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Unusual Presentations for EBV and HHV8 Co-Infections: A Case Report and Review of Literature

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ABSTRACT

HHV-8 is known to be related to Kaposi sarcomas but can be responsible for other diseases such as Castleman's disease (MCD) and primary effusion lymphoma (PEL). Epstein-Barr virus, on the other hand, is generally responsible for B-lineage lymphoproliferative diseases (LPD). In this case report we describe the case of a co-infection with HHV-8 and EBV with an unusual presentation. It is in fact a Kaposi sarcoma diagnosed in a heterosexual, immunocompetent and HIV-negative patient who initially presented with nodal disease only and a severe hemolytic anaemia. The same patient was also diagnosed with a T-lineage LPD with only bone marrow localization. The overall clinical presentation evolved favorably until complete resolution with the use of chemotherapy including drugs active in both histotypes. These data are contextualized with the evidence available in the current literature regarding the most common clinical manifestations of these infections.

Categories: Infectious Disease, Oncology, Hematology Keywords: t cell lymphoproliferative disorder, autoimmune hemolytic anemia (aiha), cytotoxic chemotherapy, hiv negative kaposi sarcoma, epstein barr virus (EBV), hhv 8

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Keywords: T cell lymphoproliferative disorder, autoimmune hemolytic anemia (AIHA), cytotoxic chemotherapy, HIV-negative Kaposi sarcoma, Epstein Barr virus (EBV), HHV 8

Introduction

Isolated or synchronous infections with HHV8 and EBV can give rise to various neoplasms. HHV-8 infection, also known as human herpesvirus-8, is primarily associated with the development of Kaposi sarcoma (KS), multicentric Castleman disease (MCD), and primary effusion lymphoma (PEL). On the other hand, EBV infection, or Epstein-Barr virus infection, primarily predisposes individuals to B-cell lineage lymphomas.

KS is a low-grade vascular tumor that occurs due to HHV-8-induced endothelial cell deregulation. Typically, the onset of KS involves the appearance of isolated skin lesions [1,2]. The classification of Kaposi sarcomas is currently based on clinicopathological features observed in distinct demographic and geographic populations. Additionally, a classification based on the immunocompetence status of the host has been proposed, recognizing the common scenario of KS in viral or iatrogenic immunodeficiency, as well as the rarer occurrence of KS in immunocompetent hosts. It is worth noting that KS without skin localization is reported in less than 5% of the cases documented in the literature [3].

EBV, or Epstein-Barr virus, is a widely prevalent herpes virus that primarily infects B cells. Human infection with EBV is known to be a causative factor in many lymphoproliferative diseases (LPDs), particularly B-cell lymphomas. Additionally, EBV frequently infects epithelial cells in the nasopharyngeal region, leading to the development of carcinomas in that anatomical site.

In addition to its tropism for B cells and epithelial cells, EBV can also infect T and NK lineage cells. In such cases, the infection may be associated with the emergence of specific malignancies, although these instances are rare. Extranodal NK/T cell lymphoma (ENKTCL) is considered the prototypical EBV-driven T/NK LPD. The most commonly affected primary sites for ENKTCL include the nasopharyngeal region, skin, gastrointestinal tract, and central nervous system (CNS). Other types of T/NK LPDs include aggressive NK cell leukemia (ANKL) and nodal T/NK lymphoma. Due to overlapping clinical and morphological features among these entities, differential diagnosis can be challenging.

We present a case of an African heterosexual immunocompetent HIV-negative male who was diagnosed with a rare form of Kaposi sarcoma (KS) that primarily affected internal organs (visceral-only KS). Concurrently, the patient was also diagnosed with an atypical T/NK lymphoproliferative disease. To treat this condition, the patient underwent chemotherapy using the COMP regimen, which consists of cyclophosphamide, nonpegylated liposomal doxorubicin, vincristine, and dexamethasone. This treatment approach aims to target and manage both the visceral-only KS and the atypical T/NK lymphoproliferative disease.

Case Presentation

We present the case of a 58-year-old black African man residing in sub-Saharan Africa. The patient had no known comorbidities and was previously in good health. He presented to the Emergency Department due to increasing asthenia (weakness and fatigue). Upon conducting blood tests, a life-threatening anemia was discovered, with a hemoglobin level of 4.7 g/dL. The leukocyte and platelet counts were within normal ranges. Biochemical analysis indicated signs of acute hemolysis, manifested by indirect hyperbilirubinemia (total bilirubin 1.8 mg/dL, direct bilirubin 0.48 mg/dL), and undetectable levels of haptoglobin (< 0.08 g/L). LDH (lactate dehydrogenase) levels were not evaluable. Both direct and indirect Coombs tests were positive for IgG warm autoantibodies, which did not activate the complement system. These findings were consistent with a diagnosis of warm antibody autoimmune hemolytic anemia (WAIHA).

After the acute clinical presentation, the patient required blood transfusion support and was closely monitored in the Intensive Care Unit. High-dose steroid therapy was initiated, with the patient receiving methylprednisolone at a dose of 200 mg per day for the first three days.

To investigate further, gastroscopy and pancolonoscopy were performed, but no abnormalities were found. Subsequently, an abdominal CT scan was conducted, revealing enlarged lymph nodes at the splenic hilum, along the external iliac vessels, and in the inguinal region on both sides. These lymph nodes formed a conglomerate with a major axis of approximately 4 cm at the splenic hilum. Basal FDG-PET CT scan showed metabolically active lymphadenopathies, especially along the external iliac and inguinal axes (SUV max 6.5), as well as in the bilateral axillary region. Additionally, diffuse increased FDG uptake was observed in the bone marrow.

Various infectious disease tests were performed to determine the underlying cause. These tests included a blood smear to rule out malaria, HIV, EBV, CMV, human T cell lymphotropic virus 1 (HTLV), Leishmania, and Bartonella serum antibodies. Polymerase chain reaction (PCR) tests were conducted to detect Parvovirus B19, EBV, CMV, and HHV-8 in blood samples. The patient tested negative for malaria, HIV, HTLV, Leishmania, Bartonella, CMV, and EBV IgM, as well as Parvovirus B19. However, the patient tested positive for CMV and EBV IgG. Furthermore, EBV-DNA (99 copies/mL) and HHV-8 DNA (25590 copies/mL) were detected.

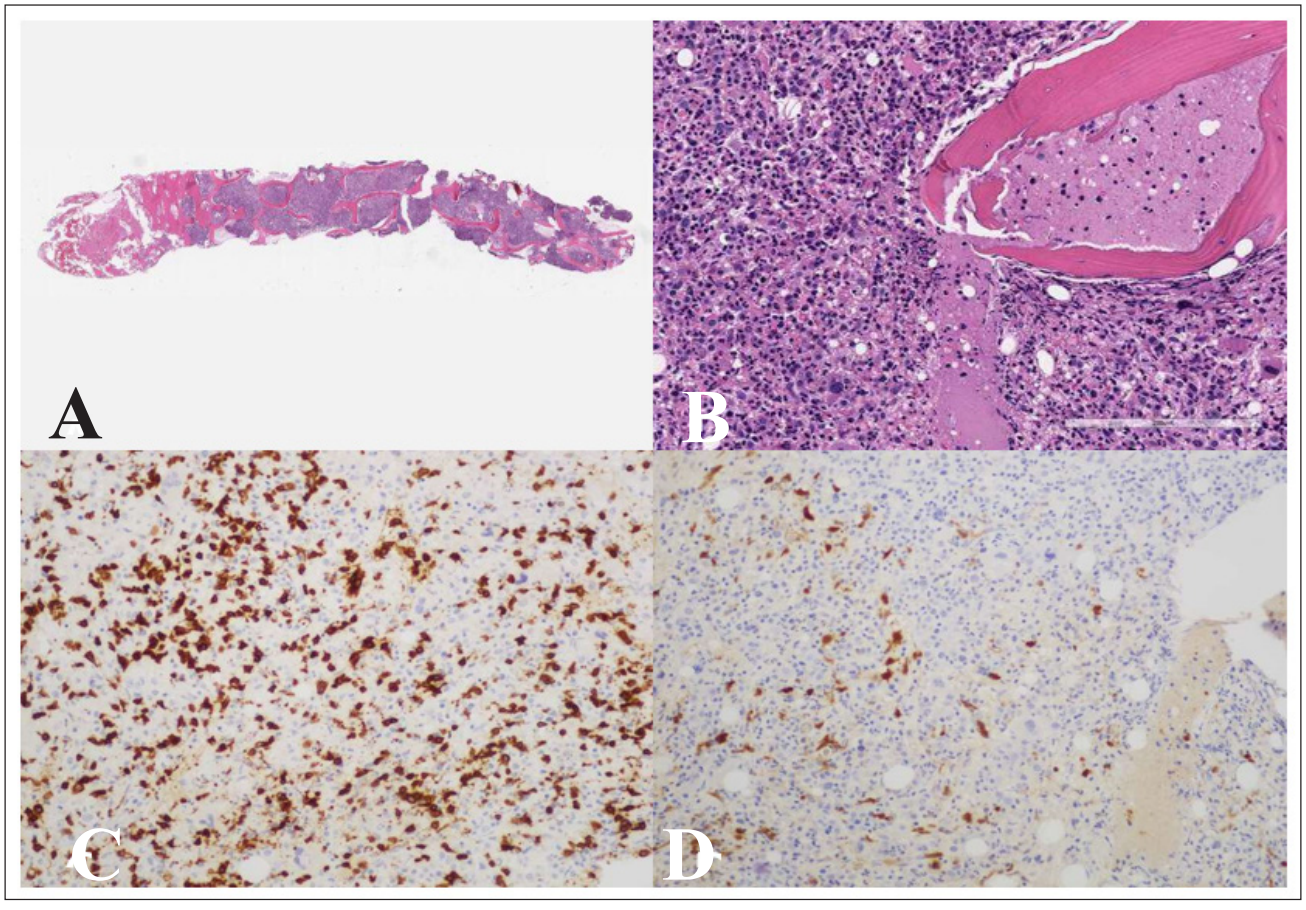

Figure 1: Bone Marrow Biopsy.
Haematoxylin-eosin stains, low (A) and high power (B) respectively. CD3 (C) and CD30 (D).

The presence of a clonal population in peripheral blood supported this diagnosis, but further molecular analysis could not be performed due to the decalcification process of the bone marrow biopsy. Consequently, in situ hybridization for EBV-encoded small RNA (EBER test) was also not feasible. The high cellularity of the hematopoietic marrow could be attributed to either a secondary lymphoproliferative disorder or a reactive response to hemolysis.

Given the uncertain diagnosis, a multidisciplinary discussion took place, and the hematologist decided to perform a lymph node biopsy in an attempt to clarify the diagnosis. An inguinal lymph node was surgically removed, and histopathological analysis was performed. Surprisingly, the examination of the lymph node histology revealed a pseudonodular proliferation of vessels in certain areas, exhibiting a lobular capillarylike pattern. Associated with this vascular proliferation, there was a fusiform proliferation of cells that showed strong positivity for endothelial immunohistochemical markers such as CD34, CD31, and ERG. Focal positivity for HHV-8 was observed, but there was an absence of significant nuclear atypia. (Figure 2)

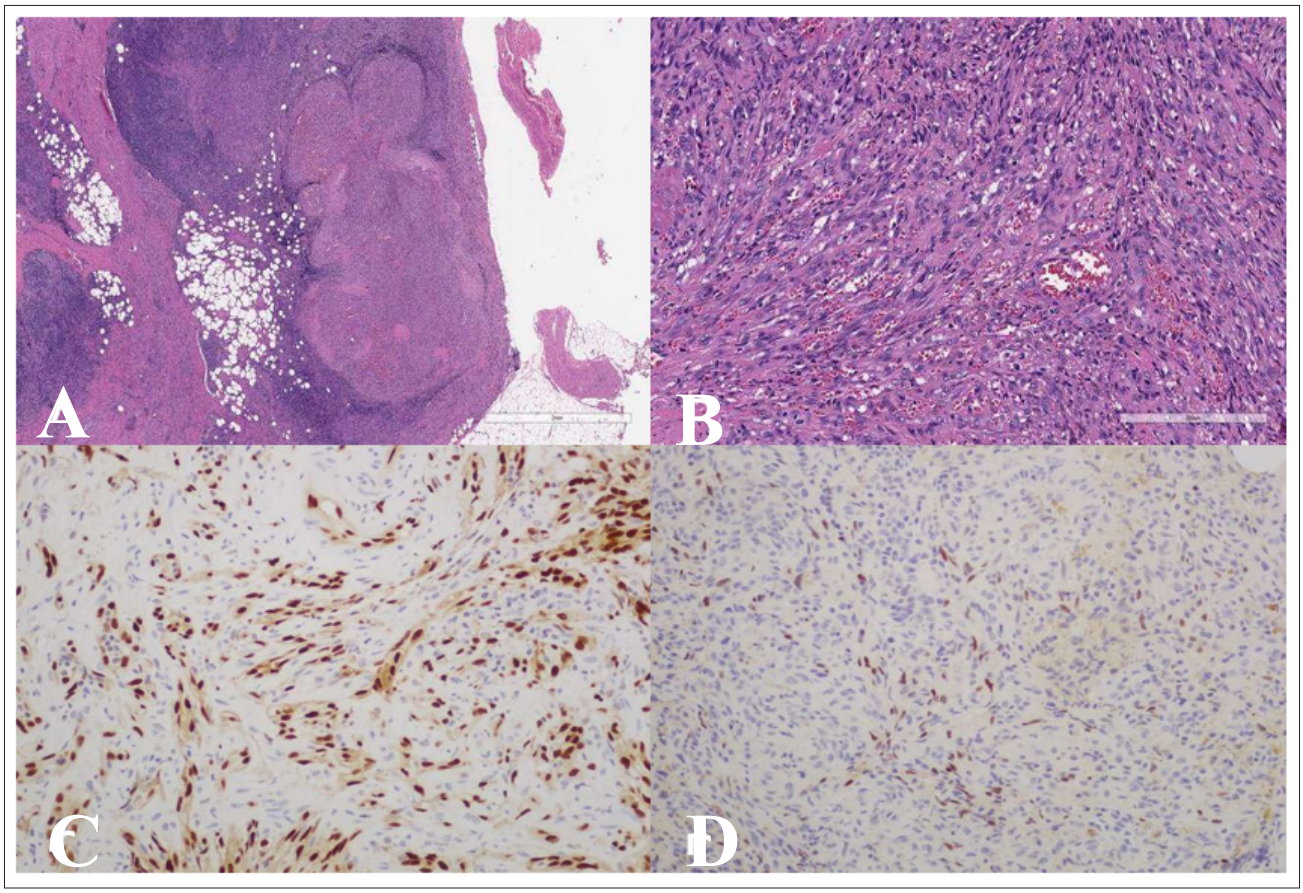

Figure 2: Right Inguinal Lymph Node Biopsy.
Haematoxylin-eosin stains, low (A) and high power (B) respectively. ERG (C) e HHV8 (D).

No atypical T/NK proliferation was observed in the lymph nodal biopsy. Based on the morphological and phenotypical characteristics, the hypothesis of an unusual nodal-only manifestation of Kaposi's sarcoma was favored. To confirm this, a thorough dermatological evaluation was conducted to rule out skin involvement of Kaposi's sarcoma. Additionally, an equally meticulous endoscopic evaluation of the respiratory and gastrointestinal tract was performed, which revealed no mucosal localizations.

Further investigation was conducted to differentiate between a lymph node manifestation of Kaposi's sarcoma and angiofollicular lymph node hyperplasia associated with human herpesvirus 8 (HHV-8)-related Castleman disease (CD). HHV-8 was tested using immunohistochemistry on the bone marrow biopsy, but the results were negative, ruling out HHV-8 involvement.

Therefore, the final histopathologic diagnosis was consistent with two different neoplastic processes: nodal only localization of Kaposi's sarcoma and an unusual T/NK lymphoproliferative disorder.

At this point, a chemotherapy regimen directed against lymphoproliferative disease, including nonpegylated liposomal doxorubicin, the gold standard in the treatment of KS, was chosen as the most appropriate therapeutic measure. The patient was treated from January 2023 to April 2023 with 4 cycles according to the COMP regimen (cyclophosphamide 750 mg/mq, non-pegylated liposomal doxorubicin 50 mg/mq, vincristine 1.4 mg/mq dose, and betamethasone 6 mg/mq), with each cycle repeated every 21 days, administered at 65% of the theoretical dose. Chemotherapy was subjectively well tolerated without any severe side effects. Hemolytic anemia partially improved soon after the first cycle of chemotherapy, and by the end of the second cycle, no further blood transfusion was required.

After completing 4 cycles of treatment, the patient underwent a bone marrow biopsy, which showed no evidence of hematologic disease. Simultaneously, a restaging FDG-PET CT scan was performed, which revealed only residual minimal tracer uptake in the right inguinal (SUV max 3.17 vs. 6.25) and right external iliac lymph nodes (SUV max 3.03 vs. 5.58), without significant hypermetabolism in the bilateral axillary area. There was a reduction in hypermetabolism in the splenic area, with restoration of the physiological spleento-liver uptake ratio, and a marked reduction in glucose metabolism in the bone marrow. No other areas of significant tracer uptake related to the origin of the disease were observed. (Figure 3)

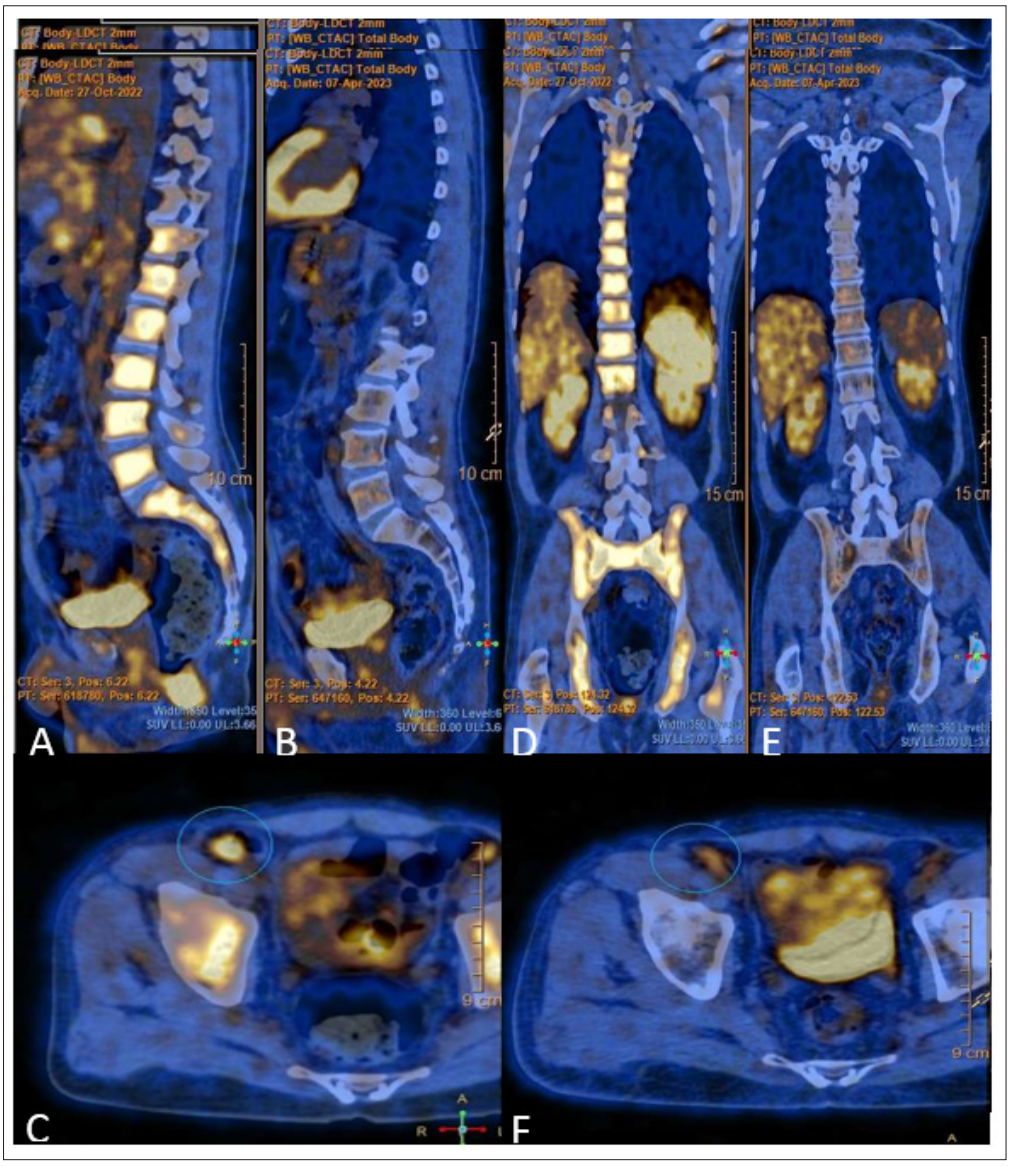

Figure 3: FDG PET-CT Findings at Baseline and After Treatment.
FDG PET-CT at baseline (A, B, C) and after treatment (D, E, F).

Hematological tests, including complete blood count and differential, and blood chemistries, including electrolytes, liver enzymes, serum protein, serum bilirubin, and serum creatinine, were within normal ranges. Upon clinical examination, no palpable lymphadenopathy was observed, except for two non-specific pericentimetric lymph nodes near the site of the previous biopsy. Two months later, microbiology tests showed a decrease in HHV-8 serum virus copies, with lower but persistent viral detection (5576 copies/ml, Met. Polymerase Chain Reaction).

To date, after three months of patient-tailored hemato-oncologic systemic treatment, the patient is in excellent general condition and asymptomatic. The patient, suffering from KS and T/NK lymphoproliferative disorder, has shown positive treatment response and overall improvement.

Discussion

HHV8 is associated with KS and a wide spectrum of lymphoid proliferations, mostly B-cell related. The majority of clinical manifestations of KS overlap independently of the epidemiological and pathogenic context, and cutaneous lesions (multiple, pigmented pink to purple macules or papules, raised or flat, usually painless) are almost always present. Visceral lesions (most commonly documented in the pulmonary, pleural, and gastrointestinal areas) are generally uncommon and mostly related to AIDS-related KS [1,3].

The relationship between HHV8 and T-cell disorders is not well established, with only a few case reports describing NK/T lymphomas arising in immunodeficient or immunosuppressed patients. The literature provides limited case reports describing the simultaneous diagnosis of multiple HHV-8-associated neoplastic diseases or the coexistence of KS and HHV-8-unrelated LPDs [4].

In the case of KS in immunodeficient patients, regardless of the cause of immunosuppression, treatment focuses on curing the underlying condition (e.g., antiretroviral therapy for HIV or discontinuation/modification of immunosuppressive therapy in transplant patients) [5,6]. When the immunosuppressive cause cannot be identified or the initial strategy is insufficient, drugs targeting the tumor cells (e.g., liposomal anthracyclines, liposomal daunorubicin, pegylated liposomal doxorubicin) or those modulating the immune context (monoclonal antibodies) may be used. However, the scientific evidence supporting these treatments is generally based on small retrospective case series and clinician experience rather than well-conducted clinical trials [7-9].

Extranodal NK/T-cell lymphoma (ENKTCL) primarily originates (70-90% of cases) in the upper aerodigestive tract, specifically the mucosa of the nasal cavity and adjacent structures. Rarely, it can affect the bone marrow and other organs, including the skin, digestive tract, lungs, and liver.

The Epstein-Barr virus (EBV) has tropism for B cells, epithelial cells, and, to a lesser degree, NK/T-cells. Human infection with EBV is known to cause various LPDs, primarily B-cell lymphomas. The presence of episomal EBV in the host genome is a defining feature of nearly all types of NK/T-cell LPDs, and distinguishing between them is challenging due to the phenotypic and genotypic overlap between NK and T cells.

The uniqueness of the reported case lies not only in the uncommon occurrence of two rare viral diseases but also in the distinctive clinical manifestations at the onset, which posed challenges in diagnosing the clinical presentation. The presence of severe and acute depletion anemia, in addition to being life-threatening, raised critical issues in terms of differential diagnosis. While warm autoimmune hemolytic anemia (WAIHA) is a well-known paraneoplastic disorder in lymphoid malignancies, it has also been reported in association with solid tumors. In rare cases, WAIHA has complicated the clinical course of KS. In our patient, WAIHA presented as a life-threatening condition initially in association with KS. The severity of the anemia necessitated the immediate initiation of high-dose steroids, intensive care monitoring, and multiple blood transfusions. Despite the occurrence of peripheral hemolysis, the reticulocyte count was inappropriately low, which is recognized as an unfavorable prognostic factor in WAIHA [10]. We hypothesize that the infiltration of T-cells in the bone marrow might have suppressed reticulocyte production, further exacerbating the severity of the anemia. Steroids resulted in a partial response in WAIHA, and complete resolution was achieved after the third cycle of chemotherapy. Therefore, as commonly observed in paraneoplastic WAIHA, tumor-directed treatment was necessary to induce complete remission of the autoimmune manifestation.

WAIHA can also be caused by secondary hemophagocytosis, which involves the destruction and engulfing of hematopoietic or erythrocyte cells by reactive histiocytes. This can be triggered by EBV infection and T-cell malignancy. In our case, the presence of warm autoantibodies (non-complement activating IgG, negative for Anti C3d, positive for Anti IgG and Anti POLY) in the serum and on the surface of blood cells (resulting in pan-agglutination), positive direct and indirect Coombs tests, non-conjugated hyperbilirubinemia, and undetectable haptoglobin led us to suspect an autoimmune hemolytic anemia (AIHA) rather than a hemophagocytic form. To investigate other possible autoimmune diseases, antinuclear antibodies (ANA) were tested and found to be positive with a titer of 1:80 (negative < 1:80) and a dotted cytoplasmic pattern. Extractable nuclear antigens (ENA), including anti-Sm, anti-Sm/RNP, anti-SSA-Ro60, anti-SSA-Ro52, anti SSB, anti-Scl-70, anti-Jo-1, and meth. CLIA, were only positive for nuclear anti-Sm (27.5 CU; negative < 20). However, these results were not considered relevant in this context.

The treatment of extranodal NK/T cell lymphoma (ENKTCL) is similar to that of other aggressive nonHodgkin lymphomas (NHL). The gold standard chemotherapy regimen is CHOP (cyclophosphamide, doxorubicin [adriamycin], vincristine, prednisolone) [10,11]. However, in the case of NK/T-cell nasal type lymphoma, the CHOP regimen is suspected to have poor efficacy due to the high expression levels of the multidrug resistance P-glycoprotein, which makes drugs like cyclophosphamide and doxorubicin ineffective. It should be noted that such high P-glycoprotein expression is not reported in atypical or bone marrow localization of the disease.

Several studies have demonstrated that, in the CHOP regimen, the anthracycline component can be replaced with non-pegylated liposomal doxorubicin, resulting in good treatment outcomes with lower toxicities. One example of such a modified regimen is the COMP regimen. Additionally, other polychemotherapy regimens, including SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide), DDCP (dexamethasone, gemcitabine, cisplatinum, peg asparaginase), IMP L-asp (ifosfamide, methotrexate, etoposide, prednisolone, L-asparaginase), AspaMetDex (L-asparaginase, methotrexate, dexamethasone), and MEDA (methotrexate, etoposide, dexamethasone, L-asparaginase), have been evaluated in Phase II/III trials and retrospective studies.

In the case of the reported NK/T-cell LPDs in this patient, we chose the COMP regimen for treatment, considering the proven efficacy of liposomal anthracycline in the treatment of KS as well.

Conclusions

This case highlights the atypical presentation of Kaposi sarcoma in a heterosexual and immunocompetent patient. The co-infection with HHV-8 and EBV may have influenced the unusual spectrum of neoplastic manifestations observed in this case.

The presence of hemolytic anemia as a paraneoplastic manifestation of solid tumors should be considered. Once the diagnosis of Kaposi sarcoma is established following the finding of hemolytic anemia, it is necessary to investigate its etiology and exclude concomitant diseases.

The comprehensive identification of the etiopathology of a challenging clinical picture allows for the implementation of the most appropriate therapies, especially when the clinical presentation is severe and life-threatening.

Additional information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance

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