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Case Report

CASE REPORT

Disseminated form of the Kaposi sarcoma in HIV-negative patient associated with Hodgkin's lymphoma

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Abstract

We report a case of a 35-year-old, non-HIV-infected male diagnosed simultaneously with a disseminated form of Kaposi's sarcoma (KS; skin, stomach and colon are involved) and Hodgkin's lymphoma. There is no sign of changes in the immune status, but three herpes viruses were detected in the patient's blood (EBV, HHV6 and HHV8). He received ABVD chemotherapy and achieved complete metabolic remission for Hodgkin's lymphoma. Moreover, the signs of the disseminated KS were resolved. Our observations indicate that a combination of distinct types of viruses may play an important role in triggering the development of angio- and lymphoproliferative disorders in the same person. In addition, treatment with chemotherapy cycles, which included doxorubicin and vinblastine, led to the stable remission of both diseases.

INTRODUCTION

Kaposi sarcoma (KS) is a low-grade angio-proliferative mesenchymal disorder caused by the herpes virus of the eighth type (HHV8). The mechanisms of HHV8 action on the host cells are not fully understood, although the latest data suggest that HHV8 infects vascular endothelial cells, leading to cell reprogramming and transformation by the induction of the LJVE1, VEGFR3 and PDPN genes, whose expressions are pivotal for cancer development. Morphologically, KS consists of spindle cells carrying markers of the endothelial cells (CD31 and CD34), lymphatic epithelium cells (VEGFR3, D2-40 and LYVE-1), macrophages (CD68) and smooth muscles (SMA) and the marker of the viral damage (LANA-1; latency-associated nuclear Ag). The herpes virus is associated with KS and primary diffusion lymphoma and HIV-associated Castleman disease. The most common classical variant is typically characterized by a benign course. In 90% of cases, the affected organ is the skin with epithelia and internal organ involvement not exceeding 10%. Disseminated KS variants are more typical for HIV-positive patients, transplant recipients and cancer patients receiving chemotherapy. We report a case of the disseminated form of KS in an HIV-negative patient diagnosed with Hodgkin's lymphoma (HL) that was successfully treated.

CLINICAL CASE

In January 2018, a 35-year-old Caucasian man was admitted to the hospital. Since July 2017, he had periodically experienced upper abdominal pain and several episodes of black tarry stools associated with weight loss (10 kg over 5 months). His

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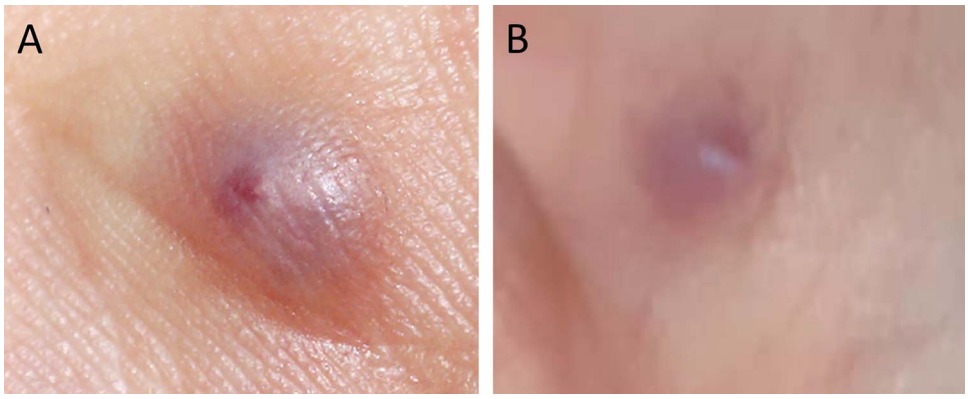

Figure 1: The KS images (A) on the hand and (B) on the feet finger.

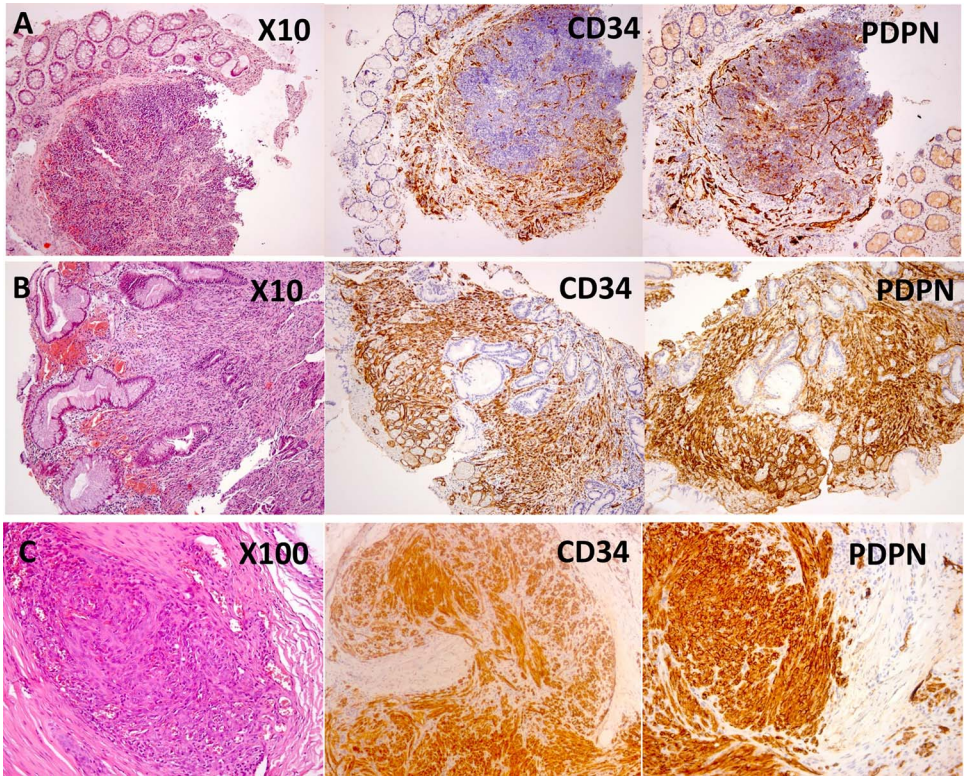

Figure 2: Histology and IHC of KS specimens: (A) biopsy of a colonic KS lesion (H&E, original magnification 10x). The cells were positive for CD34 and PDPN. (B) Biopsy of a gastric KS lesion (H&E, original magnification 10x). The cells were positive for CD34 and PDPN. (C) Biopsy of a skin KS lesion; resected nodules shoving infiltrating pump spindle tumor cells mixed with blood vessels (H&E, original magnification 100x). The cells were positive for CD34 and PDPN.

hemoglobin gradually dropped from 130 to 67 g/L. During the physical exam, reddish-blue nodules (up to 1 cm in diameter) were found on the right palm, fourth finger of the right hand and left foot, and multiple small (2–3 mm) round nodules were found in the subcutaneous fatty tissue of the upper and lower extremities (Fig. 1A). These skin lesions had existed for 4 years. The endoscopy showed multiple bright red polypoid lesions in the stomach. Similar changes were found in the duodenum. A colonoscopy revealed multiple large hyper-vascularized dark-reddish flat lesions. The colon, gastric and skin biopsies showed histological features of KS (Fig. 2). The proliferating spindle cell expressed CD34 and PDPN (Fig. 2). Anti-HHV8 antibodies were detected in the blood. A diagnosis of KS was made.

At the moment of the diagnosis, the patient had a white blood cell count of 5300 with 1760/mm^3 lymphocytes (734.58/mm^3 CD4+ and 378.40/mm^3 CD8+). His immunoglobulin (Ig) levels were in the normal range (IgA 1.95 g/L, IgG 8.87 g/L and IgM 0.69 g/L). Thus, no abnormalities in the immune status were detected. The patient was negative for HIV antibodies, but EBV DNA and HHV6 DNA were detected in the blood. Then, the patient was found with right axillary lymphadenopathy. In January 2018, a PET scan at the time of diagnosis showed hypermetabolic axillar and subclavicular lymphadenopathies (Fig. 3). Morphological and immunohistochemical studies of the affected lymph node biopsy showed a picture of the nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL; Fig. 4). He received a total of five cycles of ABVD (doxorubicin 40 mg IV, KD 80 mg; bleomycin 15 mg IV/KD 30 mg; vinblastine 10 mg IV/KD 20 mg; and dacarbazine 600 mg, KD 1200 mg) during days 1–15 of the course. The PET scan in May 2018 revealed

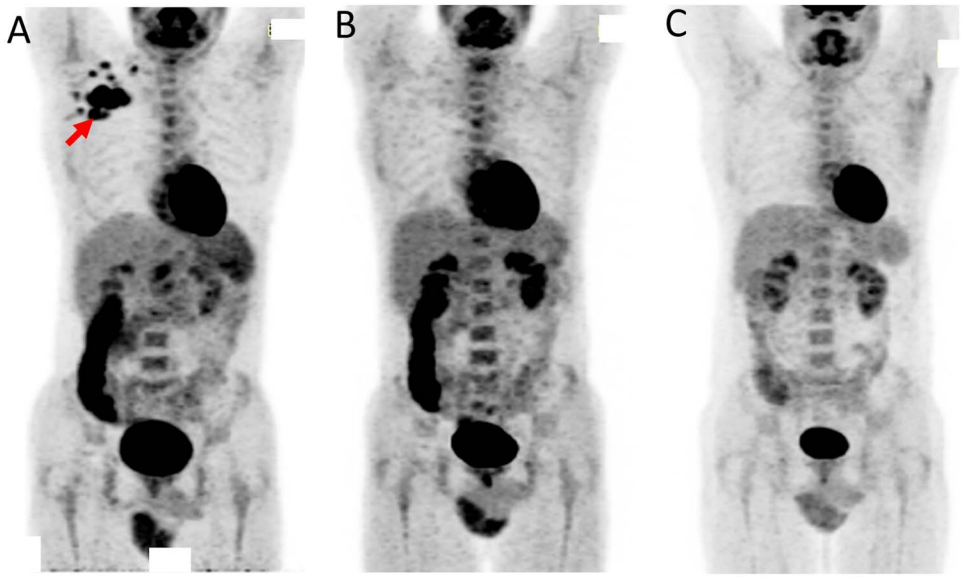

Figure 3: PET scan imaging: (A) PET scan on January 2018 at the time of diagnosis, shoving hypermetabolic paraclavicularic, retropectoral and axillary lymph nodes (red arrows). (B) PET scan on May 2019, no suspect FDG uptake, complete remission. (C) PET scan on December 2019, no suspect FDG uptake, complete remission.

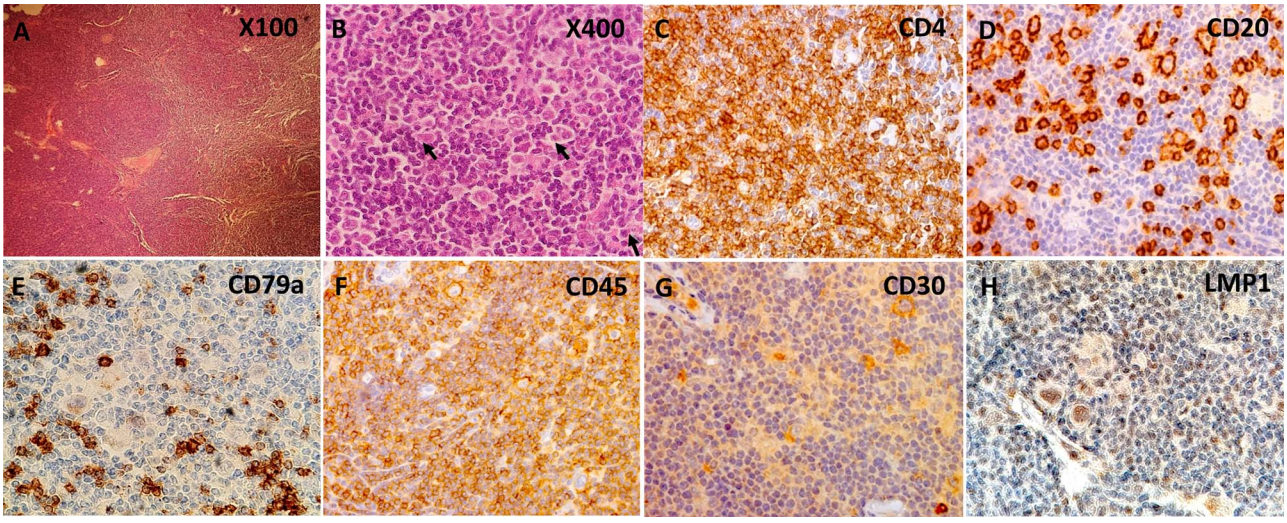

Figure 4: Diagnosis of the nodular lymphocyte-predominant Hodgkin lymphoma. (A) The nodular architecture of NLPHL (H&E, original magnification 100x). (B) Lymphocyte-predominant (LP) cells in the NLPHL with typical popcorn morphology indicated by the arrows (H&E, original magnification 400x). (C) Extensive background of CD4+ T-lymphocytes (original magnification 400x). Immunohistochemical (IHC) characterization of LP cells: (D) positive membranous and cytoplasmic staining of CD20 (original magnification 400x), (E) weak positive cytoplasmic staining of CD79a (original magnification 400X), (F) positive membrane staining of CD45 (original magnification 400x) and (G) weak positive staining of CD30 (original magnification 400x). (H) NLPHL with positive LMP1 expression noted in the LP and T cells (original magnification 400x).

a complete metabolic response (Fig. 3). The colonoscopy and endoscopy were normal. In December 2019, 19 months after the last ABVD course, our patient was still in complete remission of his lymphoma (Fig. 3). The DNA of the EBV and HHV6 viruses became undetectable in the blood. No sign of KS recurrence was found in the gastrointestinal tract, but the patient had several new KS nodules on his right foot (Fig. 1B). The patient is under continuous observation.

DISCUSSION

Based on the cases described in the literature, it is possible to conclude that KS development is typically associated with a patient's immunosuppression of different origins, such as HIV and/or herpes virus infections, post-transplantation therapy and anticancer chemotherapy [1, 2]. However, cases of KS in HIV-negative patients without deterioration of the immune status also have been reported [3–5]. In the case of our patient, we did not find any changes in the immune status. All parameters were in the normal range: IgA 1.95 g/L, IgG 8.87 g/L, IgM 0.69 g/L, CD4 42.2% (N 36–55) and CD8 21.5% (N 17-37)). No concomitant immunosuppressive diseases or HIV infection was found. However, we found HHV6/EBV DNA and an antibody against the HHV8 virus in the patient's plasma.

Every virus in this combination is involved in carcinogenesis. Moreover, KS is associated with HHV8, whereas EBV plays an important role in the development of classical HL (cHL), and HHV6 establishes latency in lymphocytes and possesses a strong

immunomodulatory capacity that can trigger both immunosuppressive and chronic inflammatory pathways.

In our case, we made the NLPHL diagnosis using morphological and IHC studies (Fig. 4). The NLPHL is a rare subtype of HL, representing 5% of all cases. In contrast to cHL, it is generally considered EBV negative (4–5% EBV-positive cases) [6]. In the biopsy of our patient, we found the EBV marker LMP1 and weak CD30 positive staining, which is typical for the EBV-positive NLPHL (Fig. 4) [6]. Hence, our patient had a rare type of HL associated with EBV.

These facts support the hypothesis that the combination of viruses plays a key role in the development of NLPHL and KS in our patient. The precise mechanism of this process is not yet clear, but the influence of EBV/HHV6/HHV8 on lymphoid cells may lead to the deterioration of the apoptotic process and the development of indolent immunodeficiency, which triggered the development of two neoplastic processes [5, 7, 8]. Moreover, we would like to note an aggressive course of KS, which is atypical for HIV-negative patients. Multiple foci of skin lesions on the upper and lower extremities, damage to the gastrointestinal tract and, consequently, repeated bleeding provide a characteristic picture of the increasing anemia. In the literature, the recommended therapy for KS is liposomal doxorubicin, vinblastine and taxane [9, 10] The patient's polychemotherapy courses for the underlying disease (HL) contained the recommended doxorubicin and vinblastine. Thus, the therapy was equally successful in achieving the remission of both diseases: KS and HL. The patient remains in complete PET/CT remission for 19 months after the end of HL therapy. The KS lesions were not detected by the control colonoscopy and endoscopy, but new lesions appeared on the skin of the lower limb. The DNA of the herpes virus was not detected by the PCR. Further follow-up of the patient will continue.

Thus, we described for the first time the case of the parallel development of HL and KS on the background of the infection with three herpes viruses. This demonstrates the importance of viruses in cancer development, although further studies of the precise mechanisms are needed.

CONFLICT OF INTEREST STATEMENT

No conflict of interest declared.

ETHICAL APPROVAL

This work was approved by the ethical committee of the Main Military Clinical Hospital named after N.N. Burdenko.

CONSENT

All consent forms were signed by the patient.

GUARANTOR

Victoria Tutaeva MD, PhD

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