Unraveling the spectrum of Inflammatory Myofibroblastic Tumors (IMT) in the lung

**Case Series**

- 2 Parenchymal
  - 17 y: a rare ETV6-NTRK3 fusion
  - 5 y: a challenging diagnostic
    - ALK translocation

- 1 Pleural
  - 18 y
    - a rare pleural IMT
    - ALK translocation

- 1 Endobronchial
  - 42 y
    - an aggressive relapse
    - ALK translocation

**Implications**

- Identify gene re-arrangements holds promise for targeted therapies
- Multidisciplinary approach is needed
- Diagnostics can be challenging: peroperative frozen section can be helpful
- Early detection and complete surgical removal are crucial
- Close surveillance due to potential relapse
Unraveling the Spectrum of Inflammatory Myofibroblastic Tumors in the Lung: A Comprehensive Case Series Highlighting Endobronchial, Pleural, and Lung Parenchymal Tumors

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Glossary of abbreviations:

IMT: Inflammatory myofibroblastic tumor
ALK: Anaplastic Lymphoma Kinase
VATS: video-assisted thoracoscopic surgery
RATS: robotic-assisted thoracoscopic surgery
CRP: C reactive protein
WBC: White blood cell count
PET-CT: Positron emission tomography-computed tomography
CT: computed tomography
MSI: Microsatellite Instability
FISH: Fluorescence in situ hybridization
NGS: Next-generation sequencing
MRI: Magnetic resonance imaging
CGH: comparative genomic hybridization

Central picture Legend: Four lung IMT cases (rare ETV6-NTRK3 fusion, uncommon pleural IMT and aggressive relapse).

Central message: Diverse lung IMTs are showcased with complex diagnostics, treatment strategies and gene-guided therapies. It emphasizes multidisciplinary care, early detection and full resection for best outcomes.

Perspective statement: The complexity of diagnosing and treating diverse IMT’s in the lung is highlighted. Perioperative frozen section can help with treatment decisions and multidisciplinary collaboration is crucial. Identifying gene-rearrangements for potential targeted therapies are emphasized. Early detection, complete surgical resection and close surveillance are essential due to potential aggressive relapse.

Abstract

Objectives:
Diverse cases of inflammatory myofibroblastic tumors (IMTs) in the lung (pleural, endobronchial and parenchymal) are presented while discussing the (preoperative) diagnostic challenges and treatment modalities. Other objectives include emphasizing the significance of gene rearrangements and highlighting the multidisciplinary approach in addressing IMTs.

Methods:

Four cases of IMT in the lung are presented, including a young adolescent girl with an ETV6-NTRK3 gene rearrangement, a 5-year-old boy with challenging preoperative diagnosis, and two middle-aged women with respectively pleural and endobronchial tumors with one peribronchial relapse.

Results:

The cases demonstrate the diverse clinical presentations and diagnostic complexities associated with IMT in the lung. Surgical resection remains the primary treatment modality, with complete resection leading to a cure in most patients. Unfortunately, aggressive relapse can occur, as in our last case of an endobronchial tumor. Frozen section may confirm the presence of malignant cells perioperatively and impact further treatment. The presence of gene rearrangements, such as ETV6-NTRK3, suggests potential therapeutic implications.

Conclusion:

Early detection and complete surgical removal of IMT are crucial for effective treatment. Identifying gene rearrangements, such as ETV6-NTRK3, holds promise for targeted therapies.
Diagnostic challenges, including the controversy of biopsies and preoperative evaluations, underscore the importance of a multidisciplinary approach. Anatomopathological recognition of IMT stays demanding. Close surveillance is necessary due to potential relapse, while frozen section perioperatively can help further treatment. This case series emphasizes the diagnostic challenges and therapeutic considerations for IMT in the lung.

**Keywords:** inflammatory myofibroblastic tumor, ETV6-NTRK3 gene rearrangement, peribronchial relapse, pleural inflammatory myofibroblastic tumor

**Introduction**

Inflammatory myofibroblastic tumors (IMT) are a heterogeneous group of neoplastic diseases composed of myofibroblastic spindle and inflammatory cells. It is defined as an extremely rare
intermediate-grade malignancy (prevalence of 0.04% to 0.7%), primarily occurring in the abdominopelvic region (75% of the cases) and the lung. (1, 2) They are most frequent in adolescents and children, irrespective of gender and race and represent one of the most common primary lung tumors in the pediatric age group. (2-5) Pulmonary IMT is mostly located in the parenchyma and rarely found endobronchial. Only 136 cases were retrieved in English literature, accounting for 5% to 12% of IMT cases. (3, 6, 7) A primary IMT of the pleura is even more uncommon and typically results from pulmonary involvement. (8)

The etiology of IMTs is not fully understood but it is suspected to develop secondary to infectious or autoimmune diseases or due to a genetic mutation. Previously described risk factors include smoking, minor trauma and IgG4-related disease. (4) When occurring in the lung, IMT is mostly asymptomatic but can cause pulmonary complaints such as cough, dyspnea, hemoptysis or thoracic pain. (9) In approximately 20% of the cases, general symptoms like malaise, fever and weight loss arise. (4) As per the latest World Health Organization Classification of Tumors, IMTs are categorized as intermediate-grade neoplasms of soft tissue that rarely metastasize. The College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC) recommend the classification of IMTs using the Pathologic Soft Tissue Stage Classification (pTNM; AJCC 8th Edition). This classification system defines primary tumor (T), regional lymph node (N), and distant metastasis (M) categories based on the anatomical location of lesions. These anatomical locations include: head and neck, trunk and extremities, abdomen and thoracic visceral organs, retroperitoneum, orbit. Even though metastases are rare in IMTs; local recurrences can occur in up to 25% and be aggressive. (8, 9) Lung IMT can extend towards mediastinum, diaphragm, pleura or chest wall and metastasis may be more frequent in the absence of ALK reactivity. (10) The exact overall survival is not known in pulmonary IMT but a
ten year retrospective analysis of 23 children with pulmonary IMT showed a 5-year event-free survival rate of 86%, while the 5-year overall survival rate was 100%. Histopathologic and immunohistochemical analysis is required to differentiate IMT from other infectious, autoimmune or malignant lesions. Fine needle aspiration attempts often give false positive and false negative results. In case of an endobronchial IMT, bronchoscopy is rarely successful for diagnosis, bronchoscopic biopsy can be done not always showing clear diagnosis of IMT, while transbronchial biopsy has infrequently been used to diagnose IMT.

Different gene rearrangements are seen in IMT's. Roughly 50 to 80% of IMT harbor Anaplastic Lymphoma Kinase (ALK) gene rearrangements (seen on immunohistochemistry) for which the molecular pathogenesis is unknown. In the absence of ROS1 gene rearrangement or ALK gene rearrangement, an ETV6-NTRK3 translocation has been described. It is suspected to be presented in 10-15% of all ALK-negative IMTs however, its clinical relevance is unknown. All cases were pulmonary IMTs in young patients.

As per the recommendations of the European Society for Medical Oncology (ESMO), surgery is the main treatment modality for local IMT. ESMO guidelines emphasize the importance of having a specialized surgeon perform the surgical management in favourably a sarcoma center. The standard surgical procedure involves en bloc resection with R0 margins. Depending on the tumor’s size, the surgical approach may entail a wide local excision (WLE), which includes the removal of the IMT along with some surrounding normal tissue to ensure complete excision. A complete resection will lead to a cure in the majority of patients. Currently, there is no indication for adjuvant therapy after complete resection. However, in certain cases, adjuvant corticosteroids and/or radiotherapy may be considered to reduce the risk of local recurrence and
even chemotherapy such as paclitaxel and carboplatin can be given in rare cases, although the lack of prospective data presents a challenge. (20)

ALK inhibitors can be used in patients with recurred or unresectable tumors and if ALK positivity is seen on immunohistochemical staining of the (biopsied) tissue. (1, 23) Crizotinib, a tyrosine kinase inhibitor (TKI) targeting ALK, MET, ROS1 and RON, has only recently been approved by the FDA (July 2022) as monotherapy in adult and pediatric patients older than one year with unresectable, recurrent or refractory ALK positive IMT’s. (24) Unfortunately, recurrent IMT with ALK gene rearrangements often develop resistance to crizotinib which is why second- or even third-line ALK inhibitors are used, with different levels of response. Approximately one-quarter of surgically treated tumors may experience a recurrence. A new surgical resection should then be carefully evaluated.

Endoscopic advancements in thoracic surgery led to more minimal invasive surgery with rigid bronchoscopic resection of endobronchial lesions and bronchoplasties by video-assisted or robotic assisted thoracoscopic surgery (VATS/RATS). However, the impact of these minimal invasive techniques on recurrence rate and survival is unknown. For endobronchial IMT, bronchial sleeve resection has been described in a few cases with good outcomes under the condition that a complete resection can be achieved. (25) There is no information on the adequate tumor-free margin.

This article reports four cases of IMT occurring in the lungs. Each patient has given (French or Dutch) consent stating that their case can be used for publication by anonymized patient data; IRB approval was not required. One in a young adolescent girl with a rare ETV6-NTRK3 gene rearrangement, the other in a 5-year-old boy for whom the preoperative diagnosis was very
difficult, and two middle-aged women, one with unusual pleural involvement and the other with endobronchial involvement with rapid and aggressive peribronchial relapse.

Case presentations

Case presentation 1:

A 17-year-old girl without any medical history presented with inflammatory joint- and muscle pain, fatigue and dyspnea at exercise for 2 months. Blood work showed signs of inflammation (CRP 14.6 mg/dl (ULN < 5mg/dl) and White blood cell counts 6500/mm$^3$ (ULN 96000/mm$^3$).

An X-ray and subsequent PET-CT scan revealed a solitary contrast-enhanced nodule of 22mm centrally located in the left lower lobe. All images of the cases can be seen in figure 5. A CT-guided biopsy showed microscopically consolidation and inflammation of the lung parenchyma without arguments for malignancy. Furthermore, additional investigations (ANA, ENA, myositis blot, ANCA, ACLA and LAC) did not show arguments for other systemic diseases. Following a multidisciplinary decision, robotic-assisted wedge resection and subsequent frozen section analysis were performed. The frozen section suggested a soft tissue tumor leading to the decision to perform a completion RATS lobectomy with lymphadenectomy.

The diagnosis of an IMT was histologically confirmed. The removal of the tumor was complete. Microscopic examination revealed a nodular lung lesion formed by spindle cells arranged in a fasciculate manner and associated with a mixed chronic inflammatory infiltrate (figure 1A). The immunostaining for ALK was ambiguous and showed a low cytoplasmic positive staining (figure 1B). A Microsatellite Instability (MSI) analysis and ALK and ROS1 fluorescence in situ hybridization (FISH) tests were negative. Next, a FusionPlex Sarcoma kit (Archer DX) has been
used, which is designed to detect fusion transcripts of: ALK, CAMTA1, CCNB3, CIC, EPC1, ESWR1, FOXO1, FUS, GLI1, HMGA2, JAZF1, MEAF6, MKL2, NCOA2, NTRK3, PDGFB, PLAG1, ROS1, SS18, STAT6, TAF15, TCF12, TFE3, TFG, USP6 and YWHAE. This NGS sarcoma fusion panel (performed on Illumina) suggested the presence of an ETV6-NTRK3 fusion transcript which was confirmed by FISH analysis with an ETV6 and NTRK3 rearrangement.

Post-operatively she recovered well without pain or dyspnea. Thoracic CT confirmed a normal postoperative status following lobectomy. Her bloodwork returned to normal and her inflammatory joint and muscle pains disappeared. At four years of follow-up, no relapse occurred.

Case presentation 2:

A 5-year-old boy had recurrent left lower lobe pneumonia, always improving under antibiotics. During his last episode, the inflammatory parameters stayed elevated (CRP 142 mg/dl, 17 10³/mm³ WBC with neutrophilia (69%), erythrocyte sedimentation rate 50 mm/h) and he kept complaining of thoracic pain. He did not have dyspnea, fever or cough. On a thoracic CT, an obstruction of the left lower bronchus was suspected by an intraluminal process. On bronchoscopy, a complete occlusion of the left lower bronchus was confirmed by a mobile, rounded, shiny, pale intraluminal mass. The rest of the bronchial tree appeared normal. A pulmonary MRI showed a cystic lesion (4 x 2.7 cm) which appeared polylobular and septalized with a discrete contrast enhanced center leading to the differential diagnosis of a bronchogenic neurenteric cyst, esophageal duplication cyst or lymphangioma. A bronchial lavage did not demonstrated the presence of an atypical mycobacterium or tuberculosis. Neuroblastoma was
ruled out after negative 24h (catecholamine) urine test. A gastroscopy and technetium scan excluded stomach mucosa in the cyst.

In a multidisciplinary approach, a rigid bronchoscopy to acquire a biopsy seems unsafe and non-feasible. A lower lobectomy through thoracoscopy was performed. A revision thoracoscopy was done due to slow re-expansion development of the upper lobe, which was without complications. At pathology, an IMT was diagnosed and confirmed by the pathology department in Boston, USA and the Bordet Institute in Belgium, FISH analysis revealed an ALK translocation. Here, a multicolor FISH reaction was performed on a paraffin section of the biopsy with the LSI ALK (2p23) dual color break separate rearrangement probe (ALK = anaplastic lymphoma kinase) (Vysis LSI ALK [2p23] dual color break separate rearrangement probe, Abbott ref. 05J89-001).

Bi-annual PET-CT and MRI showed no recurrence, up to 10 years.

Case presentation 3:

A 28-year-old non-smoker woman complained of left thoracic pain with nocturnal cough and dyspnea. A thoracic CT demonstrated a pleural mass in the left fissure (66 x 56 mm) occluding the upper lobe and lingular bronchus. A PET-CT showed a highly metabolic active intrafissural mass without lymph nodes or metastasis. A bronchoscopy confirmed the left upper lobe compression due to an external mass effect. Mucosal and transthoracic biopsies couldn’t provide a definitive diagnosis. Therefore, resection of the mass was carried out by a thoracotomy. Postoperatively, a positive serology for mycoplasma pneumonia was treated by antibiotics without further complications. Anatomopathology reveals an IMT, probably from pleural origin (though inconclusive), with an ALK gene translocation on FISH analyses (the same as described in case 2 has been used). At 7 year follow-up with CT thorax, no recurrence was seen.
Case presentation 4:

A 42-year-old woman presented with a non-productive cough, dyspnea at exercise, wheezing and thoracic oppression. A trial with antibiotics didn’t improve her symptoms. She had no relevant medical history and never smoked.

A thoracic CT demonstrated a mass in the right truncus intermedius. A bronchoscopy confirmed a tumor occlusion by an ovular lesion covered with normal mucosa. Macroscopically a carcinoid was suspected. A loop excision of the ovular lesion was performed via rigid bronchoscopy.

Anatomopathological examination confirmed the presence of a mesenchymal tumor consisting of spindle cells, specifically an IMT requiring full tumor excision. The cells had a poorly delineated pale eosinophilic cytoplasm and elongated, monomorphic nuclei. These nuclei were characterized by an apparent membrane, fine chromatin and small vesicular nucleoli (figure 2A). There were no signs of lymphovascular invasion or invasive growth in the lung parenchyma.

ALK staining showed a diffused strong positive expression (figure 2B). FISH tests showed an ALK positivity in 78% of the analyzed nuclei. A comparative genomic hybridization (CGH) test could not be performed due to insufficient DNA material.

A PET scan and a brain MRI didn’t reveal metastases. Due to the localization and the involved margins after the former rigid bronchoscopic loop-resection, an excision of the membraneous part of the intermediate bronchus with pericardial reconstruction by RATS and lymphadenectomy was performed. Macroscopical examination of the surgical specimen confirmed the presence of scar tissue following the previous resection and margins were free on frozen section analyses. A definite anatomopathological study could only demonstrate lymphocytic inflammation in the bronchial tissue and lymph node without signs of malignancy.
Postoperatively the patient developed a hemothorax requiring a thoracic exploration which could not show any active bleeding or lymphatic leak.

At her postoperative consultation, two months following surgery, she complained of persistent wheezing. A bronchoscopy confirmed a rapid tumor recurrence with complete occlusion of the right truncus intermedius with a symphysis of the anterior and posterior walls. A thoracic CT confirmed this local recurrence starting from the lobar bronchus of the right lower lobe (figure 3), however, an extension to the middle lobe bronchus couldn’t be ruled out. No invasion outside the bronchus was seen on CT.

A RATS right lower lobe lobectomy was performed, however, per-operative frozen section analysis demonstrated involved margins to the middle lobe requiring a completion bilobectomy.

Final pathology revealed an IMT with negative margins. The growth of the lesion was peri-bronchial and not exclusively endobronchial. There was no parenchymal involvement. The patient recovered well from the procedure. Thoracic CT's until four years postoperatively could not reveal any recurrence.

**Discussion and Conclusions**

IMTs are a heterogeneous group of rare lesions primarily found in the lung or abdominopelvic region. Surgical resection remains the main modality for obtaining both an accurate diagnosis, as this can be very difficult, and a benefit in terms of long-term survival.\(2, 6, 9\)

Identification of the ETV6-NTRK3 chimeric tyrosine kinase in IMTs is consistent with the role of an oncogenic tyrosine kinase in the pathogenesis of this tumor type and seems to represent
another member in the list of IMT driver genes in addition to ALK, ROS1, and PDGFRβ. Our first case presented signs of inflammation and inflammatory joint and muscle pains which all subsided after the resection. The correlation between systemic symptoms and gene rearrangement is unknown due to the small number of patients. However, the therapeutic impact of such gene rearrangements could be significant as such tumors might be sensitive to NTRK inhibitors. In fact, several preclinical and clinical studies have shown promising sensitivity to larotrectinib (LOXO-101), an inhibitor of the TRK family, and this in pediatric fibrosarcoma's with ETV6-NTRK3 fusions. (17) Our patient recovered well and didn’t experience relapse until four years after surgery.

IMTs are hard to diagnose preoperatively. A patient can present with nonspecific symptoms or can be asymptomatic and imaging can be misleading. In our second case of a 5-year-old boy with recurrent pneumonia, extensive diagnostics were performed with the differential diagnosis of a bronchogenic neurenteric cyst while postoperative pathology was suggestive of IMT. Here, the challenge of the pathological diagnosis of IMT is highlighted since multiple pathology departments had to confirm the diagnosis. Since the sensitivity of FISH and NGS (RNA) is higher than immunohistochemistry (SMA, pankeratine, ALK etc), it is always advised to check for ALK gene rearrangements as well as fusions of ROS1, PDGFRβ, RET and NTRK (especially when ALK appears negative).

In our third case, a middle-aged woman with noteworthy respiratory symptoms, a large intrafissural mass was seen on CT and suspected as pleural from origin. Biopsies were inconclusive. Following multidisciplinary consultation, the challenging mass was resected. On pathology IMT is diagnosed, presumably but not conclusive, from pleural origin. The case
enhances both the difficulty of interpreting biopsy results as defining the origin of the IMT. No recurrence occurred in 7 years of follow-up.

Immunohistochemistry and molecular analyses are frequently pivotal in enabling pathologists to establish the diagnosis of IMT; however, the availability of sufficient tissue, which can occasionally pose a limitation, is crucial for conducting these analyses. Consequently, biopsies sometimes only confirm an inflammatory lesion and their use is therefore sometimes controversial. The contribution of per-operative frozen section analysis is also doubtful, however the frozen section analysis in our last patient did demonstrate malignant cells, leading to a completion bilobectomy.(26-29)

For endobronchial IMTs, local resection by rigid bronchoscopy and even laser therapy have been described with good outcomes.(16, 25) In our last patient case, a loop excision was completed by a RATS bronchoplasty and reconstruction. However she experienced a rapid and aggressive relapse. The relapse demonstrated extension in the peribronchial tissue while not invading the parenchyma. This extension was not noted in the original operation specimen nor seen on a thoracic CT. Whether this extension was present before the first surgery (skip lesion) or induced as seeding due to bronchoscopic loop excision or reconstructive surgery by RATS is unknown. To our knowledge, this peribronchial invasion has not been described before. In patients undergoing locoregional treatment, rigorous surveillance with thoracic CT and bronchoscopy is warranted. Also note that in this case, since it states as a recurrent disease, a TKI like crizotinib could have been given following the FDA approval of the latter. Unfortunately, when we dealt with this case, this guideline was not yet available. It was then only suggested for unresectable disease.
From our experience, a few suggestions are made when handling pulmonary, endobronchial or pleural IMT. An overview of how to diagnose IMT is seen in table 1 and a work-up overview can be seen in figure 6. At diagnosis a CT-thorax (or MRI if a pediatric patient is encountered) should be done, followed by a biopsy. If a pulmonary or pleural IMT is seen, a CT guided biopsy should be performed. In case of endobronchial IMT a rigid bronoscopic with loop resection (or biopsy) can be done, or if necessary a bronchoscopic transbronchial biopsy. At pathology, like described above, immunohistochemistry (SMA, pankeratine, ALK etc) and NGS should be done while looking for ALK gene rearrangements as well as fusions of ROS1, PDGFRβ, RET and NTRK. We recommend to perform a PET-CT scan, as IMT can also exhibit increased FDG avidity and metastasis can be revealed. Several authors have explored the use of FDG-PET/CT in IMT, with some studies revealing significantly elevated SUV values. The reported SUV values range from 5 to >35 g/ml in different studies. This wide range of values makes it challenging to distinguish IMT from other neoplasms. The underlying reason for such heightened uptake in these benign tumors likely stems from the intense associated inflammation. This inflammation results in increased metabolic activity, consequently leading to elevated uptake on FDG-PET/CT scans. Additionally, a few researchers have noted heightened uptake in somatostatin receptor imaging methods, such as 111In octreotide and 68Ga DOTATOC.(30) This increased uptake is attributed to the enhanced expression of somatostatin receptors in the inflammatory cells. If the diagnosis, after imaging and pathology, stay doubtful, a surgical resection should be performed with an intra-operative frozen section. In pulmonary or pleural IMT, depending on the location and the size of the tumor, a wedge resection could be performed only if a complete resection is feasible. If this is not the case, a lobectomy has to be performed. For endobronchial IMT, a loop excision can be done but only if adequate margins can be expected. Again, intra-operative frozen
section can help in such cases. When in doubt, we advice to perform an endobronchial resection. We recommend a follow-up with CT thorax at 3 and 6 months and thereafter every year during ten years. We would not advice routine bronchoscopy.

To conclude, early detection and complete surgical removal of the tumor is fundamental for treating IMT in the lung, specifically for endobronchial localization. Although ALK gene translocations are seen more often, other translocations like ETV6-NTRK3 such as in our first case, can have a therapeutic impact for example with the use of NTRK inhibitors. Our second and third case show that diagnosing IMT preoperatively is challenging. The use of intraoperative frozen section analysis may confirm the presence of malignant cells and have an impact on further treatment. Endobronchial IMT can have a spread peribronchial not noticed on thoracic CT or rigid bronchoscopy. While case series demonstrate adequate tumor control with endobronchial resection, our last case highlights the need for a close follow-up due to a possible spread to the exterior wall of the bronchus. Lastly, a multidisciplinary approach is mandatory for diagnosing and treating IMT.

References


**Tables**

**Table 1: Diagnosing pulmonary IMT (including pleural and endobronchial)**

<table>
<thead>
<tr>
<th>Symptom(s)</th>
<th>Laboratory tests</th>
<th>Imaging</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Elevated CRP, sedimentation and WBC - Normo-, hypochromatric,</td>
<td>CT thorax - Solitary, well-circumscribed, peripheral - Mostly in lower lobes</td>
<td>MRI thorax - Low intensity on T2-weighted images - Targetoid, hetero- or homogeneous mass</td>
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<tr>
<td>Chest pain</td>
<td></td>
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<td>Pulmonary/pleural:</td>
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<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
<td>Endobronchial:</td>
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<tr>
<td>Haemoptysis</td>
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Journal Pre-proof
- Fever
- Malaise
- Weight loss.
- Unusual calcifications (15%)
- Hyper- or hypovascularization
  - With or without calcifications
- Rigid bronchoscopic loop resection or biopsy
- Transbronchial biopsy
  - When in doubt: intra operative frozen section

| Abbreviations: CRP (C-reactive protein); PET-CT (Positron Emission Tomography and Computed Tomography); CT (Computed Tomography); AJCC (American Joint Committee on Cancer); SMA (Spinal Muscular Atrophy); NGS (Next generation sequencing); ALK (Anaplastic lymphoma kinase); ROS (reactive oxygen species); NTRK (Neurotrophic tyrosine receptor kinase) |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|

Legend of figures

**Figure 1:**
H&E staining of the tumor reveals spindle cells associated with a mixed chronic inflammatory infiltrate (A). ALK staining shows a low level cytoplasmatic expression (B).

**Figure 2:**
H&E staining of the tumor cells with a poorly delimited pale eosinophilic cytoplasm and elongated, monomorphic nuclei (A).

ALK staining shows a *diffuse positive* nuclear staining (B).

*Figure 3:*
Thoracic CT-scan showing the bronchial tumor (*arrow*) starting from the lobar bronchus of the right lower lobe. Extension to the mid-lobe bronchus cannot be ruled out.

*Figure 4:*
Four rare cases of IMT in the lung with the diagnostic and therapeutic consequences.

*Figure 5:*
All CT, PET-CT and/or MRI images of all four cases.

*Figure 6:*
Overview of work-up for pulmonary IMT.
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<td>- Solitary, well-circumscribed, peripheral</td>
<td>-Active on PET-CT</td>
<td>-Pulmonary/pleural: CT guided biopsy</td>
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<tr>
<td>-Chest pain</td>
<td>-Normo-, hypochromatic, or microcytic anemia</td>
<td>- Mostly in lower lobes</td>
<td>-Staging by Pathologic Soft Tissue Stage Classification (pTNM; AJCC 8th Edition)</td>
<td>Endobronchial: -Rigid bronchoscopic loop resection or biopsy</td>
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<tr>
<td>-Dyspnea</td>
<td>-thrombocytosis -hypergamma-globulinemia</td>
<td>- Targetoid, heterogeneous or homogeneous mass</td>
<td>-Transbronchial biopsy</td>
<td>-NGS (ALK gene, ROS1, PDGFRβ, RET and NTRK)</td>
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Figure 1
Unraveling the spectrum of Inflammatory Myofibroblastic Tumors (IMT) in the lung

Case Series

2 Parenchymal
- 17 y: a rare ETV6-NTRK3 fusion
- 5 y: a challenging diagnostic ALK translocation

1 Pleural
- 18 y: a rare pleural IMT ALK translocation

1 Endobronchial
- 42 y: an aggressive relapse ALK translocation

Implications

- Identify gene re-arrangements holds promise for targeted therapies
- Multidisciplinary approach is needed
- Diagnostics can be challenging: peroperative frozen section can be helpful
- Early detection and complete surgical removal are crucial
- Close surveillance due to potential relapse

Figure 4: Graphical abstract visualizing four rare cases of IMT in the lung with the diagnostic and therapeutic consequences.
Case 1: 17-year-old girl, nodule left lower lobe (PET-CT and CT)

Case 2: 5-year-old boy, nodule left lower lobe (MRI)

Case 3: 28-year-old woman, pleural mass in left fissure (PET-CT and CT)

Case 4: 42-year-old woman, mass right truncus intermedius (PET-CT and CT)

Figure 5
Figure 5: diagnosing, staging and treating pulmonary IMT. The main treatment modality of IMT consists of curative operative intent. When pathology remains unclear at biopsy or the diagnosis is doubtful an intra-operative frozen section should always be performed. If recurrence occurs or margins are not free, a re-resection should be performed with afterwards treatment by chemotherapy and TKI’s (in function of NGS). If the tumor seems unresectable, or there is evidence of lymphadenopathy or metastasis, chemotherapy and TKI’s should be given. Since AE’s and resistance often occur, second (lucartinib, ensartinib, ceritinib, brigatinib) or third (lorlatinib) generation TKI’s should be given. In case of an ETV6-NTRK3 fusion, we would recommend to give lorlatinib in second line.
Inflammatory Myofibroblastic Tumors

Case Series
- Parenchymal
- Pleural
- Endobronchial

Highlighting
- Complex diagnostics
- Targeted therapies
- Complete surgical resection

MULTIDISCIPLINARY APPROACH