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Lymphocyte-Predominant Pleural Effusions

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The presence of lymphocyte-predominant (>50% of pleural fluid leukocytes) pleural fluid assists the differential diagnosis of a pleural effusion by suggesting the presence of a limited list of etiologic conditions. Healthy adults have <1,800 cells/ μ l in the small volume (0.26 ± 0.1 ml/kg) of pleural fluid that normally exists in the pleural space¹. Macrophages represent the majority (75%) of these cells with lymphocytes (23%) constituting most of the remainder. The presence of a lymphocyte-rich effusion indicates the chronic nature of an effusion in that acute pleural inflammation or injury attracts neutrophils to the pleural space.

Most transudative effusions are lymphocyte predominant with congestive heart failure being the most common condition associated with pleural lymphocytosis². Lymphocytosis in the presence of a transudate has no diagnostic importance.

The detection of lymphocytosis has the greatest value in assisting the differential diagnosis of an exudative effusion. The presence of >80% lymphocytes in pleural fluid suggests the following conditions: tuberculous pleurisy, chylothorax (*see also page 15*), primary or secondary pleural lymphoma, adult T cell leukemia, yellow nail syndrome, the late phase of post cardiac surgery pleural effusion, acute lung rejection, chronic rheumatoid pleurisy, and sarcoidosis³. In conditions such as pleural malignancy or tuberculosis, macrophage-derived, cytokine-mediated signals stimulate cancer cells (in malignant effusions) or pleural structural cells (in tuberculous effusions) to release soluble interleukin-8, which promotes the recruitment of lymphocytes to the pleural space⁴. In chylothorax, lymphocyte-rich chyle flows into the pleural space. The mechanism of recruitment of lymphocytes to pleural fluid is ill defined in the other conditions listed above.

Tuberculous effusions feature a polyclonal influx of lymphocytes into the pleural space. These lymphocytes are primarily activated T cells with a predominance of helper (CD4) cells⁵. The presence of >80% pleural fluid lymphocytes with a pleural fluid protein >4g/dl strongly suggests tuberculous pleurisy.

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Carcinomatous effusions are less commonly characterized by lymphocyte counts >80%, which usually range between 50 and 70%. These lymphocytes – termed “tumor-associated lymphocytes” – represent a polyclonal response to malignant infiltration into the pleural space and have the potential to lyse tumor cells⁶. Lymphoma that involves pleural membranes induces an influx of monoclonal lymphocytes into pleural fluid. Primary effusion lymphoma (PEL) is a recently recognized type of lymphoma that occurs predominantly, but not exclusively, in human immunodeficiency virus-seropositive patients with acquired immunodeficiency syndrome⁷. Cytologic examination of the pleural fluid from patients with PEL reveals medium to large atypical lymphocytes characteristic of lymphoma with a high mitosis rate. Patients with Hodgkins or non-Hodgkins lymphoma that involves the pleural space have a predominance of monoclonal lymphocytes. Unexplained lymphocyte-predominant exudative effusions warrant additional diagnostic tests, such as immunophenotypic analysis and cytogenetic and molecular studies, which can confirm the diagnosis of pleural lymphoma.

The diagnosis of a lymphocyte-predominant exudative effusion requires a comprehensive clinical evaluation. Often the patient’s history (history of breast cancer, recent tuberculosis exposure or cardiac surgery), physical examination (yellow nails, active synovitis with rheumatoid nodules), or initial testing (positive PPD, pleural fluid cytology) confirms a specific diagnosis. Lymphocyte-predominant effusions that remain unexplained after an initial evaluation, however, may require pleural biopsy.

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**Two Rare Cases of Lymphocytic Effusions:
What are the Diagnoses?**

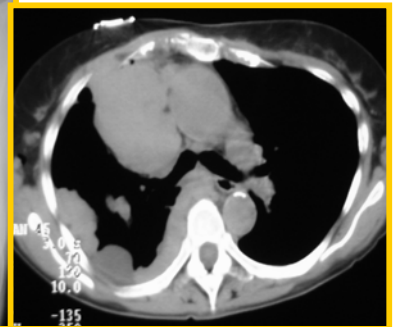
Jose Manuel Porcel & Antonieta Salud *Lleida, Spain*

Case 1:

A 67-year-old woman presented with dyspnea and cough. A chest film showed a large right pleural effusion. Thoracentesis revealed an exudate with WBC count 11,200/μL consisting of 100% lymphocytes. Cytological examination showed a large population of mature T cells.



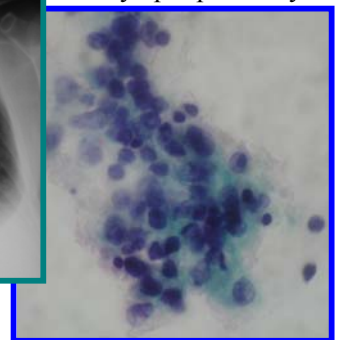
Post-drainage x-ray and CT scan demonstrated a lobulated anterior mediastinal mass with extensive pleural implants.



Case 2:

A 72-year-old man presented with fatigue, progressive exertional dyspnea and orthopnea. Treatment for presumed congestive heart failure was ineffective. Physical examination revealed pallor, jugular venous distension, peripheral edema, decreased breath sounds and dullness to percussion over the lower half of both hemithoraces, hepatomegaly, as well as axillary and inguinal lymph nodes of >2 cm in diameter. A chest film showed moderate bilateral pleural effusions, but no interstitial pulmonary edema. Echocardiogram also demonstrated a normal LV ejection fraction.

Pleural fluid analysis showed: WBC count 3,420/μL with 95% lymphocytes; protein 7.2g/dL (serum protein 11.4g/dL); LDH 398U/L (serum LDH 293U/L); glucose 100mg/dL; ADA 18.3U/L; pH 7.39; negative bacterial cultures. Clusters of lymphoplasmacytoid



cells were seen on cytological examination.

For the diagnoses, go to page 14.

CHYLOTHORAX

An Uncommon Cause of Lymphocytic Effusions

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Chylothorax is the occurrence of chylus in the pleural space. Fat in the intestines is absorbed into the lymphatics, which drain via the thoracic duct into the systemic circulation. This special lymph, called chylus, contains high levels of triglycerides, cholesterol, and chylomicrons - the latter being diagnostic of a chylothorax. The average flow of chylus in an adult is 2L/day; it increases with food and drink, and decreases significantly with starvation. Leakage from the thoracic duct leads to a chylothorax.

The thoracic duct typically starts behind the aorta below the diaphragm where lymph vessels from the lower parts of the body and those from the peritoneal cavity converge. The duct ascends through the diaphragm and continues upwards on the right side of the vertebral column, then crosses the midline and empties into the left subclavian vein. As expected, most chylothoraces occur on the right side. However, anatomic variations are common: the duct may be bilateral, and there may be multiple collaterals, etc. Depending on the anatomy and where the damage occurs, the effusion can also be on the left, or be bilateral. The diagnosis is made by analysis of the fluid.

Chylothorax is uncommon, and most often due to trauma. Iatrogenic trauma, especially thoracic surgery, is now the most common cause. Chylothorax occurs after 0.5% of all chest surgeries. Non-iatrogenic trauma, ranging from traffic accidents to child labor, can also lead to chylothoraces.

Other conditions, the most common being lymphoma, can cause chylothorax by blocking the thoracic duct. Indeed, a chylothorax can be the first manifestation of an underlying lymphoma. Establishing the diagnosis can be difficult since malignant cells are not found in the pleural fluid. Rare causes of chylothorax include lymphangioliomyomatosis, yellow nail syndrome, and diseases affecting the lymph vessels.

In non-traumatic cases, a CT scan of the thorax and upper abdomen should be performed to visualize any tumor or enlarged lymph nodes. A dilated duct can often be seen in cases where lymphatic obstruction produced the leakage. Lymphography can be helpful, as can an MRI.

Conservative treatment with diet restrictions is successful in >50% of patients with traumatic chylothorax, but rarely so with chylothorax of other causes. A low-fat diet containing medium-chain triglycerides (which are absorbed into the blood) will decrease chylus production. The next step is total parenteral nutrition, which will diminish the chylous flow to a trickle. The lack of fluid pressure within the duct can allow the damage to heal, though this may take weeks. In non-traumatic cases, spontaneous resolution is less likely.

Chemical pleurodesis often fails, probably due to a protective effect of the chylus, but could be tried (eg using talc). **Surgery** is the last resort. Ligation of the duct at the level of the diaphragm is successful in up to 90% of patients. It can be achieved by thoracoscopy, but can be difficult if there are many collateral ducts. If a lymphoma is suspected, biopsies of the duct and any suspicious lesion should be made. Due to the rich network of collaterals of the lymphatic system, lymph stasis after surgery is not a concern.

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WHAT ARE THE DIAGNOSES?

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Case 1: Invasive thymoma with pleural metastases

Mediastinoscopic biopsies of the mediastinal and pleural lesions both revealed invasive thymoma. Despite chemotherapy, the disease accelerated, leading to death 14 months after the diagnosis.

Case 2: Waldenstrom's macroglobulinemia

Laboratory tests revealed a hemoglobin level of 8.9 mg/dL, and an IgM kappa-chain monoclonal protein (76.1 g/L). Bone marrow contained 36% of plasmacytoid lymphocytes. Waldenstrom's macroglobulinemia with pleural involvement was diagnosed. The patient responded to systemic chemotherapy and is alive at 28-months follow-up.

Clinicians should consider the possibility of metastatic thymoma and plasma cell disorders in otherwise undiagnosed lymphocyte-rich pleural effusions.

BIOLOGY OF LYMPHOCYTES IN THE PLEURAL SPACE

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Lymphocytes are the major cell type found in pleural effusions secondary to many causes including malignancy and tuberculosis. In these disorders, CD4⁺ T cells predominate and account for approximately 70% lymphocytes present. CD8⁺ T cells account for approximately 15%, B cells for 5-10% and natural killer (NK) cells for fewer than 5% of the lymphocytes present within these effusions. This brief review will outline the principal functions of each lymphocyte subset and highlight aspects relevant to their presence within the pleural space.

T cells develop in the thymus and are characterised by the presence of the T cell receptor complex in association with CD3. The majority falls into one of two subsets, defined by expression of the CD4 and CD8 co-receptors. CD4⁺ T cells recognize peptides derived from exogenous proteins, presented by MHC class II molecules. Following antigen-stimulation, CD4⁺ T cells may differentiate into Th1 or Th2 type cells. Interleukin (IL)-12 promotes differentiation into Th1 cells; this subset of CD4⁺ T cells predominantly produces IL-2, IFN- γ and TNF- α and provides help for the development of effective CD8⁺ T cell responses. In contrast IL-4 promotes differentiation into Th2 cells; this subset of cells produces IL-4, IL-5, IL-10 and IL-13 and provides help for B cells, thus promoting the development of humoral immunity¹. In pleural effusions, the functional subset of CD4⁺ T cells varies and shows some correlation with the etiology of disease. Tuberculous pleuritis is associated with a strong Th1 response, whereas malignant effusions are usually associated with a Th2 response². The predominance of Th2 cytokines in these malignant effusions may contribute to impairment of cytotoxic T cell function.

CD8⁺ T cells recognize peptides derived from cytoplasmic proteins, presented at the cell surface by MHC class I molecules. Following antigen-stimulation, CD8⁺ T cells acquire effector function, including the capacity to kill and to produce cytokines. CD8⁺ T cells may also differentiate into type 1 and type 2 cells that secrete IL-2, IFN- γ and TNF- α or IL-4, IL-5 and IL-10 respectively. The cytolytic capacity of CD8⁺ T cells is suppressed in malignant pleural effusions³.

Smaller subsets of T cells also exist. Of recent interest are regulatory T (Treg) cells that can inhibit T cell activation through contact dependent mechanisms or production of cytokines such as IL-10 and TGF- β . A number of Treg subsets have been described, including the CD4⁺, CD25^{high} subset, cytokine-producing CD4 and CD8⁺ T cells,

NK T cells and $\gamma\delta$ T cells⁴. Currently, the importance of these cells in pleural disease is uncertain.

B lymphocytes are characterized by the presence of the B cell receptor, a cell surface immunoglobulin. On antigen-stimulation, these cells may differentiate into plasma cells and produce antibody molecules with the same antigen specificity as their surface receptor. Conventional B cells (B2 cells) are generated by the bone marrow and have a diverse repertoire of receptors. They comprise the majority of circulating B cells and are the dominant source of IgG antibodies. B1 cells comprise a minority of circulating B cells. Most B1 cells express CD5, are capable of self-renewal and are dominant producers of low-affinity IgM antibodies. These cells accumulate in body cavities such as the pleural space. The chemokine CXCL13 is required for B1 cell homing to body cavities and antibody production⁵.

NK cells are an important component of the innate immune system and are defined by expression of CD56 and lack of expression of CD3. Their activity is regulated by integration of signals from a wide range of activatory and inhibitory surface receptors. Expression of inhibitory receptors capable of recognizing autologous MHC class I molecules usually serves to prevent NK cells from killing autologous cells. Virus-infected cells or malignant cells that have down-regulated MHC class I molecules may become targets for NK cell activity. NK cells in malignant pleural effusions have impaired ability to kill both autologous tumors and classical NK cell targets. More recent work has emphasized the importance of NK cells as producers of pro-inflammatory cytokines and has highlighted their importance in promoting maturation of dendritic cells and the development of adaptive immune responses⁶.

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If you have an interesting case of pleural disease to share, or any comment on the Newsletter, please contact:
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