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COEXISTENCE OF HHV-8-ASSOCIATED PLASMACYTIC MULTICENTRIC CASTLEMAN DISEASE, KAPOSI'S SARCOMA, AND MULTIPLE MYELOMA IN A HIV-NEGATIVE PATIENT

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ABSTRACT

Background: Multicentric Castleman disease (MCD) is a rare, aggressive lymphoproliferative disorder. Human herpesvirus-8 (HHV-8) has an important role in the pathogenesis of the disease and its association with Kaposi's sarcoma has been reported, especially in people living with human immunodeficiency virus (HIV). In this report, we present the case of HHV-8 positive MCD accompanied by Kaposi's sarcoma and multiple myeloma in an HIV-negative patient.

Case Report: A 78-year-old man with Kaposi's sarcoma presented with B symptoms, pancytopenia, lymphadenopathy, and splenomegaly. The bone marrow biopsy demonstrated 70% lambda-restricted monotypic plasma cell infiltration consistent with plasma dyscrasia. Also, the patient was diagnosed with HHV-8 positive MCD as a result of inguinal lymph node excisional biopsy. Treatment was initiated including ganciclovir and methylprednisolone and followed by rituximab. The patient passed away at the 24th hour of rituximab infusion due to shock.

Conclusions: MCD and associated malignancies are difficult to treat and have a poor prognosis. More studies and data are needed to manage these patients.

KEYWORDS

Castleman disease, Kaposi's sarcoma, multiple myeloma, HIV, HHV-8

LEARNING POINTS

- Multicentric Castleman disease (MCD), often linked with human herpesvirus-8 (HHV-8) and Kaposi's sarcoma, is rare and aggressive condition, particularly in human immunodeficiency virus (HIV)-positive patients.
- The coexistence of MCD, Kaposi's sarcoma, and multiple myeloma is exceptionally rare in HIV-negative, immunocompetent patient.
- This case highlights the challenges in diagnosing and managing complex presentations of MCD and related malignancies, with poor outcomes despite treatment.

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INTRODUCTION

Castleman disease (CD) is a relatively rare lymphoproliferative disease with unicentric or multicentric subtypes with distinct disease courses. Histopathologically, it appears as hyaline vascular, plasmacytic, or mixed type[1]. While the unicentric disease has a milder course with regional node involvement, the multicentric disease may progress aggressively with generalized lymphadenopathies, hepatosplenomegaly, constitutional symptoms, and cytokine storm, particularly via IL-6. Multicentric Castleman disease (MCD) is classified as human herpesvirus-8 (HHV-8)-associated and idiopathic forms. The HHV-8-associated form mainly indicates human immunodeficiency virus (HIV) positivity or occasionally is explained by other immunosuppressive conditions[2]. The coexistence of CD and Kaposi's sarcoma (KS) is not surprising since HHV-8 is involved in the pathogenesis, but this is limited to a few cases in HIV-negative patients and to the best of our knowledge, coexistent multiple myeloma (MM) has not been previously reported in the literature[3–7]. In this study, we present a case of HHV-8 positive MCD in an HIV-negative immunocompetent patient with KS who was also diagnosed with MM.

CASE DESCRIPTION

A 78-year-old male patient with diabetes and KS in his medical history was referred to our center for pancytopenia. The patient had weight loss, fever, bilateral cervical, supraclavicular, axillary, and inguinal lymphadenopathies, splenomegaly, and characteristic KS lesions on the left foot on physical examination, and he was considered to be a frail patient *(Fig. 1)*. He had had surgery for KS on the sole of the left foot 2 years before presentation and received single fraction 8 Gy radiotherapy.

Laboratory investigations revealed a low hemoglobin level of 7.6 g/dl, white blood cell count of 1.2 x10^9/l, neutrophil count of 0.4 x10^9/l, platelet count of 26 x10^9/l, serum albumin 1.7 g/dl, serum creatinine 1.1 mg/dl, corrected serum calcium 10.3 mg/dl, C-reactive protein 12.1 mg/l, 1088 mg/24-h urine protein, 166 mg/24-h urine albumin and negative anti-HIV serology. As an empiric treatment of febrile neutropenia, the patient was started on meropenem 1000 mg t.i.d. The bone marrow biopsy demonstrated 70% CD138 + atypical plasma cell infiltration with a lambda-restricted expression, without any KS or MCD involvement clue and HHV-8 stain was negative *(Fig. 2)*. Besides, a computed tomography scan of the chest and abdomen showed splenomegaly (14.8 cm), and multiple enlarged supraclavicular, axillary, mediastinal, paraaortic, parailiac, pelvic and inguinal lymph nodes measuring up to 3.3 cm in diameter. No lytic lesion was detected in the bones. Afterwards, right inguinal lymph node excisional biopsy was performed. The examination of the specimen demonstrated follicles showing regressive changes and hyalined vascular structures together with thickened mantle zones. Some of the mantle zones contained scattered CD138 + and HHV-8 + plasmoblasts. In several foci, there was CD34 + and HHV-8 + spindle cell proliferation adjacent to the lymph node capsule, hence a diagnosis of MCD and KS was made *(Fig. 3)*.

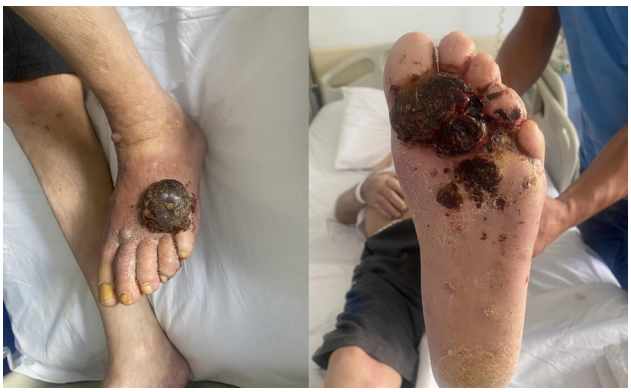

Figure 1. Brown, raised, gigantic hemorrhagic Kaposi's sarcoma lesions on the left dorsum and sole of the feet.

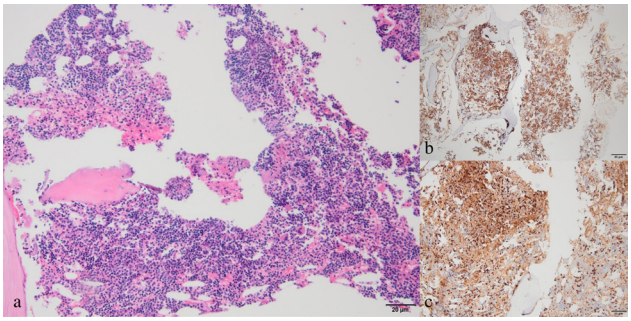

Figure 2. Bone marrow biopsy. A) Hypercellular bone marrow showing plasma cell infiltration (HE, x10), B) CD138 positivity in 70-80% cells (x4), C) Cells showing monotypic lambda expression (x10).

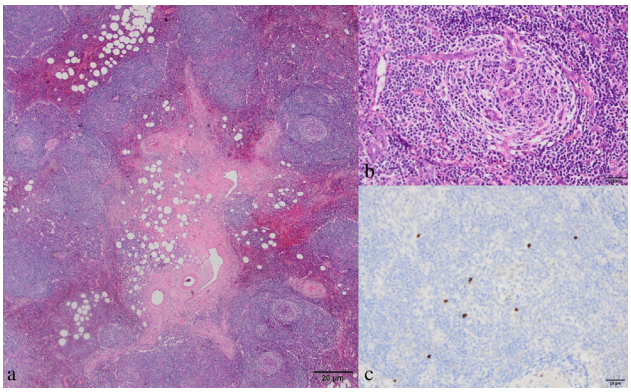

Figure 3. Excisional lymph node biopsy. A) Enlargement of mantle zones of lymphoid follicles, blastic cells with prominent nucleoli, eccentric nuclei and basophilic cytoplasm. Vascular proliferation in atrophic germinal centers and interfollicular areas (HE, x2), B) Kaposi's sarcoma (HE, x20), C) HHV-8 positive staining (x20).

The patient was evaluated by the haemato-oncology board and a treatment plan including rituximab 375 mg/m^2 weekly, ganciclovir 5 mg/kg/day, methylprednisolone (MPZ) 48 mg daily, and paclitaxel every 2 weeks were scheduled. During hospitalization, the patient received meropenem for febrile neutropenia, tigecycline for soft tissue infection, and piperacillin-tazobactam for *Streptococcus pneumoniae* bacteremia. Proper blood replacements, oral nutritional supplementation, psychological support and analgesia were administered throughout hospitalization. Once the patient

became clinically stable, ganciclovir, MPZ, and rituximab treatments were initiated. He tolerated infusion without any immediate complications. Subsequently, within 24h of receiving the rituximab, the patient developed tachypnea, hypotension, lactic acidosis, and atrial fibrillation. The patient required emergent intubation and was transferred to the intensive care unit (ICU), but he died 3 days after ICU admission due to distributive shock.

DISCUSSION

CD, also known as angiofollicular lymph node hyperplasia, is a rare disease that is poorly understood (6500-7700 cases annually in the USA)[2]. The median age of occurrence of the multicentric form is between 50 to 70 years, with male predominance. Excess cytokine secretion is the cornerstone of pathogenesis and may cause severe systemic inflammation and organ dysfunction triggered by IL-6 in MCD patients[8]. The plasmacytic variant constitutes 10-20% of CD cases and almost all of them are associated with multicentric involvement, like our case[1]. Among these, HHV-8 positive patients carry the risk of progression to plasmablastic lymphoma. HHV-8-associated MCD is often encountered in people living with HIV . While all HIV-positive MCD patients are HHV-8 positive, 2-50% of HIV-negative patients carry HHV-8[9]. Concurrent HHV-8-associated MCD and KS are not uncommon in people living with HIV. HHV-8-infected endothelial cell proliferation, vascularization, and cytokine storm underlie progression[2]. However, dual HHV-8-related diseases are exceptional in HIV-negative patients[4,5,7]. In 2015, Barbarov et al. reported a non-HIV patient with KS and MCD who died due to an aggressive disease characterized by hemophagocytic syndrome[3]. Another HIV-negative case was reported by Hwang et al. in 2019[6]. On the other hand, HHV-8 is not associated with the pathogenesis of MM. Although viral IL-6 production has been suggested to trigger abnormal plasma cell proliferation, the exact mechanisms are not clear[10]. The findings of studies investigating HHV-8 positivity in multiple myeloma are contradictory and show geographical and ethnic diversity[11]. Cases with co-occurrence of KS and MM have been reported in the literature, and the role of HHV-8 has been underlined[12]. To the best of our knowledge, our patient is the first case with concurrent MCD, KS, and MM. In our patient, lambda monotypic plasma cells in the bone marrow may be confused with CD. Also, lambda monotypic plasma cells can be encountered in a variant of CD consisting of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS). However, POEMS was excluded due to the absence of polyneuropathy and endocrinopathy in our case. Although the bone marrow was HHV-8 negative and there was no evidence of CD involvement, infiltration with plasma cells indicated a separate multiple myeloma clone. Our patient had profound anemia as MM end organ damage. Treatment of MCD and associated malignancies is complex. The main issue is the rarity of the disease and the lack of adequate randomized controlled trials. Based on available data, recent guidelines recommend rituximab for the first-line treatment of HHV-8-associated MCD[13]. In the presence of concomitant KS, the addition of anthracycline (e.g. liposomal doxorubicin) to the treatment should be considered. In 2014, Ortega et al. reported a favorable response after four cycles of rituximab and a combination of cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) in an HIV-positive patient with MCD and KS undergoing highly active antiretroviral therapy[1]. Another HIV-negative case of concurrent MCD and KS was reported by Hwang et al. The patient achieved a nearly complete response after 14 days of oral prednisolone followed by 4 cycles of chemotherapy consisting of rituximab and liposomal doxorubicin[6]. Conversely, in concomitant cases, rituximab-related KS flares have been reported regardless of HIV status[5]. In addition, as in our patient, rituximab infusion may lead to fatal cytokine release syndrome[14]. Considering our patient's active B symptoms and low performance score, intensive combined regimens could not be given.

One of the important steps of management is to determine the HHV-8 and HIV status. Antiretroviral therapy is indicated in HIV-positive patients. The use of antiviral (e.g. ganciclovir or valganciclovir) therapy for HHV-8 is limited to case reports and its effectiveness is unknown[5,15]. In 2020, Plachouri et al. reported an HIV-negative patient diagnosed with MCD and concurrent KS, treated with valganciclovir 450 mg twice daily and four cycles of rituximab plus CHOP[7]. The chemotherapy was discontinued due to severe neutropenia and pneumonia. Monotherapy with valganciclovir was continued, resulting in complete remission of lymphadenopathy and improvement in blood abnormalities over 21 months. At the 3-year follow-up, the patient remained disease-free with no recurrence of MCD or KS and no adverse effects from valganciclovir[7]. Although antiviral treatments are generally well tolerated, their bone marrow suppressive effects should not be forgotten. Data on the treatment of simultaneous MCD and MM are scarce. Yang D et al. reported a case of MCD treated with VP16 plus CHOP chemotherapy, which yielded unsatisfactory results[16]. The patient was subsequently switched to oral thalidomide combined with prednisone, leading to disease stabilization. After 3 years, the patient's MCD transformed into MM, and the combination of thalidomide and prednisone produced a notable response. Another case report described a patient with MCD and MM who was treated with bortezomib and dexamethasone[17]. This treatment resulted in significant remission, including reductions in lymph node enlargement and splenomegaly. After four cycles, the patient achieved very good partial remission and remained disease-free at the 18-month follow-up. Finally, Khan AA et al. reported a case of MCD and MM treated with bortezomib and dexamethasone, followed by maintenance therapy with thalidomide. The treatment resulted in significant improvement, including lymph node disappearance and a 90% reduction in the monoclonal protein spike. After 2 years, the patient remained in partial remission[18].

CONCLUSION

Our study presented the first case with concurrent MCD, KS, and MM in an HIV-negative patient. The treatment of MCD with concurrent KS and MM is complex, with limited data to guide management. Rituximab-based therapies are commonly used, while antiviral treatments and bortezomib-based regimens have shown promise in some cases. Individualized approaches are essential, and further research is needed to establish standardized treatment protocols for these rare conditions.

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