Casual or Causal? Two Unique Cases of Hodgkin’s Lymphoma: A Case Report and Literature Review

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Case series
Patient: Male, 38 • Male, 30
Final Diagnosis: Hodgkin’s lymphoma
Symptoms: Lymphadenopathy • shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare disease
Background: Immunosuppressive diseases and therapies have long been connected to risk of malignancies, especially lymphoma. With some diseases and drugs, the association is well established but the data is mostly anecdotal because of the rarity of the situation.

Case Reports: We present 2 rare cases. The first patient had psoriasis, was on etanercept, and developed Hodgkin’s lymphoma. This case is rare because psoriasis and etanercept do not usually cause lymphoma, and if they do, it is predominantly Epstein-Barr virus-positive non-Hodgkin’s lymphoma. The second patient had acquired immune deficiency syndrome (AIDS) and developed Hodgkin’s lymphoma while on highly active antiretroviral therapy (HAART). This case is rare because AIDS mostly causes Kaposi’s sarcoma or non-Hodgkin’s lymphoma due to immunosuppression, but whether it is AIDS or HAART therapy that leads to development of Hodgkin’s lymphoma in these patients is not clear.

Conclusions: Immunosuppression seems to be the primary culprit leading to lymphomas in these cases. The exact mechanism is still not completely understood.

MeSH Keywords: Hodgkin Disease • Lymphoma, AIDS-Related • Lymphoma, B-Cell • Psoriasis

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**Background**

Rheumatoid arthritis and Crohn’s disease have been associated with lymphoma. Psoriasis might also slightly increase the risk of lymphoma, predominantly non-Hodgkin’s lymphoma. We present the case of a patient who developed Hodgkin’s disease while on immunosuppressive therapy. This relationship is not yet well established, so we believe all such cases should be reported to establish a causality or coincidence.

We also present another case of nodular sclerosis Hodgkin’s lymphoma in a patient with HIV/AIDS who was EBV-negative and had been on HAART for a long time. This is a unique occurrence in multiple ways, leaving many questions unanswered. The possible mechanisms are explained in Figure 1.

**Case Report**

**First case: EBV-negative Hodgkin’s lymphoma in patient with psoriasis treated with etanercept**

A 38-year-old man was admitted with fever and shortness of breath (SOB). He had a medical history of psoriatic arthritis for which he failed initial therapy and was started on etanercept. He used it for 1 year and stopped about a month ago, due to lymphadenopathy. He had recently been hospitalized for 3 days for right knee pain/septic arthritis with negative work-up, and he had left axillary excisional biopsy because of suspicion of lymphoma, which showed benign cortical and paracortical hyperplasia with changes consistent with dermatopathic lymphadenopathy. The flow cytometry exam was negative for a clonal B/T cell process. He also had a history of a gunshot wound to the abdomen and right femoral artery repair. He reported having a temperature of 101 to 102 degrees Fahrenheit at home, and also reported worsening SOB in the previous few days, associated with exertion. He denied any sick contacts, chest pain, or cough associated with fever. He denied any dysuria, joint pain, myalgia, or other systemic symptoms. He also reported watery, loose, non-bloody diarrhea for about 1-2 weeks, which was greenish mixed with stool, but denied any nausea, vomiting, or abdominal pain. He had lost 40 pounds in the previous few months, which was partly intentional, as he was controlling his diet to prepare for a gastric sleeve procedure.

His vitals were significant for a fever of 102 degree Fahrenheit, a pulse of 113 beats per second, blood pressure of 133/61mmHg, respiratory rate of 18 breaths per minute, and oxygen saturation of 94% on room air. The exam was pertinent for a left supravacular firm lymph node ~2–3 cm; a ~4-cm lymph node palpable in the left axilla, lymphedema of the bilateral lower extremity, and diffuse erythema of the bilateral lower extremities with dryness of the skin. Lab data showed mild hypotension, slight hypoalbuminemia, acute inflammatory anemia, leukocytosis with mild left shift, and normal lymphocyte count. Chest x-ray and CT scan showed bilateral axillary lymphadenopathy, and a large left axillary lymph node increased in size compared to a previous CT scan. There was a new small-to-moderate left pleural effusion with atelectasis involving several segments of the left lower lobe and a new nodular right pleural mass. There was also sub-segmental atelectasis with possible right lower lobe nodule (Figures 2–4).

The patient was started on treatment for healthcare-associated pneumonia but the suspicion of an atypical/mycobacterial/fungal infection given the chronic use of immunosuppressants led to an infectious disease consult. PET/CT scan at this point was deferred due to risk of false positives. Further lab studies showed negative HIV serology, negative EBV serology, negative EBV DNA by polymerase chain reaction (PCR) method, negative serum cryptococcal antigen, negative urine histoplasmosis antigen, and negative galactomannan antigen. He was placed in respiratory isolation. Sputum cultures were negative for TB and fungus. IR thoracentesis showed reactive histiocytosis but no malignancy. Repeat CT scan showed worsening pleural mass that was larger than in a previous CT scan.

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**Figure 1. Algorithm.**
This again raised the suspicion of lymphoma and the patient underwent a pleural mass biopsy. An abdominal pelvis CT scan showed a large retroperitoneal mass. The neoplastic cells were CD 20-negative, suggesting there was no B cell lymphoma. The cells were CD 30-positive and CD 15-negative. The amount of neoplastic tissue in the chest wall specimen was too small to give a definitive diagnosis. We then biopsied the retroperitoneal mass. We were reluctant to biopsy another lymph node because the prior excisional biopsy was negative. This gave the diagnosis of stage IVB nodular sclerosing Hodgkin’s lymphoma. An MUGA scan was done and ABVD therapy was initiated.

**Second case: EBV-negative Hodgkin’s lymphoma in an AIDS patient treated with HAART**

A 30-year-old man was admitted with profound weakness, cough, and SOB. He had a history of HIV, PCP pneumonia, CMV pneumonitis, and non-collapsing type FSGS. He was on anti-retroviral therapy and his CD4 count was 154 per cubic millimeter. His vital signs showed hypotension, severe hypoxia, tachycardia and respiratory distress, and he was admitted to the intensive care unit (ICU). His exam results were significant for respiratory distress, rhonchi on the right middle and lower lobe, regular but fast heart beats, and axillary and inguinal lymphadenopathy. His lab results showed leukocytosis, a chest x-ray showed pneumonia, and he was started on broad-spectrum antibiotics for HCAP. BAL was negative for PCP this time. A chest CT scan showed axillary and mediastinal lymphadenopathy, which was thought to be reactive secondary to pneumonia. The patient was intubated at first, with successful extubation, and he was transferred out of the ICU. A repeat CT scan showed worsening mediastinal lymphadenopathy, but his pneumonia had resolved, which raised the suspicion for a malignant process. EBV serology and PCR were negative and a lymph node biopsy showed CD 15-, CD 20-, and CD 30-positive nodular sclerosing Hodgkin’s lymphoma. He was transferred to a specialized malignant hematology center because of complications and immunosuppression involved with ABVD therapy in the presence of active infection.

**Discussion**

Psoriasis is an autoimmune disease which leads to rash and scarring of the skin. The treatment options are topical steroids, and if these fail, steroids can be followed by phototherapy. The third-line therapy is systemic with methotrexate and cyclosporine [1]. The pathogenesis includes T cells, dendritic cells, and immune-related cytokines, which can be targeted by newer therapies and biologics [2]. Psoriasis has been directly associated with an increased risk of malignancy, especially lymphoproliferative disorder and skin cancer, and patients with less severe disease are at lower risk compared to patients...
with more severe disease on systemic therapies who developed more lymphomas [3]. A Finnish study reported that psoriasis increased the risk of skin cancer and non-Hodgkin lymphomas [4]. It is still a topic of debate whether psoriasis itself is the cause of lymphoma or whether its treatment leads to higher incidence [5]. One key component of psoriasis treatment, methotrexate, has been linked to lymphoma, mostly HL [6].

A key component of psoriasis treatment is TNF-alfa inhibitors; the FDA-approved ones for psoriasis are etanercept and infliximab, and adalimumab is under phase 3 trials with promising results so far. Etanercept is a fully human-soluble TNF receptor fusion protein which showed sustained improvement in signs and symptoms of moderate to severe psoriasis [7]. In an RCT, etanercept proved more efficacious than Actretin due to reduced serum levels of interleukin-17 and interleukin 22 [8]. Immunosuppressive therapies in general have been associated with increased risk of lymphoma, especially NHL, and the cause in most cases is an underlying infection like HIV or EBV [9]. After its FDA approval in 1998, 18 cases of lymphoma were reported to the FDA due to etanercept and only 1 of them was Hodgkin lymphoma [10]. These cases were mostly B cell NHL. What triggers the body to develop HL vs. NHL is a mystery. Our first patient was an unusual case who was negative for HIV, EBV, and other known infectious triggers for lymphoma. He was on etanercept for a year, which seems long enough for etanercept to cause immunosuppression. Whether it was due to psoriasis or etanercept or some other underlying trigger is unknown. Currently, data are insufficient to draw any conclusion about the etiology of lymphomas in these diseases which led us to report this case.

Approaches to management of these cases also come from anecdotal data. In our case, we stopped etanercept and switched it to infliximab due to fewer cases reported due to the latter, close to the situation in the general population. We treated our patient with ABVD regimen and he is responding well. It will be interesting to see if after completion of this treatment, lymphoma does not recur on infliximab. But if it does, TNF-alfa inhibitors will be withdrawn from our patient’s regimen, leaving him with fewer options. Another interesting key point is the CD15 negativity in our first case. CD15 is a surface protein which is diagnosed by immunohistochemistry methods; it is most often a marker of B cells and helps in diagnosing HL, but it can also be positive in T cell lymphomas and NHL, making it non-sensitive and non-specific [11].

Historically, Kaposi sarcoma (KS) is the most common malignancy in AIDS patients, which is secondary to sexually transmitted human herpes virus-8, but the incidence has decreased significantly after HAART therapy became available [12]. The second most common malignancy in AIDS patients is B cell NHL; the cause could be immunity, viruses, or HAART therapy or other carcinogenic agents. From 1980 to 2002, better treatment options for HIV/AIDS have decreased the incidence of AIDS-associated malignancies like Kaposi sarcoma and NHL [13]. In people with AIDS, the risk for KS is 100 000 times higher and risk of NHL is 280 times higher than in the general population [14]. The risk for HL is also slightly increased and is mostly of mixed cellularity and EBV-positive [15]. Our second case had nodular sclerosing EBV-negative HL, which is a very uncommon entity in an AIDS patient; therefore, we faced a dilemma.

Recently, the relationship between AIDS and HL has been elucidated. The incidence of NHL is decreasing with highly active antiretroviral therapy (HAART) available for AIDS, and it has a direct association with immunosuppression [16]. On the other hand, HAART therapy and improved CD4 counts to a certain extent do not seem to decrease the HL incidence [17]. HAART therapy may increase the risk of developing HL [18]. This risk is especially increased in the first 3 months, decreases at 4–6 months, and nullifies after that [19]. A CD4 count less than 50 has low incidence, but between 50–99 seems to be the highest risk for HL, and the risk decreases to null with a CD4 count >500 [19]. This indicates the possibility of immunosuppression as the underlying culprit, but the increased incidence at the initiation of HAART therapy underscores the likelihood of immune reconstitution inflammatory syndrome (IRIS) as a culprit [20]. To conclude, the mechanism is unknown, but it must involve immune perturbation due to AIDS and HAART therapy.

Conclusions

Immunosuppression and immune perturbation seem to be the primary culprits leading to lymphomas in psoriasis patients on etanercept and HIV patients on HAART, respectively. The exact mechanism explaining the trigger for Hodgkin’s lymphoma instead of NHL is still not completely understood and needs further investigation.

Conflicts of interest

The authors declare no potential conflicts of interest.

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