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Inflammatory myofibroblastic tumor of the lung

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Abstract

Inflammatory myofibroblastic tumors (IMT) of the lung, first reported in 1939, are considered a subset of inflammatory pseudo-tumors. They are a distinctive lesions composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils. IMTs may be benign, invade surrounding structures, undergo malignant transformation, recur or may even metastasize. They can occur due to a genetic mutation or can occur secondary to infectious or autoimmune diseases. Patients may be asymptomatic, or present with cough, hemoptysis, dyspnea, pleuritic pain, constitutional symptoms or pneumonia. In this article we review the pathophysiology, genetics, clinical presentation, imaging findings of IMT of the lung. We also discuss the various surgical and non-surgical treatment options and the prognosis associated with this disease.

Key words: inflammatory myofibroblastic tumor of the lung (IMT), inflammatory pseudo-tumor (IPT), pulmonary neoplasm, ALK, bronchoscopy

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Introduction

Inflammatory pseudo-tumors (IPT) were first described in 1905, in the orbital tissues of four patients, with infiltration of the soft tissue with lymphocytes [1]. They were labeled as 'pseudo-tumors' because they clinically and radiologically mimicked malignancies [2]. Inflammatory myofibroblastic tumors (IMT) of the lung, first reported in 1939 [3], are considered a subset of these IPTs. They are a distinctive lesions composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils [4].

IMTs account for 0.04 to 0.1% of all pulmonary neoplasms [5, 6]. They are more common in children and are the most common pediatric primary lung lesion [7, 8]. IMTs are usually benign and resection achieves complete cure. However, there are times when they invade surrounding structures, undergo malignant transformation, recur [9, 10] or may even metastasize [11, 12].

IMTs have been synonymously referred to as pseudo-sarcomatous myo-fibroblastic or fibro-myxoid lesion, plasma cell granuloma, fibrous xanthoma, plasma cell pseudosarcoma, lymphoid hamartoma, myxoid hamartoma, omental mesenteric myxoid hamartoma, inflammatory myofibrohistiocytic proliferation, benign myofibroblastoma, and inflammatory fibrosarcoma [4, 9, 13].

Pathophysiology and genetics

The exact pathophysiology and mechanism of neoplasia in IMTs is unknown. Several genes and chromosomal abnormalities have been found

to be associated with IMTs. Anaplastic Lymphoma Kinase (ALK) gene locus on 2p23 encodes a classical receptor tyrosine kinase (RTK) in mice and humans. An ALK rearrangement is discovered in approximately 40–50% of IMTs [14–17], but more commonly in younger population [18]. ALK rearrangements produce fusion proteins that constitutively activate tyrosine kinase, similar to its action in anaplastic large-cell lymphoma, diffuse large-cell lymphoma and non-small cell lung cancer (NSCLC) [18, 19]. As will be described later, the ALK-RTK can be a target for newer drug therapies.

ROS-1 is a receptor tyrosine kinase (RTK) of the insulin receptor family. Chromosomal rearrangements involving the ROS-1 gene, on chromosome 6q22, were originally described in glioblastomas as well as non-small cell lung cancers (NSCLC) [20]. Some IMTs without ALK rearrangement (ALK-negative) demonstrate ROS-1 gene fusions. One study reported that 4/9 (44%) of ALK-negative tumors had distinct *ROS1* fusions [21]. There have been some rare cases of IMT that have been negative for ALK and ROS-1 mutations [22].

A subset of IMT lack ALK oncogenic activation but contain rearrangements targeting the HMGIC (also known as HMGA2) gene on chromosome 12q15. Chromosomal aberrations involving this region are very frequent among other benign tumors, such as lipomas, uterine leiomyomas, or pulmonary chondroid hamartoma [23]. There has been a significant association between translocations in IMT and a high rate of aneuploidy [24], the presence of which correlates well with local recurrence and more aggressive biologic behavior [13]. The presence of hyperdiploidy serves as an indicator of the neoplastic nature of IMTs. Derivative of Chromosome (Der9) was reported in one case of an omental-mesenteric IPT [25]. It was an extra chromosome that evolved from a translocation between the long arm of chromosome 2 and the short arm of chromosome 9 [(2; 9) (q1, 3; p2, 2)]. Other mutations such as PDGFR-*β* fusion have also been reported in some IMTs [21].

Association with other diseases

Multiple infections including pulmonary tuberculosis, *pseudomonas* lung infection, *moraxella catarrhalis*, *actinomycetes, mycoplasma*, *mycobacteria*, *Epstein-Barr virus* and *human herpes virus 8* (*HHV-8*) have also been reported with IPTs [10, 26–40].

Patients with autoimmune conditions such as Sjörgen's syndrome have also been reported to have

lung IMTs [41] and IPTs in choroid plexus [42], liver [43] and pancreas [44]. In one patient with lung IMT, concurrent B-cell lymphoma was seen [9]. IgG4 syndrome [45, 46] has been reported with IPTs; these tumors have been seen to form a subset of this syndrome. Pulmonary and extra-pulmonary IMTs have also been reported following hematopoietic stem cell [47–49], graft versus host disease [50] and solid-organ transplant [51–54].

Classification

The classification of IMTs is listed in Table 1.

Clinical features

They may be asymptomatic, or present with cough, hemoptysis, dyspnea and pleuritic pain [5, 56]. Systemic symptoms such as fever, weight loss, malaise and fatigue can be seen in 15–30% of patients. Some may present with recurrent pneumonias [57, 58].

Imaging

Pulmonary IMTs occur more frequently in the lower lobes with a predilection for peripheral lung parenchyma and sub-pleural locations [7, 59]. On chest radiographs, pulmonary IMTs appear as solitary, circumscribed, lobulated lesions preferentially localized to the lower lobes, occasionally with pleural effusions (Fig. 1) [56]. When IMT presents as a solitary pulmonary nodule, the main radiologic differential diagnosis includes a primary or secondary neoplasm, hamartoma, hemangioma, chondroma, and pulmonary sequestration [60, 61].

On computed tomographic (CT) scans, inflammatory pseudotumors have a variable and nonspecific appearance, but most commonly they appear with heterogeneous attenuation and enhancement (Fig. 2A–C). On T1-weighted magnetic resonance (MR) images, these tumors have intermediate signal intensity and high signal intensity on T2-weighted images [60]. Calcification within the lesion occurs more frequently in children than in adults (Fig. 2A, B). The pattern of calcification can range from an amorphous, mixed, or fine fleck-like pattern to heavy mineralization.

IMTs can be discovered bilaterally, with endobronchial lesions causing atelectasis and in the pulmonary arteries [60, 62–64]. IMTs may show uptake of fluorodeoxyglucose; and it may be used to monitor response to therapy [62, 65, 66].

Table 1. Classification of IMT's

(A) Earliest classification by Cerfolio *et al.* [5]	
Non-invasive IPT	Invasive IPT
Asymptomatic patients	Younger patient with systemic symptoms of fever, fatigue, or weight loss
Small lesions that do not invade surrounding structures	It is large and may invade local mediastinal structures or the chest wall Grossly, it is an invasive tumor that grows through tissue planes Pathologically, it is characterized by nuclear atypia and a high number of mitotic figures
Usually easily removed by wedge resection	Usually requires a lobectomy or pneumonectomy for complete removal and may also require a concomitant chest wall resection

(B) Classification by Matsubara *et al.* [55]		
Organizing pneumonia	Fibrous histiocytoma	Lymphoplasmacytic
Intra-alveolar lymphohistiocytic inflammation converting peripherally to intra-alveolar fibrosis and centrally to interstitial fibrosis (because of fibroblasts proliferation)	Predominant spindle cell proliferation, histiocytes in a storiform pattern and loss of the alveolar architecture	Predominant lymphocytes and plasma cells with little fibrosis

(C) 3 basic variants of IMT [4] as per WHO classification of soft tissue tumors		
Resembling nodular fasciitis	Resembling fibrous histiocytoma or fibromatosis	Resembling scar or desmoid tumor
Loosely organized myofibroblasts in an edematous myxoid background with plasma cells, lymphocytes, eosinophils, and blood vessels	Dense aggregates of spindle cells arrayed in a variable myxoid and collagenized background admixed with a distinctive inflammatory infiltrate, diffuse clusters of plasma cells, and lymphoid nodules	Collagen sheets with scattered plasma cells and eosinophils

Figure 1. Chest X-ray showing well circumscribed right lower lobe lesion

Interestingly, a positive uptake in 111 In-Diethylene triamine pentaacetic acid (DTPA)-D-Phe1 scan (Octreoscan) has been described implying response to somatostatin analogue receptors [67].

Associated serum biochemistry and histopathology

Laboratory evaluation may reveal microcytic anemia; increase in acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); thrombocytosis and polyclonal hypergammaglobulinemia. These findings have been attributed to overproduction of interleukin (IL)-6 [39, 57, 68].

On biopsy, the predominant cells seen are spindle cells. They are seen as interlacing fascicles among a polymorphous inflammatory infiltrate consisting of mature plasma cells and small lymphocytes [10, 12]. Spindle cell proliferation is noted to be more marked in IMT, whereas lymphoplasmacytic infiltration is more prominent in IPTs [69]. An example of histopathology slides including immunohistochemistry from a patient with IMT is demonstrated in the attached figures (Fig. 3, 4A, B, 5–7). On immunohistochemistry (IHC), virtually all IMTs show reactivity for vimentin. The reactivity for smooth muscle actin and muscle specific actin varies in pattern. Desmin and focal cytokeratin immunoreactivity is identified in some cases. Myogenin, myoglobin, and S100 protein are negative [4, 12].

ALK expression may be negative by IHC; rearrangement for ALK locus by fluorescence in situ hybridization (FISH) may be required [39] or newer IHC methods may have to be adopted [70]. Another difference between IPTs and IMTs is that on the basis of IHC and FISH characteri-
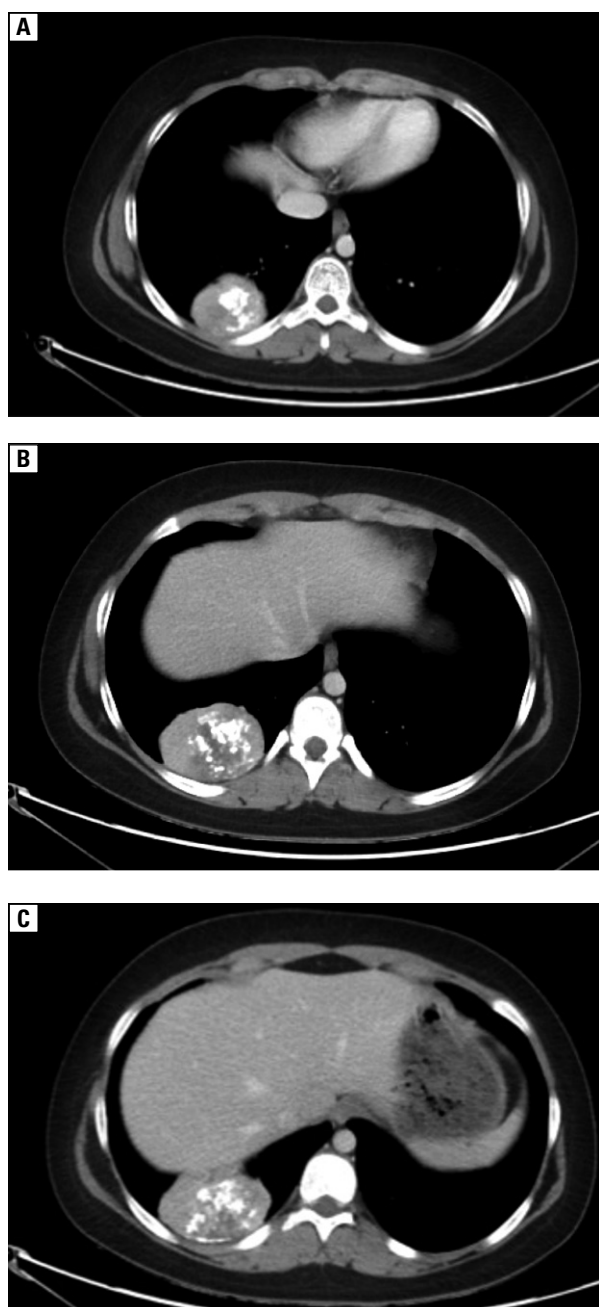
Figure 2A–C. Computed tomography of the chest showing a mass in the right lower lobe with interspersed calcification

Figure 3. Low magnification image showing extension of the tumor extending to the visceral pleura indicated by the black arrows

hyaluronan as a surrogate marker that correlated with changes in the IMT [14]. This needs further investigation.

Treatment

Surgery is considered the mainstay of treatment. If complete resection is not possible, due to anatomic location or co-morbidities, then medical therapy in conjunction with radiation therapy could be considered.

Surgery

Complete surgical resection, when possible, is the best method for diagnosis and treatment [56, 61] (Fig. 4A, B). Lobectomy and pneumonectomy should be performed if required for complete cure. A recurrence rate of 8% was reported with a primarily surgical approach. However, it is unclear if the recurrence was local or distant [9].

Bronchoscopy and endobronchial resection

Rigid bronchoscopy and endobroncial resection (by surgical excision or laser) has been successful for IMTs confined to the trachea and smaller airways [71–74]. In some cases, this has been combined with use of steroids, with mixed results [75]. These patients should also be followed closely and may require more extensive surgery if persistence of the lesion is seen [76].

Chemotherapy

Chemotherapy is useful in cases of multifocal, invasive lesions or in cases of local recurrence [77]. Carboplatin and Paclitaxel have been reported to be useful in some cases [78], but this response does not appear to be generalizable to all cases [79].

stics, IMTs have not been found to always be IgG4 related [46]. As seen later, this fact may explain the response to steroids.

Prior to surgery, it is recommended to have liver function testing, pulmonary function testing and staging CT scans of the chest and upper abdomen. This helps to evaluate for concurrent IPTs/IMTs in other parts of the body [5]. Since morphological features do not predict biologic behavior, and the ploidy of the tumor needs to be determined [13]. One study reported serum
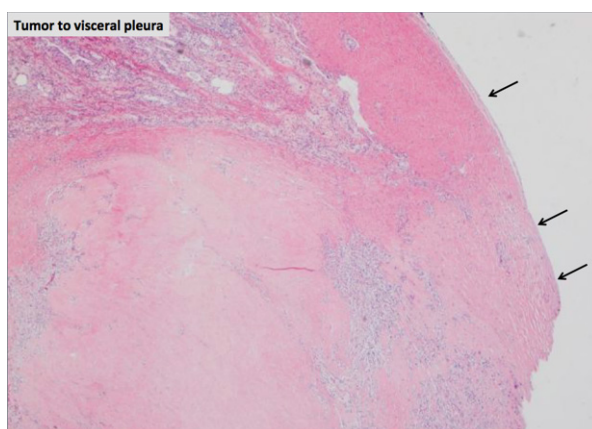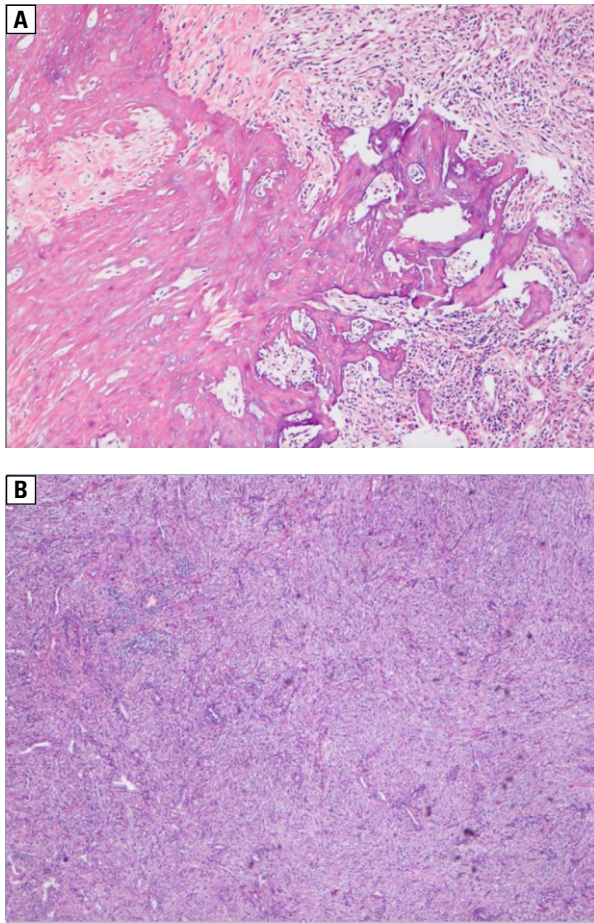
Figure 4A, B. Histopathology of the tumor demonstrating spindle cells

Figure 5. Black arrows represent myofibroblastic cells: spindle cells with long cytoplasmic processes which are characteristic in IMT. White arrows pointing to plasma cells with characteristic perinuclear cytoplasm which are often seen in IMT

Arrows represent infiltrative inflammatory cells around a bronchiole that shows mucus plugging with inflammatory cells

Figure 6. Arrows represent infiltrative inflammatory cells around a bronchiole that shows mucus plugging with inflammatory cells

Steroids

The use of steroids for IMTs is controversial. They were initially recommended to reduce surrounding inflammation, particularly in CNS IMTs [9]. IMT response to steroid therapy [68, 80] and steroids along with antibiotics [10], has been well-documented. One case of recurrent IPT, 11 years after steroid therapy, responded to repeat steroid therapy [25]. Some believe that the cases of IPTs/IMTs that responded to steroids could be based on the fact that they are IgG4-related, and this needs to be confirmed with histopathology [81]. However, other studies have reported worsening of IMT with steroids [82, 83]. Moon *et al.* [83] reported aggravation of pulmonary and bone metastases, as evident by radiologic worsening on bone scan and CT scan, as well as increased fibroblastic cell proliferation in cultures, in the presence of dexamethasone. However, we need larger studies to make determination of the efficacy of steroids for IMTs.
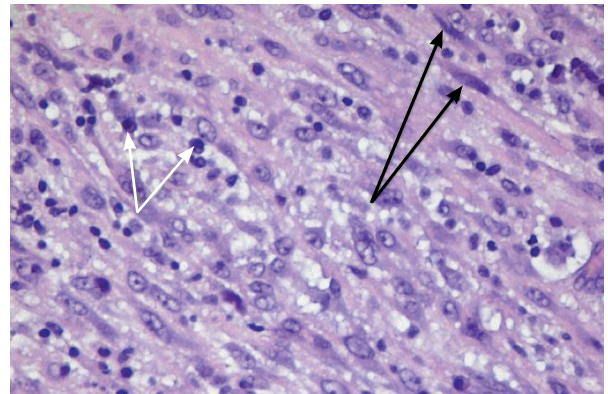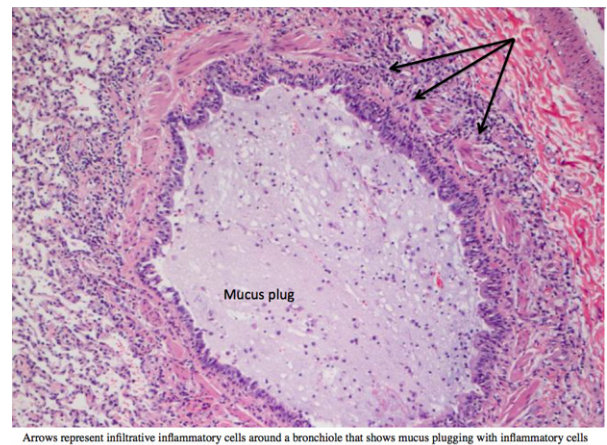
Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs like Celecoxib have been used for some cases of histologically-proven IMT that are negative for ALK and ROS-1 mutations [22, 84]. This was based on the hypothesis that NSAIDs inhibit cyclo-oxygenase-2 (COX-2) enzyme and vascular endothelial growth factor (VEGF) signaling, thus interfering with angiogenesis. It was also observed that the level of ALK positivity in these cases did not correlate with the intensity of COX-2 or VEGF staining [85].

ALK RTK inhibitors and ROS-1 TK inhibitors

ALK RTK inhibitors (Crizotinib, Alectinib and Ceritinib) have been noted to be effective for
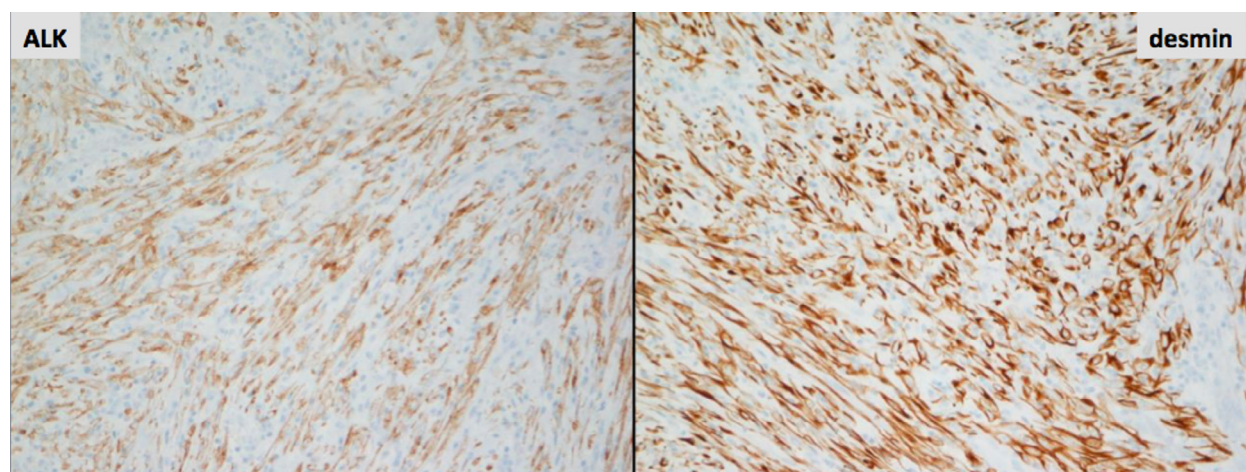
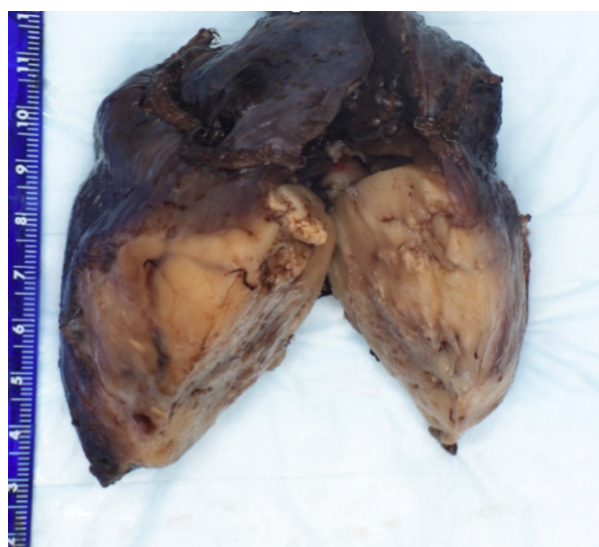**Figure 7.** ALK and desmin staining of histopathologic sample

Figure 8. Gross pathology sample of a surgically removed IMT from a young adult

extra-pulmonary [86–88] and pulmonary IMTs [15]. They may be effective agents for patients with advanced or potentially unresectable ALK-rearranged IMTs, regardless of the location of the primary lesion [15]. Crizotinib has also proven to be effective in IMTs harboring ROS1 kinase fusions [21, 89].

Radiation

Radiation treatment has been shown to be of some benefit in pulmonary IMT [90, 91]. Failures of radiation therapy have, however, been reported suggesting that surgical excision should be primary therapy [81]. Radiation is typically reserved for palliation, to alleviate the mass effect of the IMT, or in conjunction with chemotherapy for cure in patients who are not amenable to resection [9]. As

with chemotherapy, there is currently no evidence to support routine use of radiotherapy in patients who have complete resection.

Prognosis

Pulmonary IMT, if left untreated has shown an approximately 8% rate of growth on follow-up studies. In some cases of pulmonary IMT, spontaneous resolution has also been observed [92–94]. Prognosis is excellent after radical surgical excision, with 5-year survival rates greater than 91% [5, 95–97]. Patients who underwent complete resection showed better survival rates [12]. One study reported a 60% recurrence rate in those receiving incomplete resection [5]. Interestingly, IPTs confined to the lung recurred less frequently than extra-pulmonary IPTs; but, if the IPT spread outside the lung, it recurred more frequently than extra-pulmonary IPTs that had spread to different organs [98].

A combination of cellular atypia, ganglion-like cells, TP53 expression, and aneuploidy may help to identify IMT with a more aggressive potential [4]. *ALK*-positive IMT is associated with better prognosis than *ALK*-negative IMT, as ALK-negative is associated with higher rate of metastasis and resistance to therapy [69]. Pulmonary IMT patients should have long-term follow up, due to the risk of recurrence and sarcomatous transformation [99]. Sarcomatous transformation has also been noted in extrapulmonary tumors [100].

Conclusion

Inflammatory myofibroblastic tumors (IMT) of the lung are a distinctive lesion composed of

myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils. IMTs may follow a benign course, be locally invasive or metastasize. Patients may be asymptomatic, or present with cough, hemoptysis, dyspnea, pleuritic pain, constitutional symptoms or pneumonia. Diagnosis is predominantly made using various imaging modalities and with histological confirmation. Genetic testing should also be conducted to assess for the possibility or targeted adjuvant therapies. Primary treatment of choice is surgical resection as well as chemotherapy. Though rare, IMT should be on the differential in patients who clinically present with signs and symptoms of lung mass.

Acknowledgements

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