COMENTÁRIO EDITORIAL

Fernando Barata, Denny Marques, Ana Figueiredo
Serviço Pneumologia, Centro Hospitalar e Universitário de Coimbra
fjssbarata@gmail.com

Rare and unpredictable inflammatory myofibroblastic tumor

In this issue of the *Revista Portuguesa de Cirurgia Cardio-Torácica e Vascular*, Cabral D. *et al.* report findings based on a clinical case of inflammatory myofibroblastic tumor.This is a rare and unpredictable case that confounds diagnosis and treatment. Male, 55-year-old, admitted with pneumonia. Three months after a left lower lobectomy a new IMT nodule in left superior lobe was excised. Four months later, endobronchial involvement and liver metastases. Ten months after surgery bone lesion with histology show undifferentiated sarcoma.

Inflammatory myofibroblastic tumor (IMT) of the lung is a spindle cell proliferation of unknown etiology that is most often seen in young children, adolescents, and non-smoking adults. These tumors are relatively common in children, accounting for 20-50% of all pediatric primary lung tumors, however they comprise less than 1% of all adult lung tumors.[1]

There is significant controversy and confusion regarding the pathogenesis and histogenesis of these uncommon tumors or tumor-like masses. Much of the confusion has been caused by the varying degrees of inflammatory cell infiltration noted on pathologic examination and the observation that the disease process, although usually following a benign course, is sometimes invasive.[2]

IMT has been described in a variety of extra pulmonary sites, including the brain, orbit, thyroid, bones, spleen, and lymph nodes.

A variety of terms have been used to describe lesions falling under the category of IMT.The inflammatory infiltrate usually comprised a mixed population of lymphocytes, plasma cells, histiocytes, and occasional eosinophils. The early terminology "pulmonary plasma cell/histiocytoma complex" emphasized the histologic heterogeneity and a belief in the benign nature of the lesions. Subsequently, plasma cell granuloma was the common terminology for lung lesions, acknowledging i) the circumscribed appearance, ii) the presence of plasma cells and histiocytes, and iii) generally a benign course. The term inflammatory pseudo tumor was typically used to describe extra pulmonary lesions with similar pathology.[3,4]

IMTs have been divided into 3 subgroups (organizing pneumonia, fibrous histiocytoma, and lymphoplasmacytic type) based on the predominant histopathology and cellular milieu. The plasmacytic and histiocytic varieties of IMT may mimic infections. However, whether IMTs represent a primary inflammatory process or a prominent inflammatory response to a low- grade malignancy remains a matter of debate.[1]

Asymptomatic disease is found coincidentally on imaging studies in approximately 70% of patients. Other patients may present with nonspecific symptoms of cough, chest pain, hemoptysis, shortness of breath, fever, and fatigue. Weight loss and associated anorexia are rare. Evidence of a preceding or concurrent respiratory infection, like in this case, is seen in 30% of the patients.

Radiographic findings in 90% of the patients include well-circumscribed, solitary peripheral lung nodules with a preference for the lower lobes, subpleural locations. Variable attenuation and echogenicity are noted at CT and ultrasonography.Nevertheless, similar to the case presented herein, multiple pulmonary nodules (5%) and endobronchial lesions (5%) have been reported. On CT, lesions may be associated with atelectasis and/or pleural effusions.[5,6]

A recent publication of surgical resection of 61 cases of inflammatory myofibroblastic tumor of the lung show no specific symptoms, and no specific CT imaging characteristic to distinguish from lung cancer.[7]

Fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrates increased metabolic activity in IMT lesions, creating further challenges in distinguishing benign IMT lesions from malignant disease.[8]

Tissue samples obtained from fine needle aspiration and true cut biopsies are typically too small to allow a confident diagnosis. Bronchoscopically obtained tissue biopsies have also been reported to be of limited diagnostic utility due to their small size. Thus, the role of bronchoscopy in the diagnosis of IMT has been questioned in the literature and surgical biopsies are reported as the preferred diagnostic approach.

IMT profiles are typically imunoreactive to vimentin (99%), SMA (92%), muscle-specific actin (89%), desmin (69%) and negative for myoglobin and S100 protein. Spindle cell focal reactivity to epithelial markers such as

cytokeratin, epithelial membrane antigen (EMA; 36%), and CD68 (25%) is also common.[9]

Complete surgical resection is the treatment of choice for solitary pulmonary nodules, which confers a favourable 5 and 10-year survival in these patients of 91% and 77.7%, respectively. Medical management, using glucocorticoids, chemotherapy, and radiotherapy has been anecdotally reported.

Although IMTs are typically considered to be of benign origin, their clinical behaviour is variable and may include malignant evolution associated with locally invasive, recurrent, and metastatic disease. Metastatic spread of the disease is rare (< 5%), however loco regional spread and metastases to extra thoracic sites, including the brain, have been reported. Recurrent disease may develop years after the initial diagnosis, which highlights the need for long term surveillance of these patients.[10]

In a small number of patients, during the presentation or later, more malignant variants were felt to be analogous to undifferentiated "pleomorphic" sarcomas (previously termed malignant fibrous histiocytoma) arising in soft tissues. In those cases, there is a frankly sarcomatous neoplasm lacking a significant inflammatory and/or stromal component.

Approximately 50% of patients with IMT demonstrate clonal chromosomal rearrangements at band 2p23, which is the site of the ALK-1 gene in the tyrosine kinase locus. Mutations at the ALK site have been associated with constitutive overexpression of ALK and oncogenesis. ALK-1 expression is highly specific for IMT, with variation in sensitivity depending on the site of origin.[11]

In a recent study, Crizotinib, a competitive tyrosine kinase inhibitor of ALK, induced a sustained partial response in a patient with ALK-translocated IMT. This observation may offer a new therapeutic strategy for the subset of IMT patients with the ALK mutation phenotypes.[12]

By using a battery of complementary molecular techniques, Cheng et al have shown that all the thoracic IMTs harbored a tyrosine kinase abnormality, with 30% involving a kinase gene other than ALK, including ROS1, NTRK3, and RET gene fusions.[13]

In the near future, more definitive pathologic diagnosis and molecular characterization of locally aggressive or advanced/metastatic IMTs is quite critical, as a number of clinically available tyrosine kinase inhibitors and can be used as targeted therapeutic strategies based on the specific genomic profile of these tumors.

REFERENCES

1. Sagar AE, Jimenez CA, Shannon VR. Clinical and Histopathologic Correlates and Management Strategies for Inflammatory Myofibroblastic tumor of the lung: A case series and review of the literature. Medical Oncology 2018; 35:102
2. Cohen MC, Kaschula RO. Primary pulmonary tumors in childhood: a review of 31 years' experience and the literature. Pediatric Pulmonology. 1992; 14:222–32.
3. DulskasA, KlivickasA et al. Multiple malignant inflammatory myofibroblastic tumors of the jejunum: a case report and literature review. Oncol Letter. 2016; 11:1586-1588.
4. Wang X, Chen Y, Wu X, Zhang H. Intracranial Inflammatory Myofibroblastic Tumor with negative expression of anaplastic lymphoma kinase: A Case Report and Review of the Literature. World Neurosurg. 2019; 125:117-122.
5. Mahale A, Venugopal A, Acharya V, Kishore M, Dhungel K. Inflammatory myofibroblastic tumor of lung. Indian J Radiolmag. 2006;16.
6. Cerfolio RJ, Allen MS, Nascimento AG, et al. Inflammatory pseudo tumors of the lung. Ann Thorac Surg. 1999; 67:933–6.
7. Zhang J, Chen N, Qi J et al. Surgical Resection of 61 cases of Inflammatory Myofibroblastic Tumor of the Lung. Journal Thoracic Oncology, 2019 S859.
8. Kuo PH, Spooner S, Deol P, Monchamp T. Metastatic Inflammatory Myofibroblastic Tumor Imaged by PET/CT. ClinNucl Med. 2006; 31:106–8.
9. Coffin CM, Watterson P. Extra pulmonary inflammatory myofibroblastic tumor. A clinic pathologic and immunohistochemically study of 84 cases. Am J SurgPathol. 1995; 19:859–72.
10. Patankar T, Prasad S, Shenoy A, Rathod K. Pulmonary inflammatory pseudo tumour in children. Australian Radiol. 2000; 44:318–20
11. Coffin CM, Hornick JL, Fletcher CD. Inflammatory myofibroblastic tumor: comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. Am J SurgPathol 2007; 31:509–20.
12. Butrynski JE, Hornick JL, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med 2010; 363:1727–33.
13. Chang J. Zhang L, Travis WD et al. Expanding the Molecular Characterization of Thoracic Inflammatory Myofibroblastic Tumours beyond ALK Gene Rearrangements. Journal of Thoracic Oncology 2018 14-5: 825-834