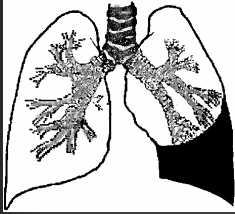


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UNCOMMON PLEURAL DISEASES

Localized Fibrous Tumor of the Pleura

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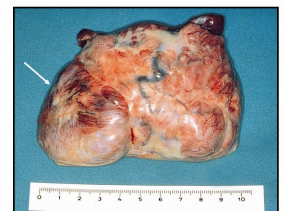
Definition: Localized fibrous tumors of the pleura (LFT) are circumscribed, solid, fibrous and benign lesions of the pleura presenting with scattered spindle-shaped cells of

low proliferation rate and low nuclear variance. Their correct diagnosis requires thorough analysis with light microscopy and immunohistochemistry.

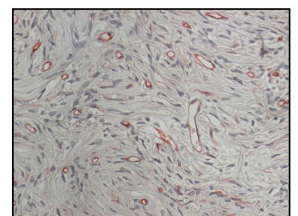
Imaging techniques, macroscopic or cytological criteria, cannot exclude other diseases, especially malignant variants. The latter are characterized by areas of necrosis, densely packed cells, and higher mitotic index (proliferation rate >5%).

Incidence and Etiology: LFT was first described by Lieutaud in 1767 and then by Wagner in 1870. The authors suggested that these lesions might derive from the endothelial layer of the sub-pleural lymphatic vessels². Therefore, the tumors were previously termed "localized fibrous mesothelioma"^{1,2}. LFTs are now classified as separate from malignant pleural mesothelioma. Whether LFTs are true neoplasms or

Localized Fibrous Tumor of Pleura: Lower left Lobe



Localized Fibrous Tumor of Pleura Microphotograph (1:240, CD34, AP)



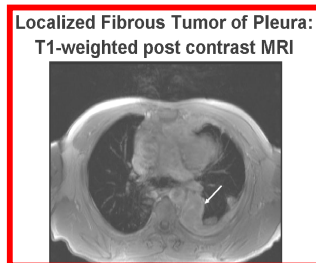
chronic proliferative inflammatory lesions of the pleura remains debatable.

The incidence of LFT is low (approximately 2.8/100,000) but accounts for ~5% of all tumors involving the pleura. In contrast to malignant mesothelioma which displays a male predominance (90%), LFTs occur more frequently in women (60%)¹⁻⁷. In previous studies, smoking and asbestos exposure were not associated with the development of LFT. Recent investigations however revealed increased numbers of asbestos fibers and a history of asbestos exposure in about 40% of cases, and a smoking burden of 20-30 pack years in about half of the LFT patients².

Ultrastructural analysis and immunohistochemistry indicate that LFTs originate from the sub-mesothelial tissues and are probably true neoplasms¹⁻⁴. The studies are supported by analysis of the thermodynamic-like pattern of structure of LFTs resulting in low proliferation rate, high extent of vascularization, structural entropy, and a very low current of entropy. LFTs are characterized by a spatial heterogeneity in expression of several antigens and galectin-dependent parameters with a preference for negative growth regulators and frequent presence of pro-angiogenic macrophage migration inhibitory factor².

Clinical and Radiologic Findings: LFTs can cause symptoms resembling those of mesotheliomas: chest pain, dyspnea and pleural effusions (~50% of patients). Clubbing or hypoglycemia occurs in 15% of the patients¹⁻⁷. Small LFTs (<3cm in max. diameter) seldom cause symptoms and are usually incidental findings¹⁻⁷. Most LFTs, when excised, measure 4-8cm (max. diameter).

Chest radiographs usually demonstrate an intra-thoracic, homogeneous, round or lobulated mass which is well-delineated. Ipsilateral pleural effusion is found in 20-30% of cases. Accompanying pulmonary atelectasis is seen in 20%. Most lesions occupy or extend into the inferior hemithorax. CT and MRI usually show a lobular mass forming one or several acute angles with the adjacent pleura. LFTs are usually heterogeneous in attenuation consistent with broad



variations in tissue density, and cannot be distinguished radiologically from malignant lesions.

Treatment: Surgery is the recommended diagnostic and curative procedure. Intra-operative frozen section service is mandatory to confirm the diagnosis and to ensure clear resection boundaries. Small tumors might be excised by video-assisted thoracoscopy, though larger ones often require a lobectomy. As LFTs arise from the visceral pleura, wedge resection might be sufficient. Tumors originating from the parietal pleura must be suspected as malignant, and often require extra-pleural resection^{6,7}. Surgical complications are rare, and most patients are discharged after 5-7 days.

Prognosis: LFTs are usually benign, and can be separated from malignant variants by histopathology. The 5-year survival rate is >95%: a recent study reports no LFT-associated death within 10 years of follow-up¹⁻³. Recurrence occurs in 5-10% of patients, usually within 4 years. Older patients with prior asbestos exposure and large tumors (>10cm in max. diameter) are more prone to develop recurrent LFTs. Radiographic follow-up is recommended for these patients for up to 5 years. Malignant transformation has been reported in one case only that seemed to display features of a LFT and a sarcomatoid mesothelioma³.

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Pleural Amyloidosis

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Amyloidosis constitutes a family of protein folding disorders culminating in the formation of insoluble β -rich fibrils. Deposition of amyloid fibrils into select organs disrupts their function, producing clinical disease. Although amyloid deposits are histologically indistinguishable in primary systemic (light chain) amyloidosis (AL), secondary (AA) amyloidosis, and transthyretin (ATTR) amyloidosis, the particular protein forming the fibrils dictates different constellations of organ involvement. Consequently, pleural effusions are reported in some but not all types of amyloidosis.

Cumulative reported experience indicate that large, persistent pleural effusions occur in 6-18% of patients with AL amyloidosis, and rarely if ever in patients with AA or ATTR amyloidosis. Comparative analyses demonstrated that pleural effusions in AL patients result from pleural surface infiltration generally in the setting of restrictive cardiomyopathy (left atrial hypertension). Approximately 40% of cases have exudative pleural fluid character, consistent with pleural surface disruption by the deposits. Amyloid cardiomyopathy, hypoproteinemia from amyloid nephropathy, and amyloid thyroid disease are individually and collectively insufficient to produce refractory pleural effusions in these patients. Pleural effusions in patients with AA amyloidosis appear to arise not from pleural amyloid infiltration but rather as a direct extension of the chronic inflammatory disease (e.g., rheumatoid arthritis, tuberculosis, or vasculitis) simultaneously stimulating amyloid formation. Similarly, pleural effusions in patients with transthyretin (ATTR) amyloidosis are a late phenomenon reflecting cardiac dysfunction, not pleural amyloid.

Management of refractory pleural effusions in AL patients is challenging. Disruption of pleural surface and heart functions produce the disease. Consequently, minimizing intravascular volume and optimizing cardiac function must first occur if fluid drainage is to have lasting effects. Serial thoracenteses initially ameliorate dyspnea and orthopnea. Ultimately, the risks of frequent pleural taps invariably prompt consideration of pleurodesis

by chest tube thoracostomy or video-assisted thoracoscopy (VATS). Chest tube placement is often complicated by persistent large volume pleural drainage, limiting opportunities to introduce sclerosing agents. Conversely, amyloid cardiomyopathy and the risks of general anesthesia prevent many of these patients from undergoing VATS. Pleurx® tube placement into the affected pleural space provides continuous access for outpatient management of refractory pleural effusions. In the near future, anti-cytokine therapy may be a viable alternative to fluid drainage and sclerotherapy. A recent publication reported successful treatment of persistent pleural effusions in an AL patient with anti-vascular endothelial growth factor antibody, bevacizumab (Avastin®, Roche). Clinical trials will be needed to determine the effectiveness of growth factor modulation in AL pleural effusions.

Persistent pleural effusions connote extremely poor survival in AL patients. Untreated, patients survive a median 1.6 months. In contrast, untreated patients with AL cardiomyopathy in the absence of pleural effusions live a median 6 months. Refractory pleural effusions occur late in AL disease, reflecting both significant heart and pleural surface disruption by infiltrating amyloid fibrils. Although AL patients with persistent pleural effusions do not qualify for high dose intravenous melphalan with autologous stem cell transplantation, new oral chemotherapies directed at the underlying plasma cell dyscrasia may provide opportunities for clinical response.

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Pyothorax-Associated Lymphoma

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In 1987, Aozasa and colleagues reported 3 patients with pleural lymphoma, which developed after chronic pyothorax resulting from artificial pneumothorax for the treatment of pulmonary or pleural tuberculosis¹. Through subsequent pathologic and epidemiologic studies in Japan, Aozasa concluded that this is a distinctive type of lymphoma and proposed the term pyothorax-associated lymphoma (PAL), defined as non-Hodgkin lymphoma of exclusively B-cell phenotype developing in the pleural cavity of patients with more than 20-years history of chronic pyothorax.

PAL is now listed as a distinct disease entity together with primary effusion lymphoma (PEL) in the recent World Health Organization classification². The artificial pneumothorax, originally established in Western countries as a form of surgical therapy for lung tuberculosis, had been more widely performed in Japan than in Western countries, especially in the 1930s to 1950s. In Western literature, malignant lymphoma has rarely been described as a complication of chronic pyothorax, but reports of malignant mesothelioma or squamous cell carcinoma in patients with chronic pyothorax are common. A case-control study in Japan revealed that employment of artificial pneumothorax to be a risk factor for development of PAL among patients with chronic pyothorax (RR 4.92; 95%CI 1.99-12.2)³. Polymerase chain reaction-single strand conformation polymorphism analysis followed by direct sequencing revealed extraordinary high frequency of p53 mutations (70% of cases), predominantly involving the dipyrimidine site. These results suggest that long-term radiation or specific drug exposure may have caused specific mutations in the p53 gene⁴.

Clinical findings: Mean age at the diagnosis of PAL is in the seventh decade of life with marked male preponderance⁵. The most common symptoms on admission are chest pain and fever. Computed tomography is superior to chest X-ray in detecting mass shadows, with a detection rate of >80% and <50% respectively. Serum neuron-specific enolase level is occasionally elevated suggesting a diagnosis of small cell lung cancer. At the diagnosis of PAL, pyothorax is free from any bacteria or infected by

nontuberculous bacilli in a majority of patients. These findings suggest that mycobacterium tuberculosis might not play a central role in lymphomagenesis in the pleural cavity.

Pathologic findings: PAL usually shows a diffuse proliferation of large cells of B-cell type, diffuse large B-cell lymphoma (DLBCL). The tumors usually show a contiguous pattern of invasion into adjacent structures, e.g. the lung and diaphragm, and remain localized in the thoracic cavity even at the time of autopsy in approximately half of patients. The gene expression profile of PAL is distinct from DLBCL of lymph node origin in its higher expression level of interferon-inducible genes⁶. PAL is strongly associated with Epstein-Barr virus (EBV) infection. A recent study suggested an etiological role for EBV in the development of PAL⁷. PAL is a distinct entity both in its clinico-pathologic presentation as well as its gene expression profile. PAL develops in chronically inflamed tissues and is thus defined as “malignant lymphoma developing in chronic inflammation.”

PAL is usually treated with chemotherapy, though some authors reported better results with radiotherapy. The most common agents used for chemotherapy are cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP).

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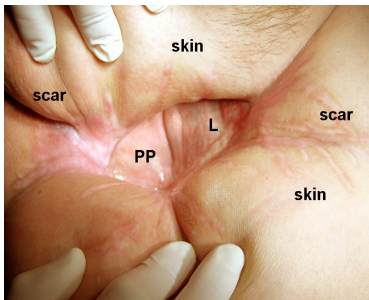
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IMAGES OF THE PLEURA

Open Thoracic Window for Empyema Brief History and Current Indications

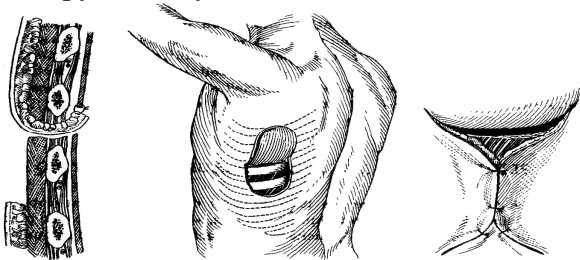
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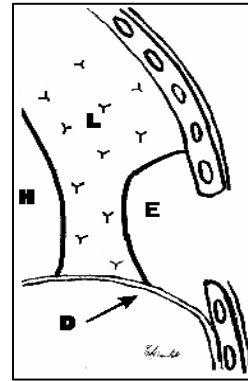
Open thoracic window (OTW) in a patient with chronic TB empyema over 7 years who failed a decortication and thoracoplasty. After creation of a window, resolution of the cavity is achieved through retraction and secondary epithelialization (L = lung, PP = paravertebral parietal pleura).

OTW is a rarely performed surgical procedure for empyema, and involves a limited rib resection which creates a direct opening of the infected pleural space to the atmosphere to facilitate drainage. It was popularized in the 1930's by Leo Eloesser (1881-1976) as a method to achieve good unidirectional drainage of TB empyema using a cutaneous flap¹. The drawings from the original article are unclear about how the flap worked as a one-way valve and most modern authors consider it as insufficient. By 1969, Eloesser admitted that advances in medical therapy had very much reduced the need for OTW³.



Reproduced with permission from J Am Coll Surg¹.

In the modern era, the procedure is performed quite differently than originally described², with resection of 2-3 ribs for at least 10-12 cm in order to achieve a window large enough to allow good visualization and toileting of the entire cavity. The wound and the empyema cavity are left wide open with daily debridement and dressings. Extra care is required in the presence of large bronchial fistulae. The procedure should not be performed in the acute



phase of an empyema due to the danger of fatal open pneumothorax, as pointed out by the Empyema Commission during WW I.

(E=empyema; L=lung; H=heart; D=diaphragm.)

The main advantage of the OTW is that it allows rapid local control of sepsis through a simple and quick procedure^{2,3}. The main disadvantage is the large open wound with unpleasant cosmetic implications and the need of daily local care. Natural resolution of the cavity occurs through retraction and epithelialization, which may take months or years. Other options to foster a faster healing process include closure of the stoma after sterilization of the cavity (Clagett procedure) or space obliteration through thoracoplasty or muscle transposition.

Due to these disadvantages and successful use of other less invasive procedures⁴, there are now few indications for OTW. It can be used in patients with chronic pleural infection who cannot tolerate a more extensive procedure and in whom other less invasive procedures have failed. One such indication is post-pneumonectomy empyema, where OTW is considered by some authors as the procedure of choice (as part of the Clagett procedure)^{5,6}. Used appropriately, OTW can be life-saving in selected patients.

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