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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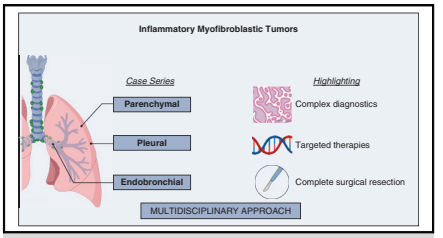
ABSTRACT

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-neurotrophic tyrosine receptor kinase 3 (NTRK3) gene rearrangement, a 5-year-old boy with challenging preoperative diagnosis, and 2 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.

Conclusions: 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, whereas frozen section perioperatively can help further treatment. This case series emphasizes the diagnostic challenges and therapeutic considerations for IMT in the lung. (JTCVS Open 2024;17:297-305)



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

The complexity of diagnosing and treating diverse IMTs 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.

Inflammatory myofibroblastic tumors (IMTs) are a heterogeneous group of neoplastic diseases composed of myofibroblastic spindle and inflammatory cells. IMTs are defined as an extremely rare intermediate-grade malignancy (prevalence of 0.04-0.7%), primarily occurring in the abdominopelvic region (75% of the cases) and the lung.[1,2]

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Abbreviations and Acronyms

ALK = anaplastic lymphoma kinase
CT = computed tomography
FISH = fluorescence in situ hybridization
IMT = inflammatory myofibroblastic tumor
MRI = magnetic resonance imaging
NGS = next-generation sequencing
NTRK3 = neurotrophic tyrosine receptor kinase 3
PET = positron emission tomography
RATS = robotic-assisted thoracoscopic surgery
ROS1 = reactive oxygen species 1

They are most frequent in adolescents and children, irrespective of sex 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 have been 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 and the American Joint Committee on Cancer recommend the classification of IMTs using the Pathologic Soft Tissue Stage Classification (pTNM; American Joint Committee on Cancer 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, and 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 toward the mediastinum, diaphragm, pleura, or chest wall, and metastasis may be more frequent in the absence of anaplastic lymphoma kinase (ALK) reactivity.[10] The exact overall survival is not known in pulmonary IMT, but a 10-year retrospective analysis of 23 children with pulmonary IMT showed a 5-year event-free survival rate of 86%, whereas the 5-year overall survival rate was 100%.[11] 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[12] for diagnosis, bronchoscopic biopsy can be done, not always showing clear diagnosis of IMT, whereas transbronchial biopsy has infrequently been used to diagnose IMT.[13]

Different gene rearrangements are seen in IMTs. Roughly 50 to 80% of IMTs harbor ALK gene rearrangements (seen on immunohistochemistry) for which the molecular pathogenesis is unknown.[4] In the absence of reactive oxygen species 1 (ROS1) gene rearrangement or ALK gene rearrangement, an ETV6-neurotrophic tyrosine receptor kinase 3 (NTRK3) translocation has been described. It is suspected to be present in 10 to 15% of all ALK-negative IMTs; however, its clinical relevance is unknown. All cases were pulmonary IMTs in young patients.[14-21]

As per the recommendations of the European Society for Medical Oncology, surgery is the main treatment modality for local IMT. European Society for Medical Oncology guidelines emphasize the importance of having a specialized surgeon perform the surgical management in preferably 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, which includes the removal of the IMT along with some surrounding normal tissue to ensure complete excision.[4] A complete resection will lead to a cure in the majority of patients.[1,3] 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.[20,22]

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 targeting ALK, MET, ROS1, and RON, has only recently been approved by the Food and Drug Administration (July 2022) as monotherapy in adult and pediatric patients older than 1 year with unresectable, recurrent, or refractory ALK-positive IMTs.[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.

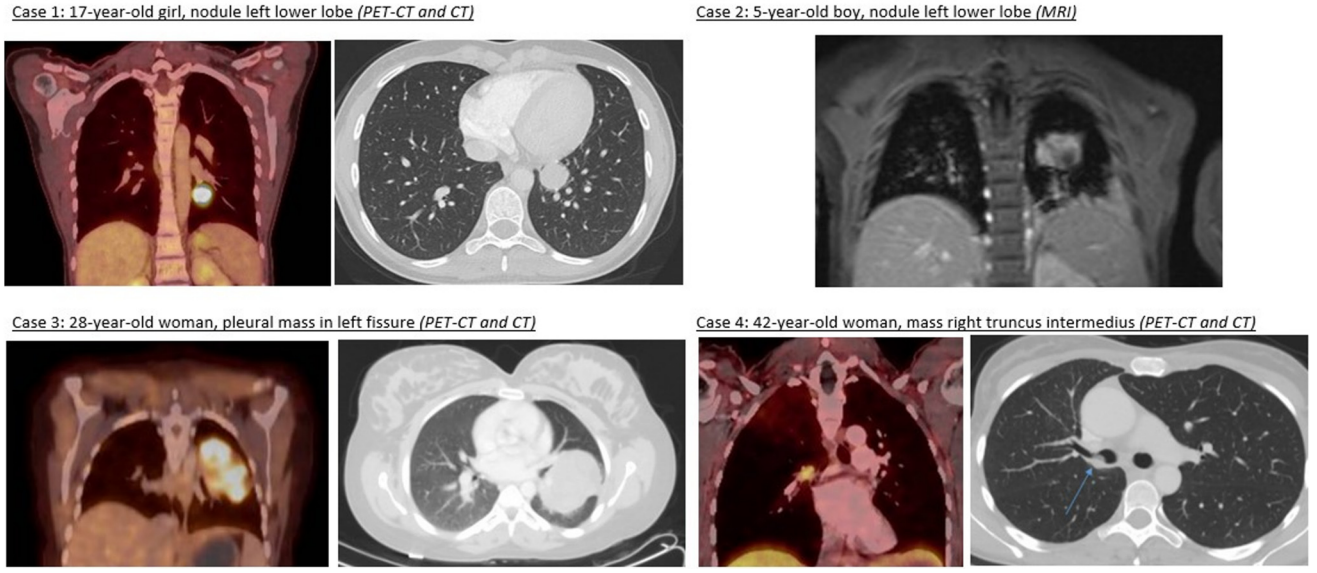

FIGURE 1. All computed tomography, positron emission tomography–computed tomography, and/or magnetic resonance imaging of all 4 cases. *PET*, Positron emission tomography; *CT*, computed tomography; *MRI*, magnetic resonance imaging.

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 (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 4 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; institutional review board approval was not required. One was 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 2 were in 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 (C-reactive protein 14.6 mg/dL [upper limit of normal <5 mg/dL] and white blood cell counts 6500/mm^3 [upper limit of normal 9600/mm^3]). A radiograph and subsequent positron emission tomography–computed tomography (PET-CT) scan revealed a solitary contrast-enhanced nodule of 22 mm centrally located in the left lower lobe. All images of the cases can be seen in Figure 1. A CT-guided biopsy showed microscopically consolidation and inflammation of the lung parenchyma without arguments for malignancy. Furthermore, additional investigations (antinuclear antibody, extractable nuclear antigen, myositis blot, antineutrophilic cytoplasmic antibody, anticardiolipin antibody, and lupus anticoagulant) 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 2, *A*). The immunostaining for ALK was ambiguous and showed a low cytoplasmic positive staining (Figure 2, *B*). A microsatellite instability analysis and ALK and ROS1 fluorescence in situ hybridization (FISH) tests were negative. Next, a FusionPlex Sarcoma kit (Archer DX) was 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 next-generation sequencing (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.

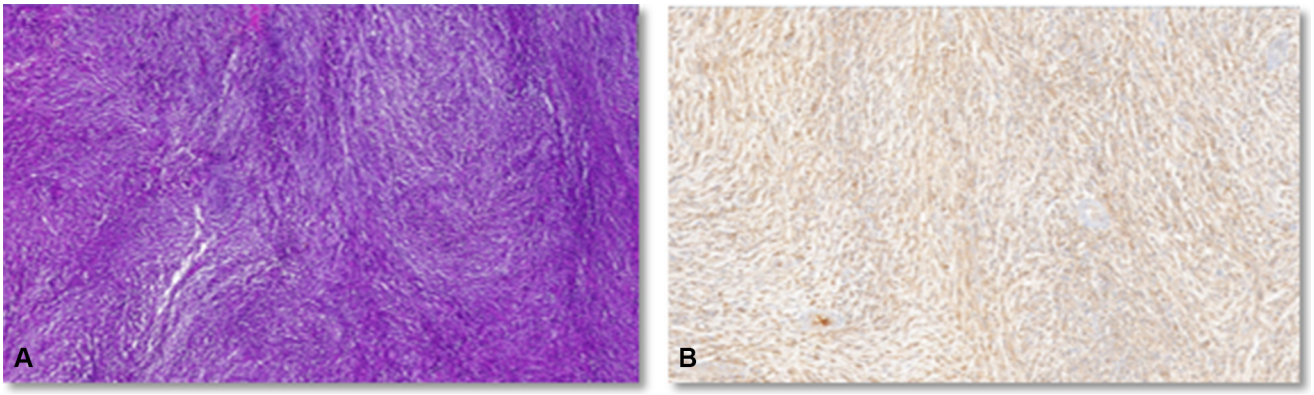

FIGURE 2. Hematoxylin and eosin staining of the tumor reveals spindle cells associated with a mixed chronic inflammatory infiltrate (A). ALK staining shows a low level cytoplasmatic expression (B). *ALK*, Anaplastic lymphoma kinase.

Postoperatively, the patient 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 4 years of follow-up, no relapse had occurred.

Case Presentation 2

A 5-year-old boy had recurrent left lower lobe pneumonia that always improved under the administration of antibiotics. During his last episode, inflammatory parameters stayed elevated (C-reactive protein 142 mg/dL, 17 10^3/mm^3 white blood cells 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 magnetic resonance imaging (MRI) scan showed a cystic lesion (4 × 2.7 cm) that 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 demonstrate the presence of an atypical mycobacterium or tuberculosis. Neuroblastoma was ruled out after negative 24-hour (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 seemed unsafe and nonfeasible. 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, Massachusetts, 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 (Vysis LSI ALK [2p23] dual-color break separate rearrangement probe, Abbott ref. 05J89-001). Biannual PET-CT and MRI showed no recurrence, up to 10 years.

Case Presentation 3

A 28-year-old nonsmoker woman complained of left thoracic pain with nocturnal cough and dyspnea. A thoracic CT demonstrated a pleural mass in the left fissure (66 × 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 revealed an IMT, probably from pleural origin (although 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 nonproductive 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

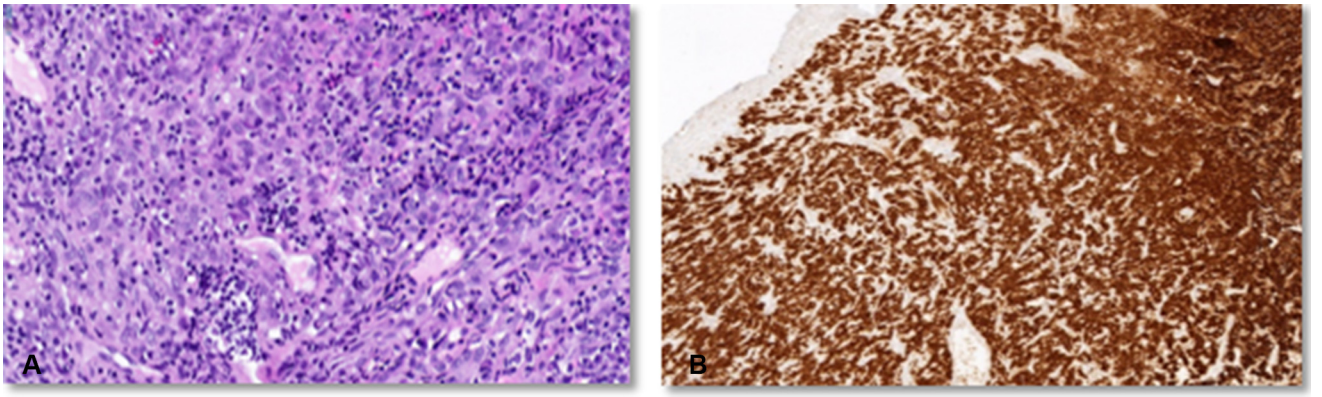

FIGURE 3. Hematoxylin and eosin staining of the tumor cells with a poorly delimited pale eosinophilic cytoplasm and elongated, monomorphic nuclei (A). ALK staining shows a diffuse positive nuclear staining (B). *ALK*, Anaplastic lymphoma kinase.

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 3, *A*). There were no signs of lymphovascular invasion or invasive growth in the lung parenchyma. ALK staining showed a diffused strong positive expression (Figure 3, *B*). FISH tests showed an ALK positivity in 78% of the analyzed nuclei. A comparative genomic hybridization test could not be performed due to insufficient DNA material.

A PET scan and MRI of the brain didn't reveal metastases. Due to the localization and the involved margins after the former rigid bronchoscopic loop-resection, an excision of the membranous 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, 2 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 4); 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 peribronchial and not exclusively endobronchial. There was no parenchymal involvement. The patient recovered well from the procedure. Thoracic CTs until 4 years' postoperatively did 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 PDGFRb.[2] 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 4 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

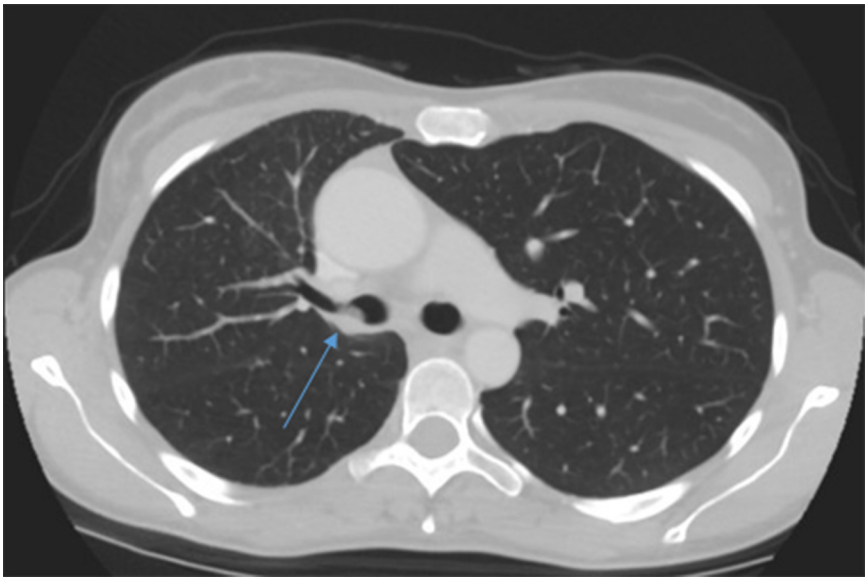

FIGURE 4. Thoracic computed tomography scan showing the bronchial tumor (*arrow*) starting from the lobar bronchus of the right lower lobe. Extension to the middle-lobe bronchus cannot be ruled out.

diagnostics were performed with the differential diagnosis of a bronchogenic neurenteric cyst, whereas postoperative pathology was suggestive of IMT. Here, the challenge of the pathologic diagnosis of IMT is highlighted, since multiple pathology departments had to confirm the diagnosis. Since the sensitivity of FISH and NGS (RNA) is greater than immunohistochemistry (smooth muscle actin, pan-keratin, ALK, etc), it is always advisable 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 in origin. Biopsies were

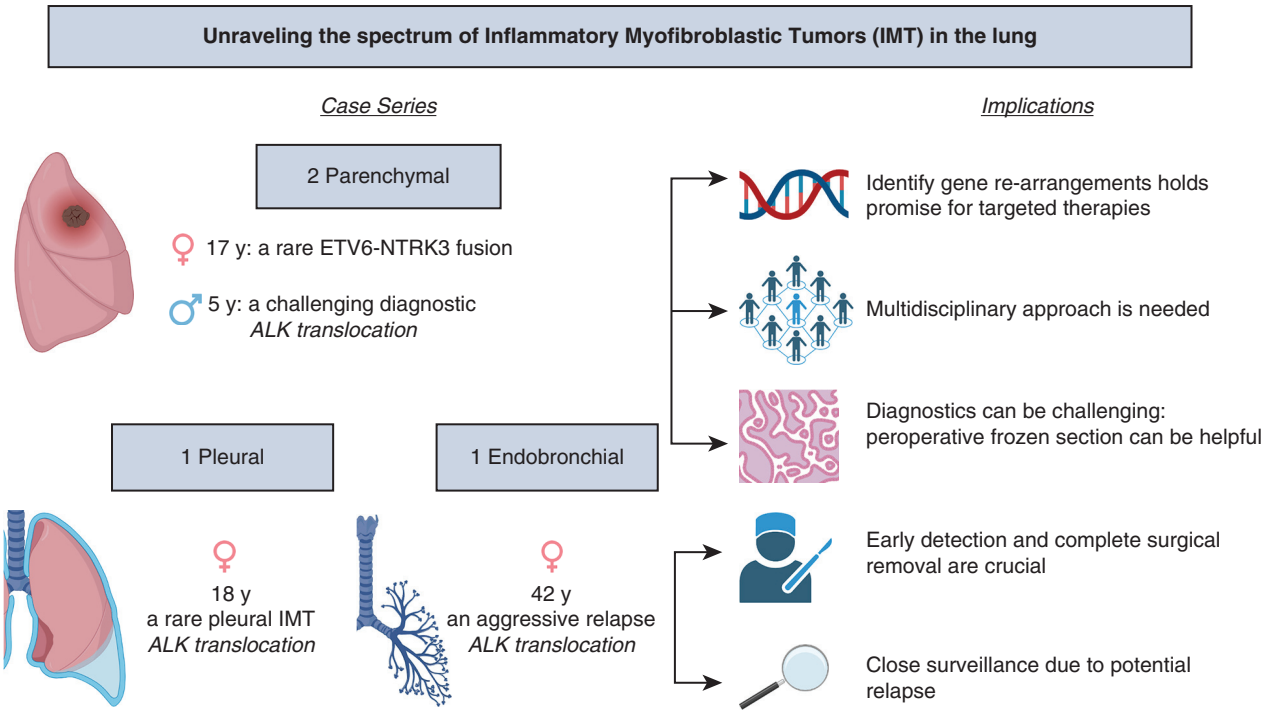

FIGURE 5. Four rare cases of IMT in the lung with the diagnostic and therapeutic consequences. *IMT*, Inflammatory myofibroblastic tumor; *NTRK*, neurotrophic tyrosine receptor kinase; *ALK*, anaplastic lymphoma kinase.

TABLE 1. Diagnosing pulmonary IMT (including pleural and endobronchial)

		Imaging			Biopsy	
Symptoms	**Laboratory tests**	**CT thorax**	**MRI thorax**	**PET-CT**	**Options**	**Pathology**
Cough Chest pain Dyspnea Hemoptysis Fever Malaise Weight loss	Elevated CRP, sedimentation, and WBC Normo-, hypochromatic, or microcytic anemia Thrombocytosis Hypergamma-globulinemia	Solitary, well-circumscribed, peripheral Mostly in lower lobes Unusual calcifications (15%) Heterogeneous or homogeneous enhancement pattern	Low intensity on T2-weighted images Targetoid, hetero-, or homogeneous mass Hyper- or hypovascularization With or without calcifications	Active on PET-CT Staging by Pathologic Soft Tissue Stage Classification (pTNM; AJCC 8th Edition)	Pulmonary/pleural: CT-guided biopsy Endobronchial: Rigid bronchoscopic loop resection or biopsy Transbronchial biopsy When in doubt: intraoperative frozen section	Immunohistochemistry (SMA, pan-keratin, ALK, etc) NGS (ALK gene, ROS1, PDGFRβ, RET, and NTRK)

IMT, Inflammatory myofibroblastic tumor; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography; *CRP*, C-reactive protein; *WBC*, white blood cells; *AJCC*, American Joint Committee on Cancer; *SMA*, smooth muscle actin; *ALK*, anaplastic lymphoma kinase; *NGS*, next-generation sequencing; *ROS*, reactive oxygen species; *PDGFRβ*, platelet derived growth factor receptor beta; *RET*, rearranged during transfection; *NTRK*, neurotrophic tyrosine receptor kinase.

inconclusive. Following multidisciplinary consultation, the challenging mass was resected. On pathology, IMT was diagnosed, presumably but not conclusive, from pleural origin. The case enhances both the difficulty of interpretating 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.

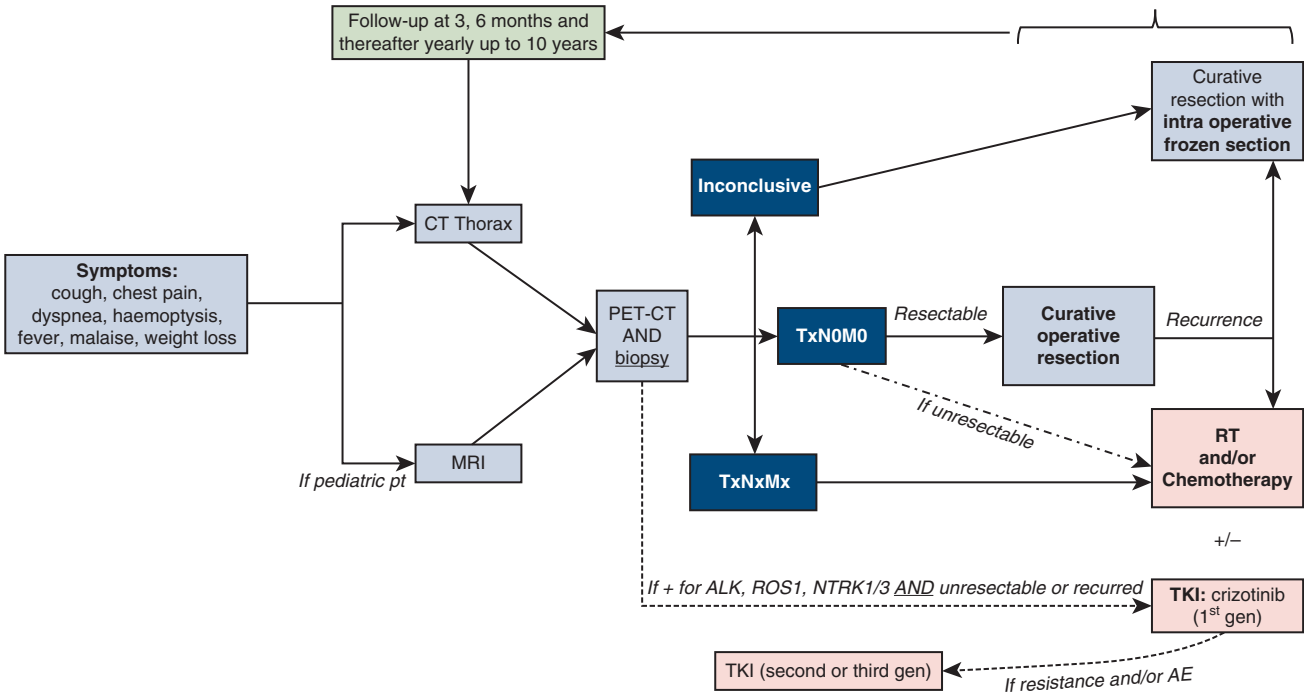

FIGURE 6. Overview of work-up for pulmonary IMT. *pt*, Patient; *RT*, radiotherapy; *TKI*, tyrosine kinase inhibitor; *AE*, adverse events; *IMT*, inflammatory myofibroblastic tumor.

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 tyrosine kinase inhibitor like crizotinib could have been given following the Food and Drug Administration 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. An overview of all cases can be found in Figure 5.

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 of the 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 bronchoscopy with loop resection (or biopsy) can be done, or, if necessary, a bronchoscopic transbronchial biopsy. At pathology, like described previously, immunohistochemistry (smooth muscle actin, pan-keratin, 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 fludeoxyglucose–PET-CT in IMT, with some studies revealing significantly elevated standardized uptake values. The reported standardized uptake 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 fludeoxyglucose–PET/CT scans. In addition, 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, remains in doubt, a surgical resection should be performed with an intraoperative 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, intraoperative frozen section can help in such cases. When in doubt, we suggest performing an endobronchial resection. We recommend a follow-up with CT thorax at 3 and 6 months and thereafter every year over 10 years. We would not recommend 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 cases 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. Although 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.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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