

Concurrent Non Hodgkin lymphoma and *Pneumocystis jiroveci* pneumonia in an AIDS patient: a diagnostic challenge.

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Abstract

Lymphoma and *Pneumocystis jiroveci* infection are well-described entities in Human immunodeficiency/Acquired immunodeficiency syndrome (HIV/AIDS) patients. They are both AIDS defining diseases according to the World Health Organization (WHO). Although they are known to occur frequently in this patient population, concurrent B cell lymphoma and *Pneumocystis jiroveci* pneumonia, has not been reported in the literature. We describe the case of an HIV/AIDS patient with no history of anti-retroviral therapy, previously diagnosed lymphoma or treatment with chemotherapy, who was diagnosed with HIV during a recent incarceration, during which he developed fever, shortness of breath and fatigue. Due to the complex nature of his clinical presentation, a pulmonary lobectomy was performed. Grossly there was an ill-defined, friable, necrotic mass. Microscopically, there was an exudate consistent with *Pneumocystis jiroveci* and atypical lymphoid cells scattered throughout the necrotic tissue. Immunohistochemical stains demonstrated positivity of these lymphoid cells with CD20, PAX5, BCL2 and MUM1 with a diagnosis of large B cell lymphoma, activated type. A case of concurrent *Pneumocystis* and B cell lymphoma developing in an HIV/AIDS patient with no history of chemotherapy has not been reported to our knowledge.

Key words

Pneumocystis jiroveci pneumonia and large B-cell lymphoma; HIV/AIDS

■ INTRODUCTION

Lymphoma and *Pneumocystis jiroveci* infection are both well-described entities in Human immunodeficiency Virus / Acquired Immune deficiency Syndrome (HIV/AIDS) patients. They are both included in the World Health Organization (WHO) list of AIDS defining diseases. While it is relatively straightforward to diagnose these two diseases separately in an HIV positive patient, as they occur frequently; it is an uncommon event to have them occur simultaneously. This can prove to be a diagnostic challenge. According to recent literature, there has been a case report of Human T-lymphotrophic Virus 1 (HTLV-1) associated Adult T cell leukemia/lymphoma presenting as granulomatous *Pneumocystis jiroveci* pneumonia (PJP)[1]. There are also various reports of granulomatous and non-granulomatous PJP in patients with lymphoma after Rituximab therapy. It has been suggested that the prophylactic use of trimethoprim/sulfamethoxazole may prevent PJP in patients receiving

chemotherapy. However, a case such as this, with concurrent B cell lymphoma and *Pneumocystis* infection, with no history of chemotherapy, has not been reported. This case demonstrates that although a patient's immunologic status can guide clinical suspicion, it should also not restrict it to one specific diagnosis. These patients are at risk for having multiple and simultaneous disease entities. HIV-infected patients have an increased proclivity for developing malignancy. The gamut of neoplasms in this particular population has changed and keeps changing due to the use of antiretroviral therapy. Developed countries have seen a decrease in AIDS defining malignancies and an increase in non-AIDS defining malignancies due to antiretroviral therapy. Nevertheless, this pattern has not been observed in patients who have not received therapy, such as those in developing countries, with limited access to anti-retrovirals. *Pneumocystis jiroveci* pneumonia is the most common opportunistic infection in HIV patients. Prior to prophylactic treatment and/or antiretroviral treatment, about 80% of these patients became infected with *Pneumocystis* and about half of them died [2]. The estimates for 2006-2009 suggest that the overall incidence of HIV is relatively stable at about 50,000 yearly infections [3]. The incidence of PJP has declined to about 3%

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since the introduction of antiretroviral therapy. Often time, it occurs in persons previously undiagnosed with HIV or not receiving therapy as in our case [4].

■ CLINICAL HISTORY

The patient was 32 years old at the time of diagnosis. He had a negative HIV test 10 years before. He was incarcerated for 2 months before his hospitalization and during this time he was diagnosed with HIV. While incarcerated, he developed shortness of breath upon exertion, fever and fatigue. He was treated with an unknown antibiotic but failed to improve. Two weeks after his release, he visited the hospital due to increasing shortness of breath and sharp left-sided chest pain. He was diagnosed with a left sided pneumothorax. In addition, a 6.8cm thick walled cavitary lesion was noted in the left upper lobe and there was a right-sided pleural effusion with consolidation in the right lower lobe. The patient was noted to have a CD4 count of 13. His white blood cell count was 2.86. He stated that he recently experienced a 15-20 lb weight loss, fever and night sweats. Due to his HIV status and the character of the lesion, an infectious etiology such as tuberculosis was considered. He had a negative PPD test upon incarceration.

A sputum test was positive for *Mycobacterium fortuitum*. However, a bronchoalveolar lavage and pleural fluid examination did not reveal any significant findings. Cultures of his pleural fluid were negative. *Histoplasma* and *Legionella* urinary antigen were also negative. *Pneumocystis* was mentioned as a possible factor due to the patient's elevated LDH level. While he was hospitalized he was also diagnosed with Hepatitis B infection and was reported to have high levels of EBV (Epstein Barr virus) Immunoglobulin (Ig) G.

■ PATHOLOGIC FINDINGS

A left upper lobectomy was performed on the patient. Upon gross examination, there was an ill-defined, white mass with necrosis and cavitation (Fig 1). It was challenging to properly assess the mass present in the lung as the tissue was very friable and distorted the true character of the lesion.



Fig 1. Gross photograph of formalin-fixed specimen showing ill-defined mass with surrounding friable tissue

Microscopically, a bright eosinophilic exudate, very characteristic of *P. jirovecii* infection was present (Fig 2). The im-

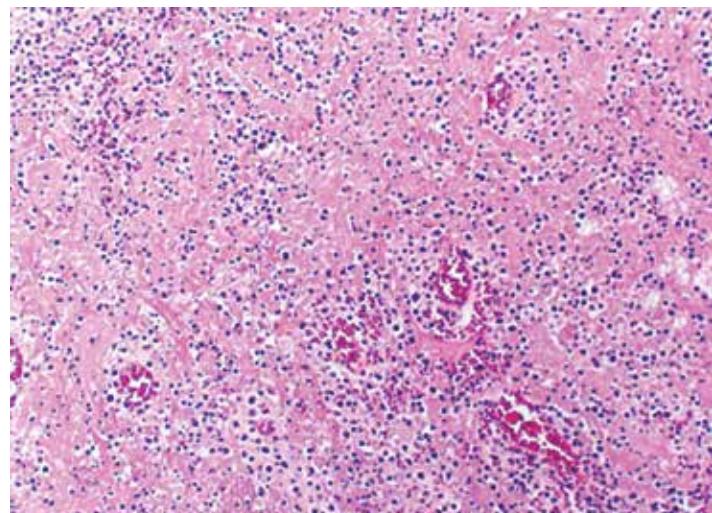


Fig 2. Eosinophilic fluid characteristic of *P. jirovecii* pneumonia 4x

munoperoxidase stain for *Pneumocystis jirovecii* was positive, confirming the diagnosis made on the hematoxylin and eosin slides. There was abundant necrosis in the sections taken as grossly appreciated. However, scattered around the necrotic debris and eosinophilic exudate, were cells with very little cytoplasm that appeared to be lymphoid in nature. Upon closer inspection, they were noted to be atypical, slightly irregular cells with prominent nucleoli (Fig 3). The necrosis obscured the architecture of these groups of cells. The clusters of cells were concentrated around blood vessels and around a bronchus. Immunohistochemical stains were performed to characterize the lymphoid cells. The combined stain for CD3/CD20 demonstrated diffuse positivity with CD20 on the lymphoid cells and scattered CD3 positive cells (Fig 4). These CD20 positive cells also stained positively with PAX5, another B cell marker. Additionally, a ki-67 proliferative index was 80% (Fig 5). Further staining revealed positively staining cells with BCL-2 and MUM1 (Fig 6). Im-

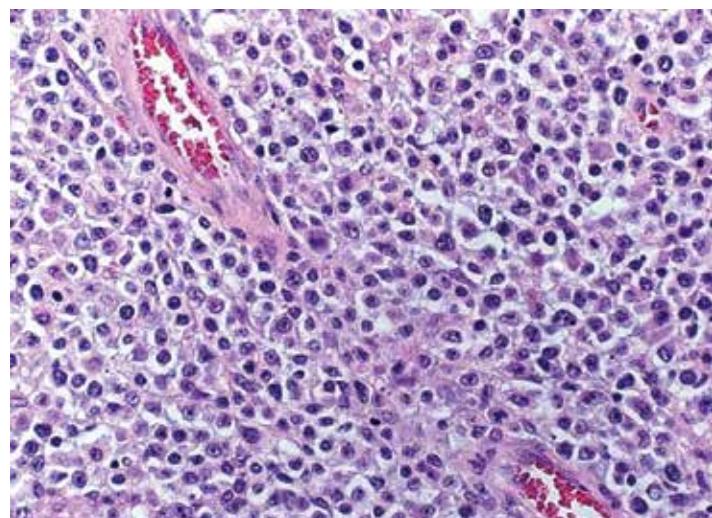


Fig 3. Atypical lymphoid cells 10x

munohistochemical stains for CD10, BCL-6, CD5 and HHV-8 were all negative. The diagnosis of large B cell lymphoma with activated phenotype was made.

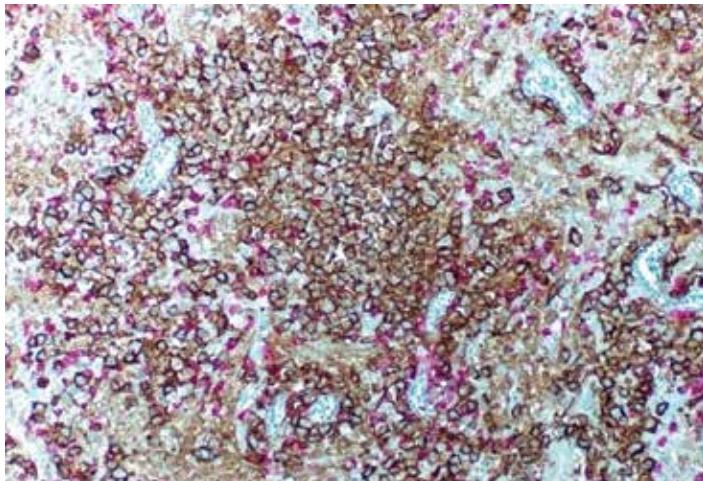


Fig 4. CD3 (red)/20(brown) combination stain, 20x . Most cells staining as B cells with scattered T cells

■ DISCUSSION

There are three AIDS defining malignancies: Kaposi's sarcoma, Non Hodgkin lymphoma and cervical cancer. AIDS related lymphoma is divided into three types: systemic non-Hodgkin lymphoma, primary central nervous system lymphoma and primary effusion lymphoma [5]. Prior to the use of HAART (Highly active antiretroviral therapy), the incidence of AIDS related lymphoma was much higher and has decreased from 29.6 per 1000 person-years before HAART to 6.5 per 1000 person-years after HAART[6]. Therapy has changed the progressive immunosuppression in HIV patients. AIDS defining malignancies have decreased but there is an increased risk of dying from cancer due to the chronicity of HIV infection. HAART along with the use of chemotherapy has improved the outcome and survival of these patients.

HIV associated lymphomas are mostly of B cell origin. About

80% occur as systemic lymphomas that are further classified as large cell or Burkitt type. Many of these patients can have normal or low CD4 counts and usually have not had opportunistic infections at the time of diagnosis. However, clinical presentation varies. Additionally, many of these patients present with extranodal disease at the time of diagnosis. Certain types of lymphomas have been associated with Epstein Barr and Human Herpes virus 8. The human immunodeficiency virus is not considered to be oncogenic, however, it is thought to play a direct pathogenic role in the development of malignancies.

Pneumocystis is a major cause of opportunistic fungal pneumonia in patients who are immunocompromised. There are four clinical forms including extrapulmonary infection resulting from dissemination from the lungs. Imaging usually shows bilateral alveolar and interstitial infiltrates that radiate from the hilum. The cysts induce an inflammatory response in the alveoli, producing an exudate that interferes with proper gas exchange. The literature states that pneumonia develops as an activation of preexisting quiescent organisms in the lungs as most children worldwide possess antipneumocystis antibodies [7]. Prophylactic treatment of AIDS patients (with less than 200 CD4+ cells/microliter), with trimethoprim-sulfamethoxazole can prevent the development of fatal pneumonia in many cases. *P. jiroveci* lacks ergosterol in its cell membrane and thus, is not susceptible to many common antifungal agents such as amphotericin [8]. The incidence of *P. jiroveci* pneumonia (PJP) in HIV/AIDS patients has decreased with the use of HAART. Of note, it is well described in the literature that non-HIV patients with B cell lymphomas, treated with cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) based chemotherapy, are at risk for developing PJP [9,10,11]. In a study of 47 patients treated with R-CHOP, Kamel et al have suggested that prophylactic treatment of PJP should be considered. Hardak et al did a retrospective study of 132 patients with diffuse large B cell lymphoma on different regimens of R-CHOP. They observed that the patients receiving prophylaxis for PJP prevention did not develop the disease.

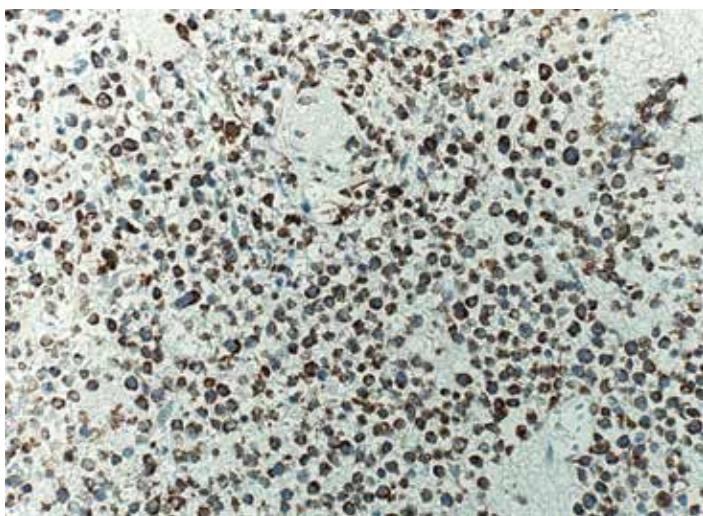


Fig 5. Immunohistochemical stain for ki-67 shows high proliferative index 10x

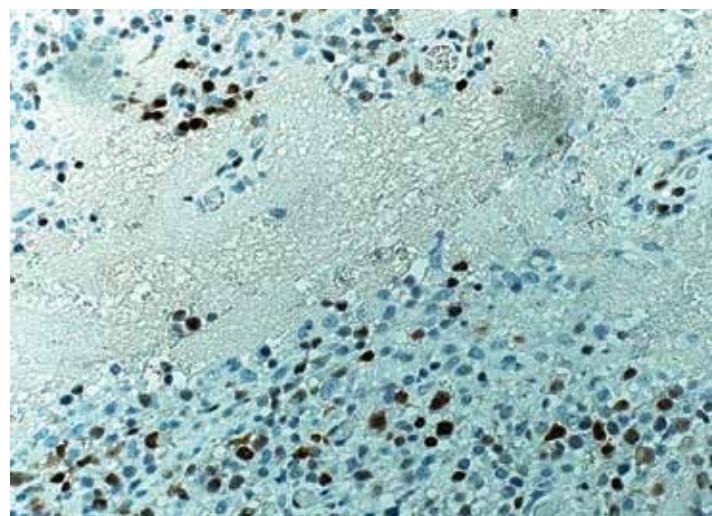


Fig 6. Immunohistochemical stain for MUM-1 showing positively staining cells 10x

As previously stated, our patient had not received HAART or CHOP-based chemotherapy prior to his hospitalization. He also had no prior diagnosis of lymphoma or PJP.

A diagnosis of lymphoma was in the differential diagnosis of our patient but not foremost due to the unusual presentation in conjunction with *P.jirovecii* pneumonia. The cavitated mass along with the clinical presentation, with exception of the lack of a cough, spoke more for tuberculosis. The increased lactate dehydrogenase (LDH) level and pneumothorax suggested PJP [12]. Serum LDH has a high sensitivity (78-100) for PJP, as shown by Quist and Ross Hill in 1995 and followed by other researchers. However, it has low specificity since many other disease processes can lead to an elevated LDH [13]. Nevertheless, the presence of night sweats, weight loss and fatigue also speak for malignancy. It is important to keep in mind that although not common, these diseases can occur together and thus, the presence of one may obscure the diagnosis of the other, especially in a recently diagnosed HIV positive patient with no history of HAART. Imaging studies are not definitive. Sputum examination and bronchoalveolar lavage are generally used for cytological identification of PJP. However, in this patient they did not reveal significant findings. This may have been due to sampling error. The diagnostic challenge for the pathologist in this case was to assess the importance of the lymphoid cells. *Pneumocystis* infection usually does not present as a solid, cavitating mass as in this patient. It has been known to present as a cystic mass in a few pediatric cases[14]. This patient had a partially cavitary and solid mass. Microscopically, the mass showed significant necrosis, which complicated the diagnosis. In this case, additional tissue was processed and the findings remained the same; necrosis, PJP and clusters of atypical lymphoid cells. The use of immunohistochemical stains was helpful in classifying these cells and arriving at a diagnosis. The diffuse CD20 positivity and high proliferative index in assessable areas alluded to the fact that the infection was obscuring a malignancy. After this first clue, the final classification as an activated phenotype was less difficult. Additionally, *in situ* hybridization studies were performed on paraffin embedded tissue block that showed positivity for Epstein Barr encoded early RNA (EBER1 mRNA). Simultaneous PJP and lymphoma, in a patient with no history of chemotherapy, has never been reported in the literature, to our knowledge.

■ CONCLUSIONS

About thirty years have passed since HIV was first recognized. Since then intense research has contributed to a better understanding of the disease process. Many patients are living longer with treatment; such as they do with other chronic disease states. Because of this, the causes of morbidity and mortality in HIV/AIDS patients are changing. In spite of this, the spread of the disease continues and many infected persons have not been tested and are still not receiving treatment. HIV/AIDS continues to be an important issue in public health.

Because this virus is still being spread and some people still do not know their status, it is vital that physicians bear this

diagnosis in mind when they are treating a patient; especially one with a disease that is known to occur in this population. It is crucial to keep in mind all the possible opportunistic diseases and malignancies that occur in AIDS patients when presented with a complicated case. The clinical scenario as well as the pathologic findings must correlate. There must be microscopic examination of the tissue, whether it may be sputum, bronchoalveolar lavage and/or biopsy or excision. In this case, the patient presented with what looked like an infectious process. However, there was an underlying malignancy that could have been overlooked had there not been an excision and careful microscopic examination of the tissue. It is unlikely that the presence of the PJP led to the development of lymphoma in this patient since there is no evidence supporting such an etiology. However, the presence of malignancy may have enhanced the development of the PJP in the exact area where the malignancy was present. The combination of an infectious process and malignancy is not unheard of and although not given clinical priority, it must always be in the differential diagnosis of the attentive pathologist, especially in a patient with no history of HAART or CHOP-based chemotherapy.

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