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REVIEW PAPER

Pulmonary inflammatory myofibroblastic tumor in children

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ABSTRACT

Inflammatory myofibroblastic tumor (IMT) is a rare neoplasm characterized by mesenchymal spindle cell proliferation with a marked inflammatory infiltrate component. Although the exact etiopathology of pulmonary IMT is still not clear, gene fusions involving anaplastic lymphoma kinase (ALK) or ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), neurotrophic tyrosine receptor kinase (NTRK), platelet-derived growth factor receptor (PDGFR) and rearranged during transfection (RET) have been recently detected in immunohistochemical assessment of this lesion. Due to its nonspecific clinical or radiological presentation, the diagnosis of IMT primarily depends on histopathological findings. Surgery remains the mainstay of treatment and provides the best chance to limit recurrence. In unresectable lesions or multifocal/metastatic disease, treatment with chemotherapy or ALK, ROS1, RET and NTRK inhibitors is recommended. The prognosis in children with IMT is generally perceived as favorable, although local invasion and metastasis have been reported.

KEY WORDS:
inflammatory pseudotumor, plasma cell granuloma, inflammatory myofibroblastic tumor.

INTRODUCTION

An inflammatory myofibroblastic tumor (IMT) is a mesenchymal tumor of intermediate malignancy composed of myofibroblastic and fibroblastic spindle cells, usually accompanied by infiltrate of plasma cells, lymphocytes and eosinophils [1, 2]. It is mainly a monoclonal tyrosine-kinase-driven neoplasm characterized by a rearrangement of the anaplastic lymphoma kinase (ALK) gene with various partner genes or fusions involving ROS proto-oncogene 1 receptor tyrosine kinase (ROS1), neurotrophic tyrosine receptor kinase (NTRK), platelet-derived growth factor receptor (PDGFR) and rearranged during transfection (RET). It generally takes a benign course, but it can be locally aggressive. In 5% of cases IMT has a risk of metastases [1–11]. Although IMT can occur in variable anatomic locations, it is more often found in the lung and liver [12]. Pulmonary IMT was the first described case of this lesion. Subsequently, for many years, this lesion was considered as a reactive change mimicking neoplasm. In recent years, attention has been paid to neoplastic behavior of some cases, which resulted in the emergence of IMT from the group of inflammatory pseudotumors (IPT). IMT has been categorized by the World Health Organization as a neoplastic fibroblastic/myofibroblastic tumor with intermediate biological potential with a tendency for local recurrence and a low risk of distant metastasis [1, 2, 13, 14]. Despite this classification, the terms IMT and IPT have been used interchangeably in the past. This may lead to confusion regarding the true incidence of IMT and its behavior.

An inflammatory myofibroblastic tumor has a heterogenous clinical manifestation. IMTs of the lung in the pediatric population most often are benign lesion and represent about 50–70% of all primary benign lung tumors in this age group [15].

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Due to its rarity, non-specific and wide clinical presentation, the diagnosis and management of pulmonary IMT are difficult. Therefore, the familiarity with this subject, the understanding of the pathophysiologic nature and natural history of pulmonary IMT can support an accurate diagnosis and help choose the best therapeutic approach.

ETIOLOGY AND PATHOGENESIS

The exact pathomechanism of neoplasia in IMTs is still unknown. Several chromosomal abnormalities have been detected. Most common rearrangements involving the ALK locus on 2p23 resulting in constitutive tyrosine kinase activation were found in approximately 50% of cases [5–7]. ALK expression in IMT is more common in younger patients, but is not restricted to this population [16]. Fusions involving other kinases, such as ROS 1, NTRK, PDGFR and RET, have also been identified in IMTs [3, 8–11].

Kinase fusions play an important role in the biology of IMTs, particularly of the lung. In a study by Chang *et al.* it was found that all lung IMTs harbored detectable kinase fusions, with 67% having an ALK fusion, 18% a ROS1 fusion, 9% a NTRK3 fusion, 3% a RET fusion and 3% a novel mutation resulting in an alternative transcription initiation in ALK [17].

CLINICAL FEATURES

The clinical picture of pulmonary IMT is non-characteristic and variable. General symptoms such as fever, lethargy or growth impairment are common clinical findings. Their occurrence is related to the production of inflammatory mediators, particularly interleukin-1 and interleukin-6 [12, 18–20]. Some patients develop paraneoplastic syndrome such as clubbing associated with digital osteoarthropathy, which usually resolves after complete excision of the lesion and may reappear as a sign of recurrence [21].

Respiratory symptoms depend primarily on location of the lesion. Pulmonary IMTs usually occur peripherally, grow slowly and show only a few respiratory symptoms and fever. Cough, chest pain, shortness of breath, hemoptysis or sputum are most often noted. Therefore, the bacterial pneumonia is usually suspected, and the antibiotic treatment is applied before a definitive diagnosis is made [12, 22].

In 10–12% of cases, pulmonary IMT occurs endobronchially and may lead to airway obstruction or even respiratory distress. Hemoptysis and cough may also occur due to bronchial wall irritation [15, 18, 23]. Aggressive manifestations of pulmonary IMT with invasion of surrounding structures of the mediastinum, diaphragm and chest wall have also been observed [24].

Some lesions are multifocal. A common association of tumor locations is the lung and head/neck, which was found in up to 21% of cases in a study by Dalton *et al.* In the described cases, the only symptoms of the lesions were neurological symptoms and no respiratory symptoms occurred [12]. Giuseppucci *et al.* reported two cases of IMT that occurred with fever and seizures, in which IMT of the brain was initially diagnosed and the lesion in the lung was detected in further diagnostic workup. No respiratory symptoms were noted in both cases. Therefore, the authors suggested that brain computed tomography should be carefully considered in patients with pulmonary IMTs, particularly in the case of invasion of cardiac structures [25].

Finally, asymptomatic cases, discovered incidentally on radiological chest examination, have also been reported and ranged from 11 to 38% of all pulmonary IMTs [15, 18, 26].

DIAGNOSTIC FINDINGS

Laboratory evaluation may be normal or reveal microcytic anemia, leukocytosis, thrombocytosis, polyclonal hypergammaglobulinemia or elevated acute phase reactants such as erythrocyte sedimentation rate and C-reactive protein [12]. These findings seem to be attributable to IL-1 and IL-6 overproduction [20].

Although the radiologic features of IMT are variable and nonspecific, they allow one to define the tumor anatomy and are helpful in planning surgical treatment.

Pulmonary IMT typically occurs as a solitary, rarely multiple, well-circumscribed peripheral mass with lower lobe predominance, occasionally with pleural effusions [27]. In some cases, pulmonary IMT presented as features characterized by poorly defined or irregular contours without completely obliterating the underlying alveolar parenchyma (Figure 1). These lesions have been reported

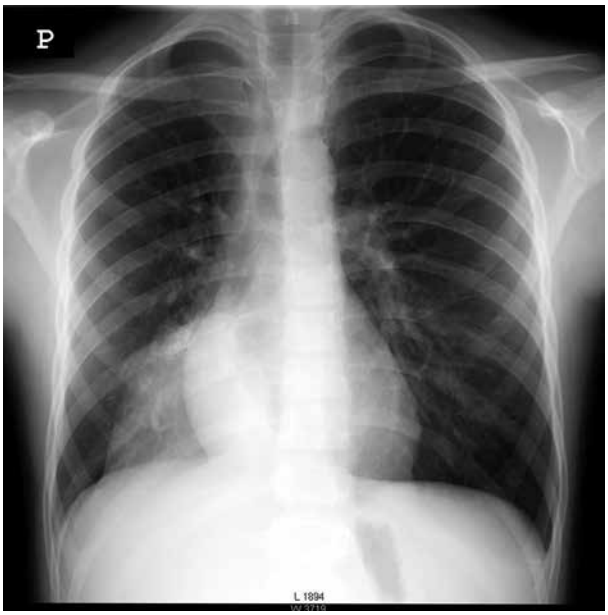

FIGURE 1. Chest radiography of the inflammatory myofibroblastic tumor of the lung. Massive atelectatic-inflammatory changes in the right lower lobe

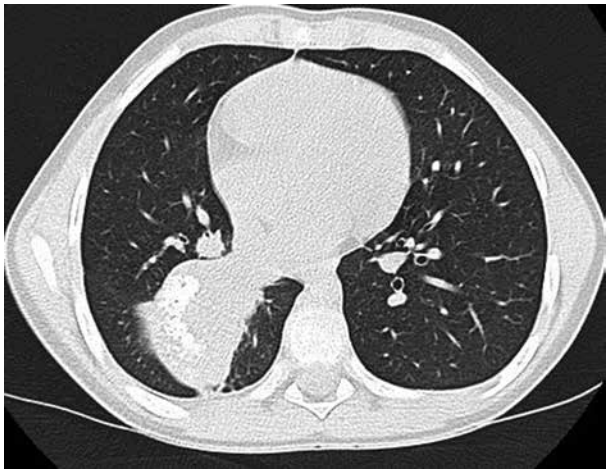

FIGURE 2. Computed tomography of the inflammatory myofibroblastic tumor of the lung. CT image shows presence of a nodule-like lesion with calcifications in the right lower lobe

predominantly in older patients. Aggressive manifestation of IMT mimicking a malignant process was also reported as presence of masses, nodules, pleural lesions or ground glass opacities on radiological images. Calcifications within the lesion, more frequently found in the pediatric than the adult population, may also indicate neoplastic potential. They may have an amorphous, mixed, or fine fleck-like pattern to heavy mineralization [27, 28].

The other nonspecific radiological features noted with IMT include interstitial pneumonia, organizing pneumonia, sclerosing mediastinitis, and bronchovascular abnormalities. In some cases, atelectasis and pleural effusion may occur, particularly in endobronchial location of the tumor [28]. Cavitation and lymphadenopathy have rarely been found with IMT [27].

The CT scans of IMT are usually nonspecific, but most commonly show solid masses with heterogeneous attenuation and contrast enhancement (Figure 2). On magnetic resonance (MR) images the pulmonary IMTs usually have homogeneous intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images compared to skeletal muscle. The degree of signal intensity in the MRI image depends on the degree and the activity of the fibrosis [29].

Positron emission tomography (PET/CT) with fluorodeoxyglucose (FDG) is sensitive but of low specificity for IMT and therefore cannot be applied to distinguish IMT from other pulmonary parenchymal masses. However, it can be useful for identification of primary location of the tumor and distant metastases, evaluation of therapeutic response in patients who have undergone conservative treatment or detection of tumor recurrence [30].

A useful method for evaluation of patients with endobronchial location of IMT is bronchoscopy. It allows one to obtain a biopsy specimen and perform surgical excision of the lesion.

HISTOLOGY

The World Health Organization (WHO) classification placed pulmonary IMT in the group of mesenchymal tumors of the thorax [1, 2]. Histologically, IMT is characterized by presence of an inflammatory infiltrate and spindle cell proliferation, which have storiform or fascicular architecture, oval nuclei, and fine chromatin. The inflammatory infiltrate consists mainly of plasma cells, lymphocytes and eosinophils [31]. Immunohistochemically, IMT is strongly positive for vimentin with variable staining for actin and desmin [32]. However, the morphological presentation of IMT is often heterogeneous and some authors suggest that establishing a diagnosis should be preceded by reference pathologist review of the histopathological sample [33].

Molecular diagnosis of a sample is recommended to identify targetable fusions in IMT including ALK, ROS1, PDGFRb, NTRK and RET. Sequencing technologies may have an advantage as they can be multiplexed and can identify not only fusions but also novel mutations, such as translation initiation mutations, as well as identify resistance mutations in TK binding domains [17, 34].

It is worth mentioning that ALK immunoreactivity is not pathognomonic for IMT and may be present in a wide variety of soft tissue neoplasms other than IMT, but usually at low levels. Moreover, ALK is expressed in the normal nervous system and plays a role in neuronal differentiation. Nevertheless, ALK expression is considered to be useful in establishing the diagnosis of IMT and deciding on treatment with tyrosine kinase inhibitors [35].

Based on the results of the histopathological examination, it is difficult to predict the course of the disease and to assess the risk of recurrence or neoplastic transformation. The possible prognostic significance of ALK expression in IMT has been explored by Coffin *et al.* The authors concluded that ALK-positive IMT was associated with local recurrence. In contrast, the increased risk of distant metastasis was confined to ALK-negative lesions [7]. The combination of features such as atypia, ganglion-like cells, TP 53 expression and aneuploidy may indicate IMT with more aggressive potential [36–38].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis varies depending on the imaging presentation and histologic assessment of the lesions.

Inflammatory myofibroblastic tumor taking the form of a lobular tumor should be differentiated from thoracic congenital malformation and various conditions resulting from infectious or reactive process such as granulomatous inflammation (fungal, mycobacterial, parasitic, sarcoidosis, vasculitis), abscess, pneumonia, septic embolus, infarction or hematoma [15, 24, 27, 39].

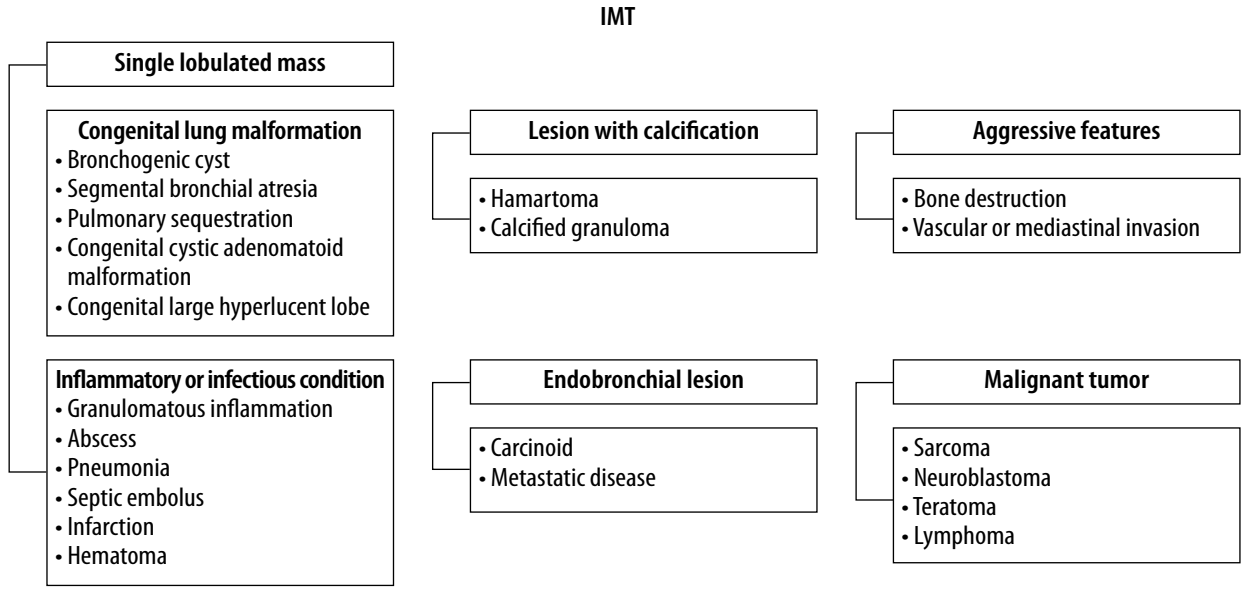

FIGURE 3. The differential diagnosis of inflammatory myofibroblastic tumor (IMT)

In a case of aggressive manifestation of IMT with invasion of surrounding structures of the mediastinum, diaphragm and chest wall, various neoplastic condition should be considered, such as sarcoma, fibrosarcoma, neuroblastoma, teratoma, pleuropulmonary blastoma, lymphoma or metastases [18, 40]. In such cases immunohistochemical studies of lesions may be helpful in distinguishing these entities.

For calcified intraparenchymal mass lesions key differential diagnoses include hamartoma and calcified granuloma.

The differential diagnoses of endobronchial lesion should include carcinoid and metastatic disease (Figure 3) [15].

TREATMENT

According to the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) and Cooperative Weichteilsarkom Studiengruppe (CWS) recommendations, complete surgical excision is the mainstay of treatment and provides the best chance of reducing the risk of recurrence [12, 26, 35, 41]. In cases of lesions limited to the airways, bronchoscopic resection may be considered [25, 42]. No adjuvant therapy after initial R0 (no neoplasm cells) or R1 (microscopic residual disease or regional lymph node spread) resection is indicated [41].

In unresectable cases due to immediate proximity to vital organs or invading surrounding structures, such as extensive mediastinal and central vasculature involvement by the tumor, partial resection with neoadjuvant therapy should be considered [33, 38, 43, 44]. It is usually also indicated for multifocal/metastatic disease.

The armamentarium of systemic therapy has been changed in recent years, and nowadays chemotherapy should been considered in relation to the availability and efficiency of ALK inhibitors [41]. Although various approaches have been used in the past (e.g. anthracycline/ifosfamide-based, or methotrexate and vinorelbine/vinblastine-based), with different clinical outcomes, vinblastine plus low-dose methotrexate is currently recommended as first-line therapy [25, 35, 43–45]. However, the response does not appear to be generalizable to all cases. According to a study by Casanova *et al.* the overall response to chemotherapy was estimated at 64% and was found in 8/10 patients given vinblastine and low-dose methotrexate [33].

The new ALK inhibitors (crizotinib, ceritinib, alectinib, and brigatinib) and, more recently, ROS1, RET and NTRK inhibitors are promising effective agents for patients with ALK positive IMT or for cases with a corresponding molecular abnormality, particularly with an advanced or unresectable tumor. There are several reports showing their efficiency and safety in pediatric patients [33, 34, 46, 47]. However, some aspects related to this therapy still need to be clarified. This includes the availability and cost of ALK inhibitors, duration of treatment and long-term effects. Additionally, the risk of acquired tumor cell resistance developed during ALK inhibitor therapy should be taken into account. There is also a question about treatment of ALK-negative patients and the role of ROS1 and NTRK inhibitors [33, 34, 47].

International cooperation and data collection is a first step to establish common recommendations for management of such rare tumors as IMT. It is worth mentioning that Poland is a member of the CWS group. All patients with IMT should also be registered in the European Soft Tissue Sarcoma Registry (SoTiSAR registry) in Poland.

There are limited literature data describing the use of radiotherapy. Currently it is used vary rarely and re-

served exclusively for cases of aggressive IMT that do not respond to other treatment, e.g. surgery, chemotherapy and kinase inhibitors [33].

The use of systemic steroids for IMT treatment is historical and controversial. There are reports indicating their tumor-promoting effect, and therefore such a therapeutic approach is not recommended [48–50].

Although there are some reports of spontaneous regression of the lesion, experts do not recommend waiting with treatment in the case of suspected IMT [35].

PROGNOSIS

The prognosis in children with IMT after complete surgical resection is generally favorable [33, 35]. Some authors suggested that expression of ALK may be a positive prognostic indicator and does not seem to be related to recurrence or distal metastasis [7]. The overall survival rate was estimated approximately at 90% of cases [15]. However, untreated pulmonary IMT has shown an approximately 8% rate of growth in follow-up studies [12].

The recurrences of pulmonary IMTs, usually between three months and seven years after treatment, most often occurred in children with multifocal expression of the tumor or with incomplete lesion resection [33, 51].

Distant metastases are rare, occurring in less than 5% of cases [12]. Metastatic lesions of IMT are associated with a poor prognosis and an approximately 30-fold increase in recurrence rate [52].

Patients with pulmonary IMT should have long-term follow-up, due to the risk of recurrence and sarcomatous transformation [12]. Therefore, cross-sectional imaging at three months, six months and one year should be performed, followed with yearly ultrasound or cross-sectional imaging for surveillance [12].

CONCLUSIONS

Pulmonary IMT has been considered as a diagnostic challenge due to its rare occurrence and wide range of clinical manifestations. It can be misdiagnosed as bacterial pneumonia, congenital thoracic malformation and a malignant process. Due to its heterogeneous histological presentation, a second opinion from a pathology expert in mesenchymal tumors may be needed to establish a proper diagnosis of IMT. Nowadays, molecular sequencing of IMT is recommended to identify targetable fusions due to the availability of novel, highly efficient ALK inhibitors. However, their role as a first therapeutic option still needs to be clarified, and surgery remains the mainstay of treatment of pulmonary IMT.

DISCLOSURE

The authors declare no conflict of interest.

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