The great pretender - pulmonary inflammatory pseudotumour. Imaging findings with pathologic correlation.

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Learning objectives

- Pathophysiology of pulmonary inflammatory pseudotumour, otherwise known as inflammatory myofibroblastic tumour. The latter is currently the preferred term and will be used further in text.
- Spectrum of radiologic findings.
- Case-based review of imaging findings with radiologic - pathologic correlation.
Background

Inflammatory myofibroblastic tumours (IMT) formerly described as inflammatory pseudotumour, with an unpredictable behavior ranging from benign to low-grade malignant, are classified as intermediate grade tumours, with potential for recurrence and rare metastasis, in the current WHO Classification of Tumours of Soft tissue and Bone (6).

IMT is a rare, usually incidentally diagnosed condition, clinically and radiologically mimicking a malignant process (1). It was first described in the lung in 1939, but other sites, including head and neck, heart, gastrointestinal tract, mesentery, retroperitoneum, hepatobiliary system, genitourinary tract, and soft tissues, can also be involved (2,3).

A number of terms have historically been applied to the lesion, namely, inflammatory pseudotumour, fibrous xanthoma, xanthofibroma, xantogranuloma, histiocytoma, plasma cell granuloma, pseudosarcoma, lymphoid hamartoma, myxoid hamartoma, inflammatory myofibrohistiocytic proliferation, benign myofibroblatoma, and most recently, inflammatory myofibroblastic tumour (7,8).

The lesion affects both sexes, at any ages, with a slight predominance in children and young adults (4,9).

Lung is the most frequent anatomic location for IMTs, which represent about 0.04%-1% of all lung neoplasms (10,11).

In children, inflammatory myofibroblastic tumours account for 20% of all primary pulmonary tumours and 56% of benign pulmonary tumours (8,11).
Imaging findings OR procedure details

Clinical manifestation

Between 30% and 70% of cases are asymptomatic. Symptoms are usually related to lesion's location: parenchymal, mediastinal, or endobronchial. The disease usually manifests with non-specific symptoms such as cough, dyspnea, chest pain, fever, weight loss and hemoptysis (5,8), in some cases with growth retardation, thrombocytosis, iron deficiency anemia or hypergammaglobulinemia (12).

Pathogenesis

There are many uncertainties about the pathogenesis of IMT. Several hypotheses have been proposed such as an auto-immune mechanism or infectious origin, in some instances, it has been associated with trauma, minor surgery, or concomitant malignancy (2-5).

Some studies postulate that IMT is a true neoplasm due to the presence, at the myofibroblastic component, of a fusion gene involving the ALK gene, a tyrosine kinase oncogen located on chromosome 2p23 (4). Other studies suggest that up to 30% of cases are closely related to recurrent respiratory infections which are caused by several microorganisms such as Mycoplasma, Nocardia, Actinomycetes, Epstein-Barr and human herpes virus (5,12). Some IMTs have been found to be associated with IgG4-related sclerosing disease, a systemic disease in which there is extensive IgG4-positive plasma cell and T-cell infiltration of various tissues (5).

Histologic findings

Histologically, an IMT contains cells associated with both acute and chronic inflammation (5). A lesion formed of varying proportions of spindle cells of myofibroblastic type, arranged in a fibrous, myxoid or calcified stroma, associated with an inflammatory component predominantly lymphocytic and plasmocytic, with a variable component of eosinophils (9,12).

IMT includes three main histological subtypes (4,12):

- myxoid vascular,
- compact spindle cell, and
- hypocellular fibrous patterns.
Within any one lesion, the three patterns may be equally represented with one blending into another, or one or two patterns may predominate (12).

IMTs are difficult for a pathologist to diagnose. Transthoracic fine-needle aspiration specimens are non-specific and it is often not possible to identify the disease, therefore final diagnosis is generally obtained on the resected specimen. However, even in such cases, it can be difficult to recognise the disease and to differentiate it from other lesions such as solitary fibrous tumour, lymphoma and fibrosarcoma, also malignant fibrous histiocytoma, malignant plasmacytoma, angiomyofibroblastoma or leiomyoma (4,12). The mode of tumour growth, the low mitotic index, the polyclonality of lymphoid markers and the negativity of CD34 usually remove most of these diagnoses (4).

Currently there are no definite histopathologic, molecular, or cytogenetic criteria to predict the biological behavior of the tumour (6,9).

**Radiological findings**

Inflammatory myofibroblastic tumours are solid masses and due to their variable and nonspecific radiologic aspects it is impossible to differentiate on imaging modalities whether they are benign or malignant (9,13).

Radiological appearance ranges from benign looking solitary peripheral lung nodules to endobronchial nodules in the larger airways or large aggressive looking tumours with invasion and metastases (13).

IMT typically is a solitary, peripheral, sharply circumscribed nodule or mass with lower lobe predominance, measuring 1 to 6 cm in diameter (4,14). Although there could be local invasion and primary involvement of the mediastinum, hilar structures, pleura or diaphragm, these manifestations are unusual (14).

Multiple lesions, calcifications, cavitations and lymphadenopathy are rare (13).

Calcification is more common in children and can have an amorphous, mixed, fine flecklike pattern or be dystrophic. IMTs can also be associated with atelectasis (up to 8%) and pleural effusion (up to 10%), usually unilateral (4,5,12).

**Fig. 1** on page 16 shows a histologically confirmed IMT in a child at baseline and 4 years after an attempted excision.
CASE 1.
Histologically confirmed IMT in a 6 year old girl. Contrast enhanced CT in soft tissue windows in axial (A, C) and coronal (B, D) planes. There was a large heterogeneous left lower lobe mass with amorphous calcification and signs of invasion of adjacent structures (A-B). A radical excision could not be obtained during surgery. 4 years later a local recurrence is seen (C-D).

Fig. 1

References: - Kaunas/LT

Fig. 3 on page 17 shows a case of metabolically active IMT in a young woman.
Contrast-enhanced CT shows the presence of a heterogeneous nodule or mass with variable contrast enhancement (4).

Fig. 4 on page 18 shows a case of IMT in a 58 year old woman without significant contrast enhancement, but with an associated pleural effusion.
CASE 3.
Histologically confirmed IMT in a 58 year old woman. Contrast enhanced CT on soft tissue window in axial (A) and coronal (B) planes. A large, quite homogeneous left lower lobe mass with minor contrast enhancement (asterisk), and a small associated pleural effusion.

Fig. 4
References: - Kaunas/LT

Fig. 5 on page 19 is an example of IMT on posteroanterior and lateral chest film, presenting as an incidental solitary nodule.
Fig. 5

References: - Kaunas/LT

On gadolinium contrast-enhanced MRI IMTs also appear as homogeneous or heterogeneous lesions, with variable enhancement on delayed acquisitions due to the presence of fibrosis. On T1-weighted and T2-weighted sequences, IMTs usually show areas of low signal intensity reflecting the presence of fibrotic tissue (15).

Fig. 2 on page 16 shows images from an MRI study of the same patient as in Fig. 1 on page 16 (6 years later). Note the central hypointense area in the central part in both T1-W and T2-W images consistent with fibrotic tissue.
Fig. 6  on page 20 is an example of a recurrent non malignant, but metabolically active lesion, which histologically was seen as a fibroinflammatory mass.
Fig. 6:

References: Liverpool, UK

Diagnosis

Because of the diversity of clinical and radiological manifestations of IMT, diagnosis is difficult to establish without surgical management (4).

Variable cellular composition of IMT seldom enables diagnosis to be made preoperatively with transthoracic fine-needle aspiration or bronchoscopic biopsy. Moreover, inflammation and fibrosis can sometimes represent a reaction around a malignant tumour (12). Only 6.3% of IMT cases are diagnosed based on analysis of biopsy specimens alone (16). Resection and histological, immunohistochemical investigations are essential to confirm the diagnosis (4,13).

Fig. 7 on page 21 Shows different chest film manifestations of IMT tumours.
**Fig. 7**

*References:* - Kaunas/LT

Fig. 8 on page 22 and Fig. 9 on page 23 (below) show features of histology and immunohistochemistry of IMT.
Histology

All cases had very similar histologic appearances: cellular lesions, the cells are spindle or epithelioid with multiple inflammatory elements, and there was no mitotic activity nor atypical mitosis.

Figure 1 and 2: H+E stain, 20x and 40x magnification. Cellular lesion formed by fibromyxoid stroma with a prominent vascular network. Within the stroma, medium sized monomorphic spindle cells with vesicular nuclei and small nucleole are seen. Among these cells there is a prominent infiltration of eosinophils, plasma cells, lymphocytes, mastocytes and macrophages.

Fig. 8

References: - Kaunas/LT
Treatment

Surgery should be considered as the mainstay therapy to reach a firm diagnosis and attempt a cure in IMT, even in cases of recurrence or metastases (9).

NSAIDs, steroids, chemotherapy, and radiotherapy have been used as adjuvant therapy when feasible (18). However, very scant data are available in the literature on the results of both surgical treatment and other therapies. Results of conservative treatment are extremely variable. The literature reports its inefficacy as well as its occasional ability to reduce lesion size and lead to complete regression. Efficacy of radiotherapy and chemotherapy as alternatives to surgery is controversial (12) and surgery remains the treatment of choice both for diagnostic and therapeutic reasons (11).

Prognosis
Natural history of IMT is extremely variable, ranging from benign lesions with a favorable evolution to large masses with local invasion, distant metastases, and a poor prognosis. In some cases features of local aggressiveness, with infiltration of the pulmonary vessels, heart, chest wall, diaphragm, and vertebrae can be seen; it can relapse, be multifocal, and give distant metastases. Cases of malignant transformation have also been described (9,12).

The prognosis of IMT is dependent on tumour size (less than or equal to 3 cm) and complete surgical resection. The overall 5-year survival rate varies from 74% to 91.3%, according to different authors (4,11,16). Recurrence rate after resection is 4% and appears in locations of incomplete resection (4,11).
**CASE 1.**
Histologically confirmed IMT in a 6 year old girl. Contrast enhanced CT in soft tissue windows in axial (A, C) and coronal (B, D) planes.

There was a large heterogeneous left lower lobe mass with amorphous calcification and signs of invasion of adjacent structures (A-B).

A radical excision could not be obtained during surgery. 4 years later a local recurrence is seen (C-D).

**Fig. 1**

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CASE 1.

Axial plane MRI images: T1-weighted sequence after administration of gadolinium contrast media (E) and T2-weighted sequence at the same position (F). Images were obtained 6 years after the initial diagnosis, chemotherapy and partial resection. The mass has slightly decreased in size since the previous MRI study (not shown). Hypointense area is seen in the central part (arrows) in both T1-W and T2-W images consistent with fibrotic tissue.

Fig. 2

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**CASE 2.**

A 24 year old woman. Contrast enhanced CT in axial plane, lung (A) and soft tissue (B) windows.

In the lingula there is a solitary enhancing mass, which also has high FDG uptake on PET-CT imaging (C). Histopathology results after radical excision showed findings consistent with IMT.

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**Fig. 3**

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CASE 3.
Histologically confirmed IMT in a 58 year old woman. Contrast enhanced CT on soft tissue window in axial (A) and coronal (B) planes. A large, quite homogeneous left lower lobe mass with minor contrast enhancement (asterisk), and a small associated pleural effusion.

Fig. 4
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CASE 4. Histologically confirmed IMT in a 40 year old woman. AP (A) and lateral (B) chest x-ray images showing a solitary “coin” lesion in right upper lobe.

Fig. 5

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Fig. 6:

CASE 5
41y old male, smoker, left upper lobe nodule follow up. Axial (A, D) and sagital (B, E) CT images in lung window. An irregular right upper lobe nodule with possible invasion of the pleura, which had avid FDG uptake on PET-CT imaging (C, F). Right upper lobectomy specimen showed a fibroinflammatory mass and was essentially non-specific with no evidence of neoplasia. Two years later a simmilar appearing mass is seen in right lower lobe.
Fig. 7

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Histology

All cases had very similar histologic appearances: cellular lesions, the cells are spindle or epithelioid with multiple inflammatory elements, and there was no mitotic activity nor atypical mitosis.

Figure 1 and 2: H+E stain, 20x and 40x magnification. Cellular lesion formed by fibromyxoid stroma with a prominent vascular network. Within the stroma, medium sized monomorphic spindle cells with vesicular nuclei and small nucleole are seen. Among these cells there is a prominent infiltration of eosinophils, plasma cells, lymphocytes, mastocytes and macrophages.

Fig. 8

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**Immunohistochemistry (CASE 2):**

The cells of the lesion are positive for ALK (Figure 3). Immunoproliferative marker Ki-67 score is up to 5% (Figure 4). Desmin, CD34, pS100, panCK reactions were negative.

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**Fig. 9**

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Conclusion

Pulmonary inflammatory myofibroblastic tumour should be included in the list of differential diagnoses in children and young adults, presenting with malignant-appearing lung lesion. Despite its usually benign nature, relapse and distant metastases, in some cases, even sarcomatous degeneration can occur, thus surveillance and radiologic awareness are crucial.
References


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