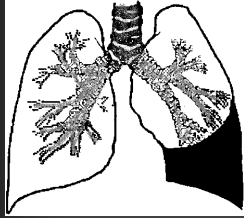


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Pleural Disease and HIV Infection

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Diagnosing Tuberculous Effusions in HIV Patients

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Tuberculous pleural effusion (TPE) is a common form of extra-pulmonary tuberculosis (TB) among HIV patients. The diagnosis is difficult both because of the pauci-bacillary nature of pleural fluid and the invasive techniques required to obtain specimens for laboratory diagnosis. Two commonly used methods, the Ziehl-Neelsen staining and the pleural fluid culture, both have low sensitivity (0-20% and 40-60% respectively)¹. Higher smear and culture positivity has been shown in HIV positive compared to HIV negative TPE patients due to the higher bacillary load in the former². Cultures often take weeks for the results to be available while histology of pleural tissue is usually non-specific in HIV patients. An indirect marker for diagnosing TPE is adenosine deaminase (ADA) activity in pleural fluid. ADA has proven to be very accurate in diagnosing tuberculous pleuritis among HIV patients with very low CD4 cell counts³. The high likelihood ratios of the ADA allow it to accurately rule in or out TPE.

A second-generation interferon gamma release assay in blood and pleural fluid was recently evaluated from HIV-infected patients with TPE⁴. The sensitivity of the QuantiFERON TB Gold test (QFT-TB) was acceptable in blood although inconclusive results increased in patients with CD4 cell counts <100/ μ L. However, except in selected cases, overall

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the test performed poorly in pleural fluid due to high interferon gamma background values^{4,5}.

The immunohistochemistry (IHC) technique using an antibody to the secreted mycobacterial antigen MPT64, specific for *Mycobacterium tuberculosis complex* organisms, has been found to be highly specific for pleural TB in HIV positive patients and is more sensitive than acid-fast staining because of its potential to detect degraded mycobacteria⁶. The sensitivity of the polymerase chain reaction (PCR) test is generally poor, although the specificity is high.

The following is therefore recommended: 1) In HIV positive patients with CD4 cell counts $>100/\mu\text{L}$, the blood QFT-TB test could be performed to support the diagnosis of TPEs in settings where pleural fluid cannot be obtained, or when time is essential for therapeutic intervention; 2) The ADA test should be included in the routine diagnostic panel of TPEs due to its high accuracy in HIV positive patients with very low CD4 cell counts, as well as its simplicity and availability in most clinical settings; 3) IHC with anti-MPT64 on tissue biopsies should be included in routine diagnosis because of its high sensitivity and specificity in HIV co-infected tissues when the typical granulomas are absent; and 4) The diagnostic usefulness of PCR on pleural biopsies lies in its ability to rule out TPEs because of its high specificity.

Culture for *M. tuberculosis* should still be undertaken as it is the recognized gold standard and offers an opportunity for resistance testing. The methods mentioned herein are complementary for a rapid diagnosis with a view to initiate anti-TB therapy to obtain a favorable outcome for patients.

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Treatment for Pleural TB in HIV Patients

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Pleural disease is a common manifestation of extra-pulmonary TB in persons co-infected with HIV. The most important first step is to start anti-TB treatment, which in industrialized and developing countries consists of a four drug initial phase (2 months of rifampin, isoniazid, pyrazinamide and ethambutol) followed by a two-drug continuation phase (4 months of rifampin and isoniazid).

Once HIV is confirmed, cotrimoxazole preventive therapy (CPT) should be started as soon as possible, unless there are contraindications. In industrialized countries, CPT is normally commenced if the CD4-lymphocyte count is <200 cells/mm³ to prevent *Pneumocystis jirovecii* pneumonia or cerebral toxoplasmosis. In many sub-Saharan African countries, CPT would be started at higher CD4-counts to prevent bacterial infections and malaria¹.

Combination antiretroviral therapy (ART) should then be considered, the timing dependent to some extent on CD4 counts. The current WHO guidelines recommend that¹: ART be commenced between 2–8 weeks after the start of anti-TB treatment if CD4-counts are <200 cells/mm³, after 8 weeks if CD4 counts are between 200–350 cells/mm³, and possibly deferred until the end of anti-TB treatment if CD4 counts are >350 cells/mm³. With mounting evidence suggesting that ART should be commenced at higher CD4-counts², these guidelines might need to be amended.

The most commonly used ART drugs are nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs] and protease inhibitors [PIs]. Most first-line ART regimens use a combination of two NRTIs (often tenofovir plus emtricitabine in industrialised countries and stavudine plus lamivudine in developing countries) and one NNRTI (either nevirapine or efavirenz). PIs are used mainly in second line ART regimens in developing countries, while in industrialized countries they are sometimes used in first line regimens. As there are no significant interactions between NRTIs and anti-TB drugs, one option is a triple/quadruple NRTI regimen^{3,4}. However, NNRTIs and PIs are metabolized mainly through cytochrome P450 (CYP450) enzymes. Rifampin induces CYP450, leading to a reduction of plasma concentrations of nevirapine by 30-40%, efavirenz by 20-25% and unboosted PIs by $>80\%$ ^{3,4}. Efavirenz is less affected and therefore has a lower

risk of acquiring drug resistance; hence, it is the preferred NNRTI to be used with anti-TB treatment³. The problem with PIs can be partially overcome by using ritonavir-boosting, but there are significant problems with toxicity. In general, PIs should not be used with anti-TB treatment. If they have to be used, rifabutin, which has less effect on CYP450, should be used instead of rifampin.

Concomitant use of ART and anti-TB drugs can lead to additional adverse drug reactions and the immune reconstitution inflammatory syndrome⁵, the latter can cause fever and paradoxical enlargement of the effusion that may require corticosteroids for resolution. Despite these challenges, concomitant use of ART and CPT improves survival, and are considered an essential component of clinical management.

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CASE REPORT

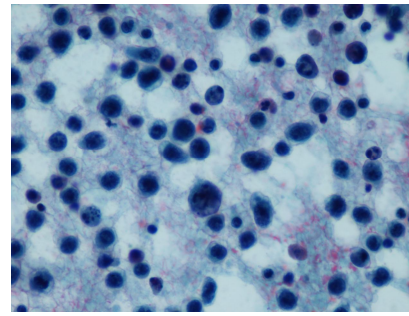
Pleural Body Cavity Lymphoma

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A 49-year-old man was evaluated for a 3-month history of fatigue, weight loss, intermittent fever, cough productive of yellowish phlegm and progressive dyspnea. He had developed multiple purplish plaques and nodules on his face, trunk and extremities a year earlier. He had had a number of homosexual relationships in the past.

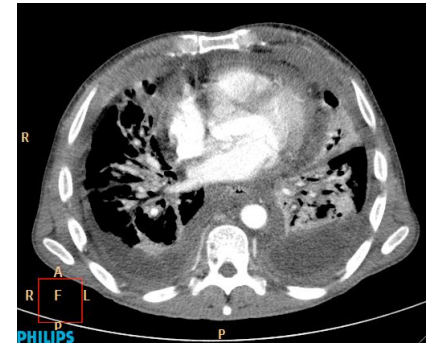
Physical examination revealed the typical skin lesions of Kaposi sarcoma. Chest CT showed a bilateral pleural effusion in the absence of other abnormalities. Results of laboratory tests included a positive HIV antibody, a CD4 cell count of 145/ μ L and a viral load of 69,000/mL. The pleural fluid was a lymphocytic exudate with a LDH level of 9350 U/L and ADA of 316 U/L. Cytological examination



showed malignant cells consistent with lymphoma (left). A genotype study of the pleural fluid disclosed a monoclonal B-cell population.

The cells stained positive for CD30, but did not express CD3, CD10, CD20, CD43, CD79 or TDT. Real-time PCR of the fluid was negative for both human herpesvirus (HHV)-8 and Epstein-Barr virus. However, HHV-8 was found in the peripheral blood by nucleic acid and serologic tests. There was no evidence of lymphoma outside the pleural cavity.

The diagnosis of body cavity lymphoma was made and 600 mL of fluid were evacuated from the left hemithorax. Antiretroviral therapy with Atripla was initiated. Two months after the initial diagnosis, the patient was well with minimal bilateral pleural effusions. His viral load had decreased to 338 copies/mL and the CD4 count risen to 350 cells/ μ L. One month later the patient was readmitted to the hospital due to worsening dyspnea and anasarca. An echocardiography suggested constrictive pericarditis. A CT revealed pericardial thickening (11 mm), bilateral pleural effusions and anterior mediastinal lymphadenopathy (above). The patient improved significantly when treated with chemotherapy (CHOP regimen) and remains alive 6 months after the diagnosis.



HHV-8 infection is strongly implicated in the pathogenesis of Kaposi's sarcoma and primary effusion lymphoma. In fact, demonstration of HHV-8 DNA in the neoplastic cells is regarded as a *sine qua non* for the diagnosis of primary effusion lymphoma.

Diagnosis: Primary non-Hodgkin lymphoma of the diffuse large B-cell type involving the pleural and pericardial cavities

HIV-related Lymphomas

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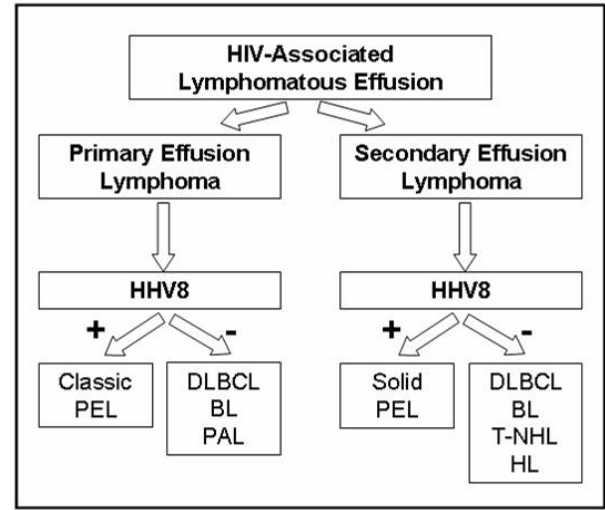
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HIV-related pleural disease may be due to infection (tuberculosis, bacterial and, more rarely, *Pneumocystis pneumonia*), malignancy (lymphoma, Kaposi sarcoma and carcinoma), Castleman's disease, post-radiation changes or may be seen accompanying systemic problems (e.g. heart or renal failure)¹⁻². The prevalence of HIV-related pleural effusion among patients hospitalized with AIDS (in the USA) varies between 2% and 20%.² Serous effusions are a well-known complication of lymphomas. AIDS-related pleural lymphomas may be primary (i.e. there is no extracavitary involvement or identifiable contiguous mass) or secondary (i.e. they are preceded by an extracavitary systemic lymphoma). Most AIDS-related lymphomas are likely to be of B-cell origin.

Lymphomatous effusions can be further categorized by their human herpesvirus-8 (HHV8) status (Figure). Classic primary effusion lymphoma (PEL) is confined to body cavities, whereas extracavitary HHV8 positive tumors resembling PEL are now referred to as solid variant PEL³. Patients with solid (tissue-based) PEL may subsequently develop lymphomatous effusions. Pyothorax-associated lymphoma (PAL) usually develops in patients with chronic pyothorax or chronic pleuritis due to therapeutic artificial pneumothorax for pleuropulmonary tuberculosis. Unlike PEL, PAL is usually accompanied by a mass in the pleural cavity. Disseminated Burkitt lymphoma (BL) may involve the pleural space, but less frequently manifests itself initially with an effusion. Neither T non-Hodgkin lymphoma (NHL) nor Hodgkin lymphoma (HL) normally produce pleural effusions. NHL of T-cell phenotype is uncommon in HIV infected patients, whereas the incidence of HL appears to be increasing in the era of Highly Active Antiretroviral Therapy (HAART).



Algorithmic approach to HIV-associated lymphomatous effusions. BL = Burkitt lymphoma; DLBCL = diffuse large B-cell lymphoma; HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; PAL = pyothorax-associated lymphoma; PEL = primary effusion lymphoma.

AIDS-related lymphomas tend to occur late in the course of HIV infection. Clinical manifestations of lymphomatous pleural effusions may be due to the effusion (e.g. dyspnea), lymphoma (e.g. B symptoms, mass effect, distant disease) and/or other HHV8-associated disease (Kaposi sarcoma, Castleman's disease). A diagnosis of lymphoma can be reliably established by evaluating pleural fluid, obtained via thoracentesis or sampled at the time of surgical exploration. Lymphomatous effusions are exudates, frequently with an elevated LDH. Cytology examination, along with ancillary studies, can help distinguish lymphoma cells from reactive lymphocytosis as well as subtype lymphomas. Pleural fluid should be submitted for immunophenotyping (e.g. flow cytometry), immunocytochemistry (e.g. immunostaining with the antibody called latent nuclear antigen-1 or LNA-1 specific for HHV8), and molecular/cytogenetic studies (e.g. c-myc gene rearrangement). The use of multiple ancillary studies enhances diagnostic accuracy⁴. If necessary, a pleural biopsy may be performed later. Alternatively, in cases where a non-diagnostic effusion is accompanied by a solid pleural tumor or mediastinal lymphadenopathy, these will need to be sampled. In addition to radiological evaluation of the effusion and associated thoracic findings, imaging studies (CT scan and/or PET) should facilitate staging. Classic PEL does not get staged, whereas the Ann Arbor

staging system is used for other lymphomas. Hence, patients with newly diagnosed lymphoma require blood tests (e.g. complete blood count, liver function tests including LDH, β 2-microglobulin, uric acid), a bone marrow biopsy and lumbar puncture.

Therapy involves a combination of managing the patient's HIV infection (HAART and prophylactic antimicrobials) and lymphoma. Regimens involving systemic polychemotherapy (e.g. EPOCH-R or CHOP-R for NHL, ABVD for HL) have been shown to be effective⁵. Patients will need to be evaluated for unwanted HAART-chemotherapy interactions. Although rituximab is typically given for B-cell lymphomas, it needs to be used cautiously in those with a CD4 <50 cells/mm³. Newer therapies, such as rapamycin, are being explored⁶. Unfortunately, the current treatment for AIDS related lymphomas, especially PEL, is disappointing. The prognosis of PEL is thus poor, with an overall survival in the 3- to 6-month range.

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Spontaneous Pneumothorax in HIV Patients

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Spontaneous pneumothorax (SP) is a rare, but serious, complication caused by the opportunistic infections and tumors associated with the human immunodeficiency virus (HIV). The incidence of SP in the general population has been estimated at 6 cases per 100,000 inhabitants per year. However, in the era prior to highly active antiretroviral therapy (HAART), SP was reported in AIDS patients with an incidence rate of 1.7-4%^{1,2}. The risk practices of HIV patients and the degree of immunosuppression are factors that influence the etiology of SP¹. The

majority of SPs in AIDS patients without HAART were related to *Pneumocystis jirovecii* pneumonia (PcP)^{1,2}. The development of SP during PcP can occur as a result of the destruction of lung tissue by the microorganism, which causes the appearance of subpleural necrosis with the formation of bullae in the lung parenchyma, either as late sequelae or in the course of the pneumonia itself. Obviously, the risk of SP rises with an increasing number of PcP episodes.

Tuberculosis (TB) is a known risk factor for SP in HIV patients. The impact of TB as a cause of SP is related to the incidence of TB in each region and to the epidemiological characteristics of the study population. In other words, in countries with a high prevalence of co-infection by HIV and *Mycobacterium tuberculosis*, the frequency of TB as a cause of SP is high. Conversely, in series from regions with a low incidence of TB, the frequency is low^{1,2}.

The most common cause of SP among injection drug users (IDU) is bacterial infection¹. IDU have a higher risk of developing respiratory bacterial infections than the general population³. This may be due to a number of factors, such as drug consumption by inhalation, bronchial aspiration brought on by drug-induced depressed consciousness, and the higher risk for presenting endovascular infections, such as right-sided endocarditis with subsequent septic pulmonary emboli.

The use of inhaled pentamidine has also been linked to SP. Some authors attribute this relationship to a persistence of *Pneumocystis* in poorly ventilated, peripheral areas of the lungs to which pentamidine is not adequately distributed, with the consequent destruction of these areas of the lung parenchyma^{1,2}. Less common etiologies of SP in HIV hosts include Kaposi's sarcoma, toxoplasmosis, fungal infections and infections due to non-tuberculous mycobacteria^{1,2}.

Approximately 15-30% of SPs are bilateral. The most common etiology of bilateral SP is PcP^{1,2}. Finally, the prevalence of opportunistic infections and tumours associated with HIV has fallen since the introduction of HAART, leading to a reduction in the incidence of SP in this population.

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