronchoscopic techniques are minimally invasive lung function preserving modalities for resection of endobronchial IMTs in adults. They are particularly useful when the tumor has essentially endo-luminal localization and complete resection of the tumor can

be performed during the bronchoscopic procedure. Regular follow-up is essential to detect residual tumor or recurrence. It may also prove useful for airway recanalization in patients who are unfit for surgery or in emergency respiratory distress as a bridge to surgical resection. In unresectable and metastatic cases, targeted treatment with ALK inhibitors may be considered standard of care as guided by the molecular profile of the tumor.

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1. Iyer A: Contributions towards conception, design, drafting and revision of the article and its scientific content, acquisition of clinical data, final approval of content
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3. Heukamp LC: Contributions towards revision of the article and its scientific content, acquisition of molecular pathological data, final approval of content
4. Thunnissen E: Contributions towards design, drafting and revision of the article and its scientific content, acquisition of clinicopathologic data, final approval of content
5. Daniels JMA: Contributions towards conception, design, drafting and revision of the article and its scientific content, acquisition of clinical data, final approval of content

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Figure legends:

Figure 1.

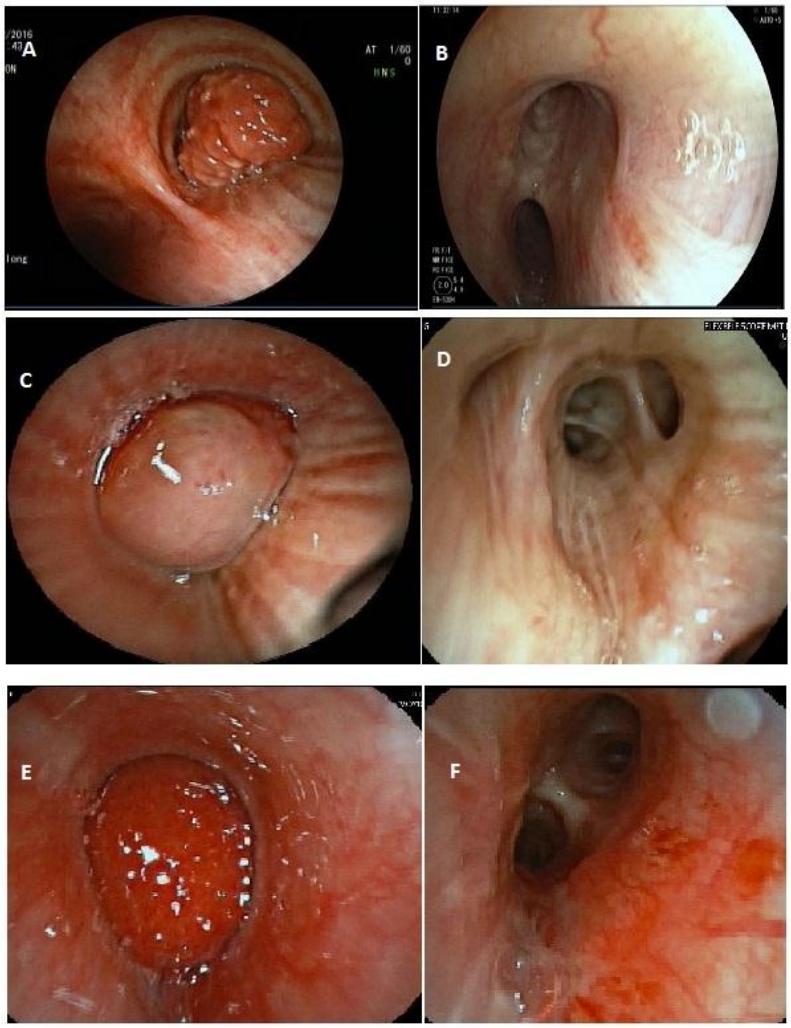
Bronchoscopic view A, C, E. before and B, D, F. after bronchoscopic resection of IMT

Figure 2

A representative overview and detail of inflammatory myofibroblastic tumor is shown.

A. Hematoxylin and eosin stain 10x and
B. 40x
C. Immunohistochemistry is positive in tumor cells for ALK (5A4 antibody, 20x), including the control appendix tissue showing negative myocytes and weakly positive ganglion cells (frame within panel C)
D. FISH analysis with an ALK rearrangement, note the split signals

FIGURE 1 : Bronchoscopic images A, C,E : Before and B,D,F after bronchoscopic treatment



Case 1 Right main bronchus

Case 2 Middle lobe bronchus

Case 3 Left main bronchus

FIGURE 2 : Histology, Immunohistochemistry and FISH in IMT