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Non Hodgkin's lymphoma of B cell type with hemophagocytosis in a patient with HIV infection

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Abstract

Human immunodeficiency virus causes chronic infection of the immune system leading to reduction of CD4 helper cells, making the patient prone for many opportunistic infections. The incidence of opportunistic infections is increased in the presence of low CD4 count. Here, we present a case of HIV infection presenting with mediastinal lymphadenopathy, treated as disseminated tuberculosis which then developed pancytopenia with hyperbilirubinemia. He was finally diagnosed to have non Hodgkin's lymphoma of B cell type with hemophagocytic syndrome at postmortem. We emphasize that when a HIV patient has a relatively higher CD4 count non infectious causes should be kept in mind while empirically treating for opportunistic infections.

Keywords

AIDS/HIV; chronic infection; mmune system

Introduction

Acquired immuno deficiency syndrome (AIDS) is the end stage of the spectrum of disease caused by human immuno deficiency virus (HIV). Decline in the immunity is a direct result of CD4 cell destruction by the virus, leading to increase in occurrence of neoplasms and opportunistic infections. Lower CD4 counts can be correlated with higher incidence of opportunistic infections. We present a 45 year old male with HIV infection, on empirical anti-tuberculosis therapy (based on pulmonary imaging) who developed pancytopenia with indirect hyperbilirubinemia. Analysis of this case allows a focused approach to arriving at differentials in patients presenting as such. This case also stresses the importance of considering non infectious causes during evaluation of opportunistic infections in AIDS and also the consequences of delay in diagnosis, a compromise usually made in resource limited settings.

Case Report

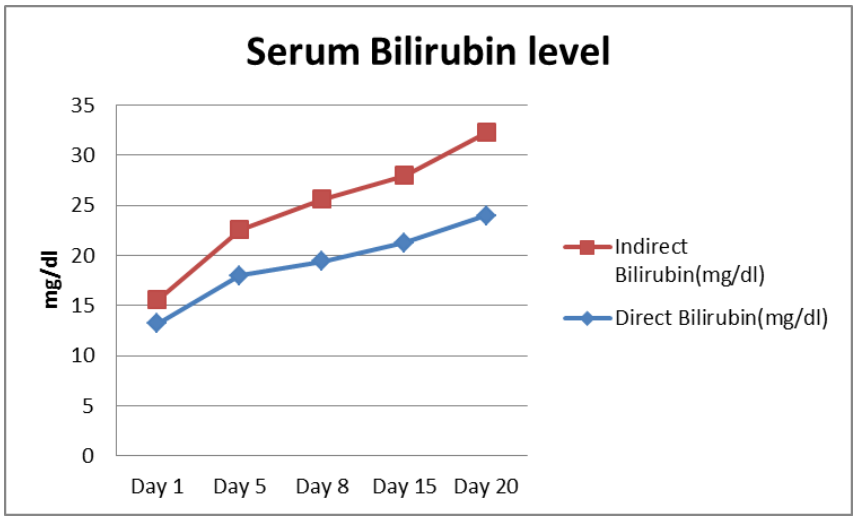
A 45 year old male with retroviral infection for six months presented with yellowish discoloration of sclera, abdominal pain for two days associated with loss of weight and appetite, pale colored stools and pruritus.

Two months prior to current admission, he presented to another center with fever of one month

duration lacking localizing symptoms. Computed Tomography study of the chest and abdomen revealed the presence of multiple retroperitoneal lymph nodes and bronchiectasis, for which antituberculous therapy was initiated. (Isoniazid + Rifampicin + Pyrazinamide + Ethambutol). Investigations done two months prior to current admission as per the records were: Hemoglobin (Hb) – 12.3 g%, Total WBC count – 6300 cells/cmm, Platelets – 1,40,000 cells/cmm, Erythrocyte Sedimentation Rate (ESR) – 88mm in 1 hour, Creatinine – 0.8mg/dl, Bilirubin – 0.6 mg%, Alanine Transaminase (ALT) – 34IU/L, Aspartate Transaminase (AST) – 24IU/L, Alkaline Phosphatase (ALP)- 258 IU/L, Gamma-Glutamyl Transpeptidase (GGTP)- 312 IU/L. His Prothrombin Time (PT) was 12 seconds and International Normalised ratio (INR) was 1.0. He had tested Human Immunodeficiency Virus (HIV) positive then with a CD4 count at that time of 326 and HIV viral load was 120000 copies. He was initiated on Anti- Retroviral Therapy (ART) with Tenofovir, Emtricitabane and Efavirenz.

He was conscious and oriented on presentation. He was found to exhibit pallor, jaundice and per abdominal examination revealed splenomegaly. He did not have asterixis and there were no focal neurological deficits.

His investigations during the current admission were: Complete haemogram (CBC) revealed pancytopenia (Hb – 8.7g/dl; Total WBC count -3000 cells/cmm; Platelets- 68,000/cmm, ESR -86mm in 1 hour). Renal function tests were normal. His liver function test (LFT) showed hyperbilirubinemia with normal ALT and AST with increase in ALP (324 IU/L) and GGTP (314IU/L). INR was 1.1. In view of hyperbilirubinemia with normal ALT, Rifampicin was stopped and other medications were continued. Despite these efforts, there was a progressive worsening of his LFT (Graph 1), hence ATT and ART drugs were withheld. Ultrasound of abdomen showed normal liver echo texture, no intra hepatic biliary radicle dilatation or common bile duct dilatation and splenomegaly. Serology for Hepatitis A, B, and C, E viruses, Cytomegalovirus (CMV) and Epstein Barr virus (EBV) were negative. Hepatitis B and Hepatitis C viruses were not detectable. Autoimmune workup (Anti-nuclear antibody (ANA), Anti Liver Kidney Microsomal (LKM) antibody) was also negative. Serum procalcitonin was carried out to rule out bacterial sepsis as a cause for cholestasis, but was found to be within normal limits. Repeated blood, urine cultures for bacteria and fungi (using Sabouraud dextrose agar incubated at 22 and 30 degree Celsius) were sterile. Finally, Magnetic resonance cholangio pancreatogram (MRCP) was done to rule out any obstructive pathology and was normal.

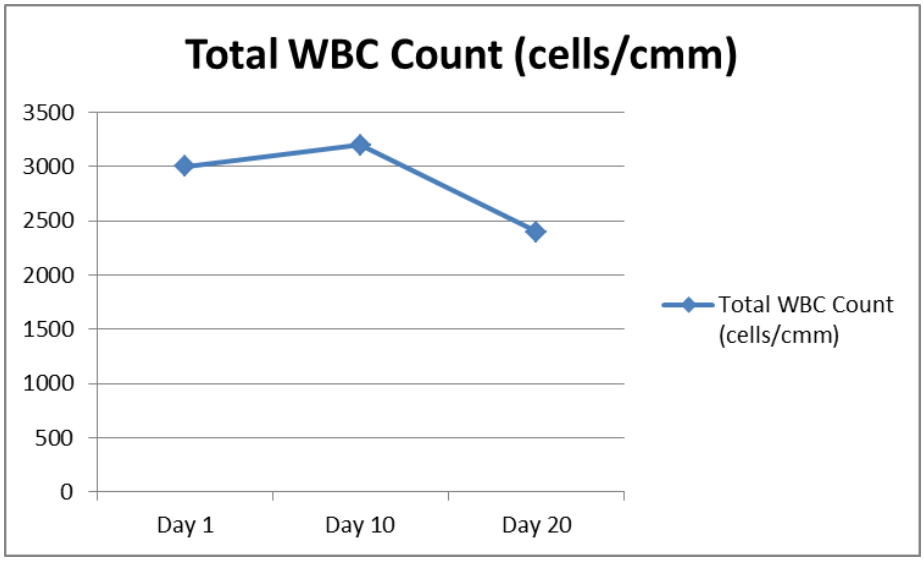


Graph 1: Serum Bilirubin level during the hospital stay.

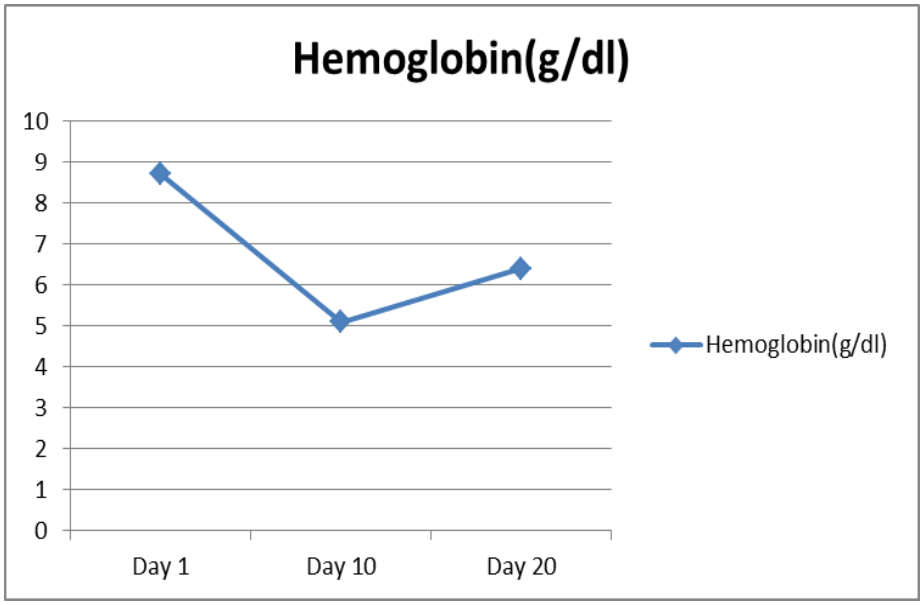
On the tenth day of admission at our centre, a complete blood count was done, showing pancytopenia (Total WBC count – 3200 cells/cmm, Hb – 5.1g/dl, Platelet count – 64,000 cells/cmm) and reticulocyte count was 14%. Serum vitamin B12 and Folic acid were within normal limits. Anaemia profile was suggestive of anaemia of chronic disease. Subsequently, bone marrow aspiration and biopsy showed a hypercellular marrow without any granuloma, fibrosis, atypical cells, hemophagocytic macrophages or infiltrative lesions.

During the course of his hospital stay, it was seen that his blood counts displayed a decreasing trend.

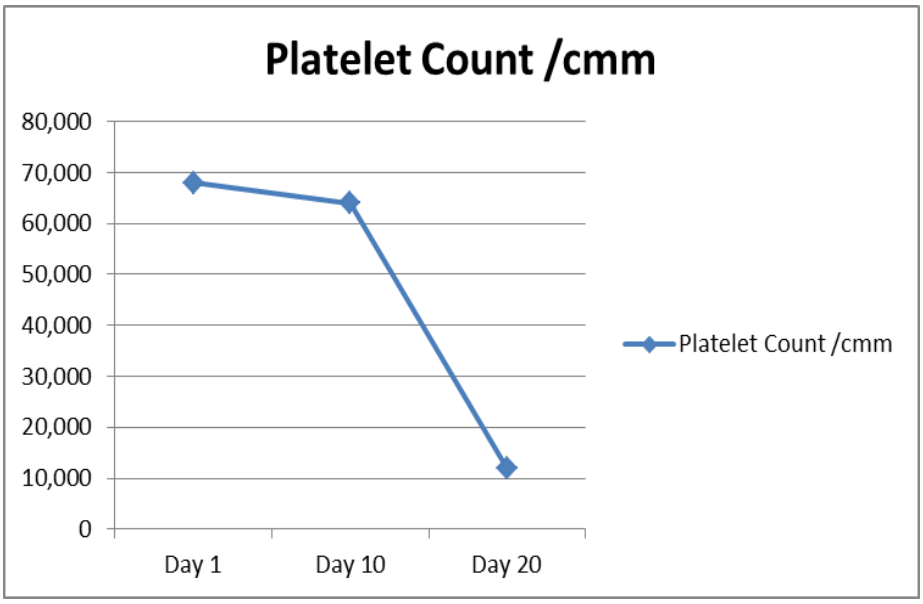
The changing trend in Total WBC counts, Hb and Platelet count during the course of hospital stay was as follows:



Graph 2: Total WBC count during hospital stay



Graph 3: Hemoglobin changes during hospital stay



Graph 4: Platelet count during hospitalization

He was treated with supportive medications including blood and blood product transfusions. Lymph node/liver biopsy was planned, but decision to carry out the procedure was deferred in view of thrombocytopenia. In spite of these efforts, the patient developed complications of intracranial cranial hemorrhage and expired. After obtaining the required permissions from his near relations, postmortem liver and spleen biopsy were done.

The sections taken from the biopsied spleen and liver showed fragments of splenic tissue and liver tissue with congestion and one fragment showed infiltration by a population of pleomorphic cells. Morphologically, the cells were round with abundant cytoplasm and irregular vesicular nuclei. Occasional giant cells were seen (Figure 1A&1B). Portal tracts were not visualised in the sections studied. In addition to these findings, the liver tissue showed intracellular cholestasis, evidence of hemophagocytosis in liver cells and sinusoidal dilation (Figure 1C&1D). The atypical cells were showing positivity for CD 45 (leukocyte common antigen) and CD 20 (Figure 2A &2B) cellular markers. These findings were consistent with non-Hodgkin's lymphoma of B-cell type with associated hemophagocytosis of liver.

Discussion

The hallmark of infection by the human immunodeficiency virus is the depletion of CD-4 T helper cells and defective macrophage and monocyte functioning. A direct consequence of this is the greater tendency of past tuberculosis reactivation with hastening of its clinical manifestations. Thus, its presentation is more sub-acute than chronic in these patients [1].

Two months prior to admission, our patient was started on ART for retroviral disease and ATT for suspected pulmonary and extra pulmonary tuberculosis. He developed cholestatic jaundice and pancytopenia and deteriorated despite discontinuing possible causative medications. In the setting of HIV infection, possible differential diagnoses for cholestatic jaundice would be medications, opportunistic infections, neoplasms, AIDS cholangiopathy and sclerosing cholangiopathy [2].

In this particular case the cause for cholestasis remained elusive despite extensive investigations.

There was no evidence of any intra-hepatic biliary radicle dilatation on ultrasonography of the abdomen, confirmed by MRCP. Hence intra-hepatic cholestasis was unlikely [3]. Then, cultures of the blood and urine including fungal cultures were done to rule out infections. Procalcitonin was also normal. These findings point towards a non-infectious cause. As certain pharmacological therapies can cause cholestatic jaundice, a detailed drug history was also elicited and none of the drugs he was taking have been implicated as causing cholestasis and pancytopenia. The possibility of HIV cholangiopathy was considered but was thought to be unlikely in view of the progressive cholestasis, no evidence of intrahepatic biliary radicle dilatation in imaging (USG or MRCP) and negative stool for Cryptosporidium parvum [4]. In fact, the presence of jaundice itself is an unusual feature of AIDS cholangiopathy [5] .

On evaluation of progressive pancytopenia, the cause was ultimately not discernible. In view of this bone marrow biopsy was done which showed the presence hypercellular marrow. The common causes for pancytopenia in HIV infection without fever diagnosed using bone marrow biopsy are [6]:

1. Infection

    Parvovirus infection

    Histoplasma capsulatum

    Mycobacterium tuberculosis

    Mycobacterium avium complex

    HIV

    Salmonella typhi

2. Miscellaneous

    Hodgkin's disease

    Hypersplenism

    Hemophagocytic syndrome

The presence of hypercellular marrow, reticulocytosis and splenomegaly was suggestive of either immune pancytopenia [7,8] or hypersplenism. Autoimmune workup (ANA, Coombs test) was negative. The possibility of haemophagocytic lymphohistiocytosis was considered in view of pancytopenia, liver involvement and increased ferritin. However this diagnosis was thought to be unlikely due to the observation that triglycerides were under normal limits, patient was afebrile and bone marrow and peripheral smear analysis did not reveal any correlative evidence. The cause for pancytopenia in this case could be explained by hypersplenism rather than the infiltrative disorder per se due to the combination of elevated reticulocyte count and splenomegaly. An additional explanation for pancytopenia is a paraneoplastic manifestation of lymphoma. However, the negative Coombs test disaffirms this as a cause for this presentation.

Hence the working diagnosis was vanishing bile duct syndrome with hypersplenism leading to pancytopenia (or a coexisting autoimmune pancytopenia). The other likelihood was lymphoma with hemophagocytosis which was ruled out in view of inconclusive bone marrow findings (no atypical cells and no evidence of hemophagocytosis). A liver biopsy was planned but was deferred in view of the

coagulopathy and thrombocytopenia. Our patient's condition continued to decline during the hospital stay and died due to intracranial bleed. Postmortem liver and spleen biopsy revealed non Hodgkin's lymphoma of B cell type with hemophagocytosis. Conclusively, this underscores the importance of arriving at a histopathological diagnosis before initiating ATT.

The final diagnosis was determined to be haemophagocytosis. Its presentation in this patient was nothing short of unusual. This patient was afebrile (although fever occurs in 70% to 100% of haemophagocytic syndromes), had hypertriglyceridemia and bone marrow aspiration and biopsy did not reveal any siginficant evidence to support the diagnosis. A study done by McCall et al has shown that few patients with HLH did not show marrow evidence of haemophagocytosis in the first biopsy but showed it only on later biopsies [9].

Diagnosis of hemophagocytic lymphohistiocytosis (HLH) syndrome relies on clinical, laboratory, and histopathological findings. Diagnostic guidelines were proposed by the Histiocytic Society in 1991 and updated in 2004 is as follows [10]:

The diagnosis of HLH can be established if one of either 1 or 2 of the criteria below is fulfilled.

1. A molecular diagnosis consistent with HLH

2. Diagnostic criteria for HLH are fulfilled (5 of the 8 criteria below):*

Fever

Splenomegaly

Cytopenias (affecting 2-3 lineages in the peripheral blood)

Hypertriglyceridemia and/or hypofibrinogenemia

Hemophagocytosis in BM, spleen, or lymph nodes

Low or absent NK-cell activity (according to local laboratory reference)

Ferritin - 500 g/L

Soluble CD25 (sIL2r) - 2400 U/ml.

Our patient fulfilled only three of the total eight criteria during the diagnostic workup but was established to have haemophagocytosis in liver biopsy at postmortem. This underscores the fact that the diagnostic criterion is primarily implied for conduct of clinical trials and it does not include all the clinical and laboratory features [11,12]. As a result of the complex diagnostic criteria and rarity of the condition the diagnosis is often delayed. Hence a high degree of clinical suspicion is very important in early diagnosis and preventing the high mortality associated with the disease [13]. There have been various causes that have been implicated in the etiology of HLH. The association of lymphoma as an etiology is well known but B cell lymphoma presenting with HLH is quite rare. The cause for pancytopenia was hemophagocytosis with or without paraneoplastic manifestation of Lymphoma [14].

The incidence of Lymphomas is much higher in HIV patients than in the general population [15]. The mode of transmission is not associated with any increase in risk of lymphomas in contrast to Kaposi sarcoma which is much more common in men who have sex with men. Most of the opportunistic

infections occur in low CD4 counts which also holds true for EBV associated Non Hodgkin's Lymphoma but HIV associated Hodgkin's lymphoma occurs in most patients with relatively intact CD4 count [16]. The initial presentation of AIDS related Lymphomas can be very subtle while in others it may be very obvious. Symptoms include but are not limited to low grade fever, unexplained fever, night sweats, adenopathy or organomegaly. The challenge lies in the exploration of various differentials that come up as a result of the incidence of these symptoms, in people diagnosed with AIDS. A high level of lactate dehydrogenase (LDH) is found in aggressive lymphomas and has prognostic implications. Excision biopsies are preferred over needle procedures as they preserve the architecture and immunophenotyping done whenever needed. Neuroimaging should be done at diagnosis as more than 17% of peripheral lymphomas in AIDS patients involve CNS. Treatment of Lymphomas is similar for AIDS and non-AIDS patients. Though with the introduction of HAART the prognosis of lymphomas has improved, the prognosis of lymphomas is worse in AIDS patients than for the same lymphomas in non AIDS patients [17,18,19].

Figures

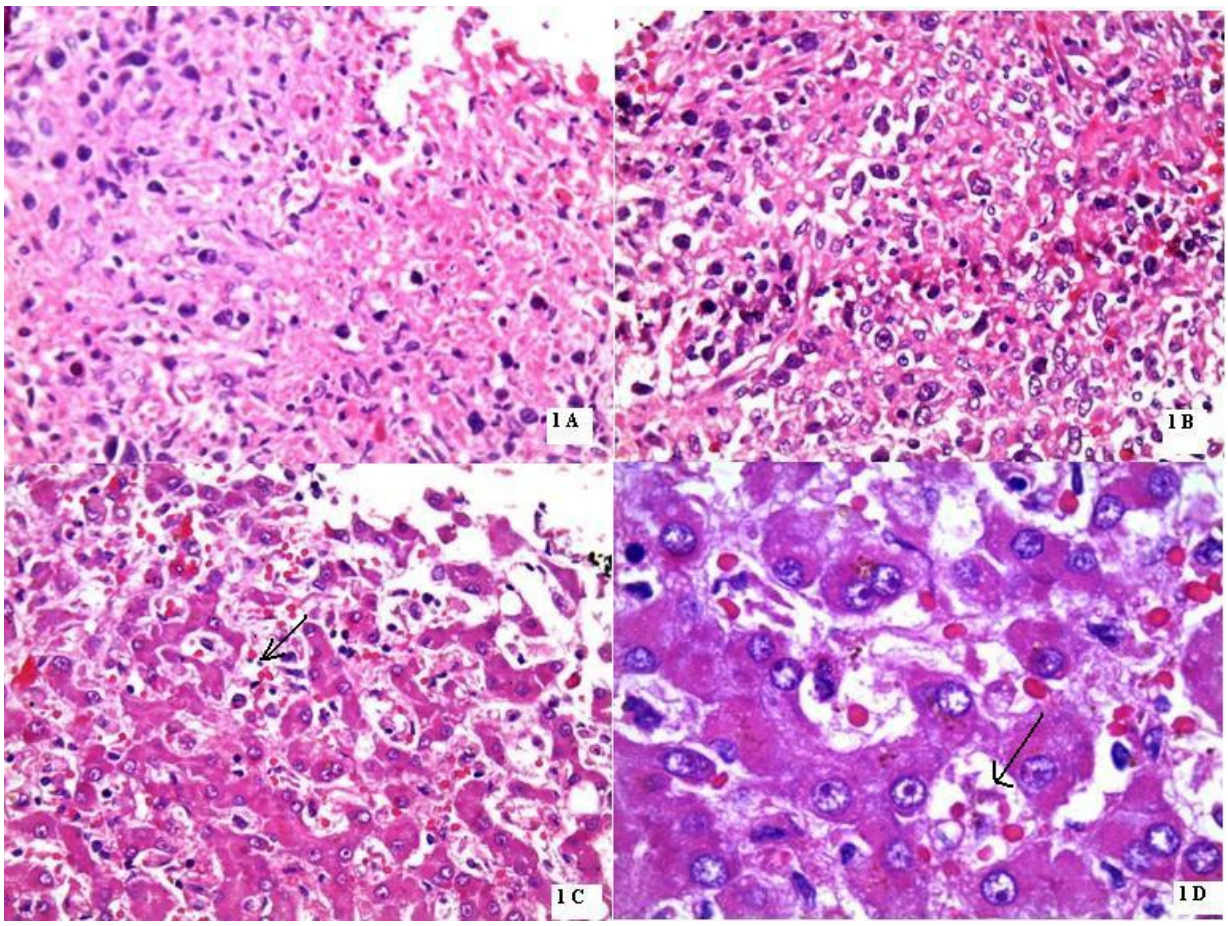


Figure 1: A: Biopsy from liver shows fragment of atypical cell collections. 100 x magnifications, H&E
B: Biopsy from spleen shows fragment of atypical cells 100x magnification, H&E
C: Liver tissue shows hemophagocytosis. 100 x magnification, H&E
D: Liver tissue reveals hemophagocytosis as pointed by the arrow. 400 x magnification, H&E

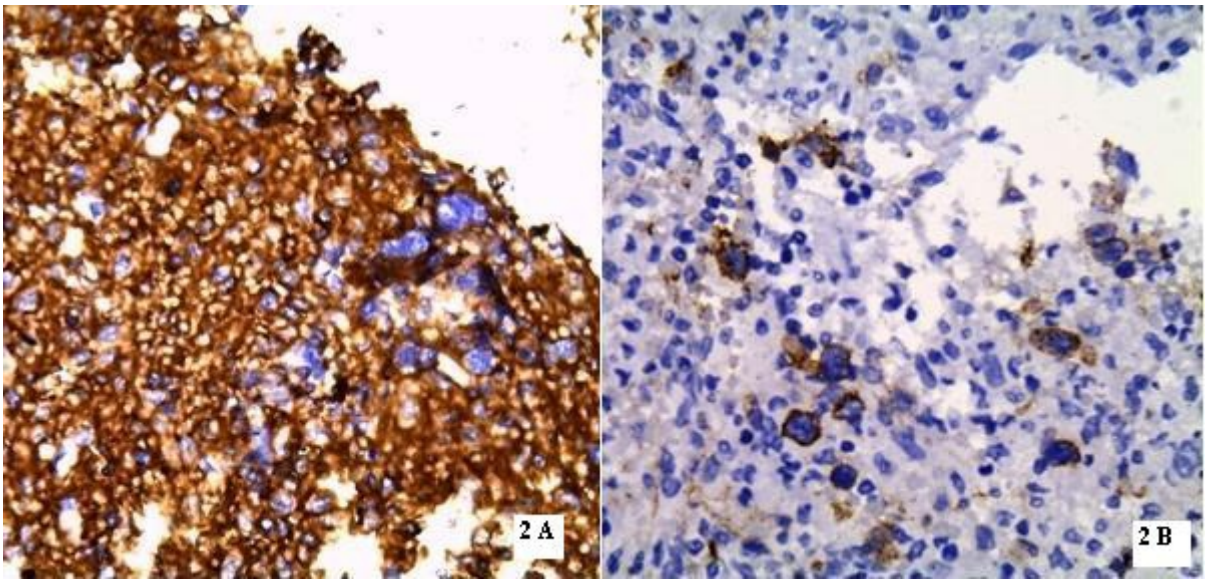


Figure 2: A: The atypical cells express strong positivity for LCA/ CD 45. 100 x magnification
B: Large cells show moderate positivity for CD 20. 100 x magnification

Conclusion

We hereby have described an unusual presentation of lymphoma in a retroviral positive patient. Hemophagocytic syndrome is known to occur with lymphomas but its association is more common with T cell lymphoma than B cell lymphoma, as was concluded in this case. The diagnostic criteria for Hemophagocytic syndrome is meant for conduct of clinical trials. It should be noted, however, that these diagnostic criteria do not reflect all of the typical clinical or laboratory features of patients with HLH, many of which are helpful in making the diagnosis. Hence treatment should not be delayed in fulfilling the criteria. A high degree of clinical suspicion is essential in early diagnosis of hemophagocytic syndrome. The microbiological diagnosis is very important when we evaluate a HIV infected patient for opportunistic infections. It is imperative that non infectious etiologies are considered during evaluation, especially when the CD4 count is not low. There is no role for empirical anti-tuberculous therapy even in resource limited settings.

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