CASE REPORT

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HHV-8-Related Three Malignancies in an Immunocompetent Patient: Kaposi Sarcoma, Multisentric Castleman Disease and Primary Effusion Lymphoma

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ABSTRACT HHV-8 is associated with Kaposi sarcoma, multicentric Castleman disease and primary effusion lymphoma mostly in immunocompromised patients. In this report, we describe a female patient without any immunosuppressive state, encountering those three malignancies throughout her lifetime. A-69-year-old female patient was diagnosed with Kaposi sarcoma in 2009 and multicentric Castleman disease in 2011. She received several chemotherapy regimens during 4 years and stayed in remission during following 5 years. Then, she was diagnosed with primary effusion lymphoma, extracavitary/solitary variant on excisional biopsy of her cervical lymphadenopathy. Despite having 5 different lines of chemotherapy protocols, including autologous stem cell transplantation, and systemic cidofovir treatment, she died because of progressive disease. HHV-8 associated malignancies are not prevalent in immunocompetent patients. Our patient, who has suffered from all three malignancies related to HHV-8, is the only HIV negative patient in the literature with primary effusion lymphoma, extracavitary/solitary variant.

Keywords: HHV-8; Kaposi sarcoma; Castleman disease; primary effusion lymphoma

Human herpesvirus 8 (HHV-8) (also known as Kaposi sarcoma Herpesvirus) is identified in and associated with some tumours such as Kaposi sarcoma (KS), multicentric Castleman disease (MCD) and primary effusion lymphoma (PEL).[1-3] HHV-8 infection is especially encountered in immunocompromised patients such as acquired immunodeficiency syndrome (AIDS), iatrogenic immunodeficiency like transplantation, and ageing. Nevertheless, it may also be a problem for immunocompetent patients.

Pathology of HHV-8 is based on its genome, which expresses genes responsible for inhibition of apoptosis, cell cycle entry and angiogenesis. It is thought that viral homologs of human regulatory genes provide stimuli for angiogenesis, B-cell proliferation and escape from immune system.[4]

Treatment of HHV-8-related malignancies are not different from HHV-8 negative ones, but management of the patients may be challenging because of the concomitant immunosuppression. In addition to chemotherapy, antiviral drugs have anecdotal clinical use.

Here, we describe an immunocompetent patient who had three malignancies associated with HHV-8 throughout her lifetime.

CASE REPORT

A-69-year-old woman applied with purple-red lesions in her hands, feet, abdomen, and back in 2009. She was diagnosed with KS on histopathologic examination of a skin lesion on her left forearm. Viral serology regarding HIV was negative. At the same time, she had splenomegaly and multiple intra-abdominal non-palpable lymphadenopathies. The diagnostic splenectomy revealed congestive splenomegaly. On 2011 she was diagnosed with mixed hyaline vascular and plasma cell type CD on excisional biopsy of her axillary lymphadenopathy. She received nine cycles of vincristine and bleomycin-based chemotherapy. After two years of remission, her skin lesions reappeared. As a second-line treatment she had single course of liposomal doxorubicin and six courses of CHOP (cyclophosphamide, doxorubicin, vincristine, methylprednisolone). She was in remission at the end of the cycles. At that time blood HHV-8 PCR and anti HHV-8 IgG was found to be positive with high titers. Two years later, her lymph nodes reappeared in multiple sites. Because of her well response before, she received 4 cycles of CHOP regimen again. After 5 years of remission in both CS and MCD, she had severe B symptoms (night sweats and fatigue), cervical and axillary lymph node enlargement. Excisional biopsy of cervical lymph node was performed and she was diagnosed with PEL, extracavitary/solid variant (Figure 1, Figure 2, Figure 3, Figure 4). Immunohistochemically, HHV-8 was positive in the pathologic specimen (Figure 4D). Because of the breast involvement, she was stage 4B PEL (Figure 5). After a detailed examination regarding heart functions, she received 1 cycle of CHOP treatment with liposomal doxorubicin. We had to switch to ICE (ifosfamide, carboplatin, etoposide) protocol as a salvage therapy, because of progression. After two cycles of ICE, she achieved partial remission and autologous stem cells were collected ($8x10^6$ CD34+ cells). Following BEAM (carmustine, etoposide, ARA-C, melphalan) conditioning regimen, autologous stem cell transplantation was performed on February 12th, 2018. Shorter than 1-month period, she had ptosis and proptosis in her left eye. Positron emission tomography-computed tomography (PET-CT) images showed progression in multiple sites, including left ethmoid

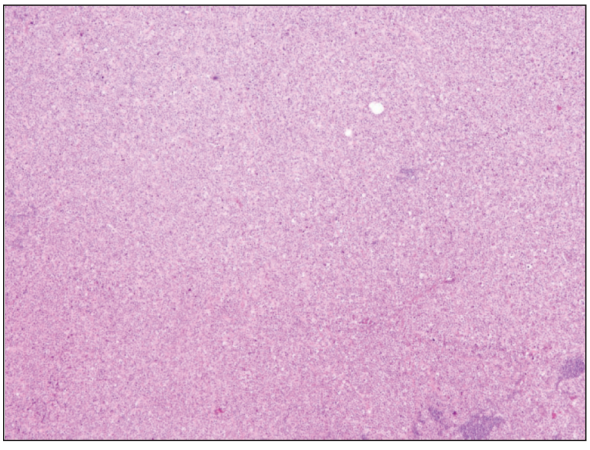

FIGURE 1: Intracavitary PEL. Diffuse neoplastic infiltration disrupting normal lymph node configuration (HE, x4).

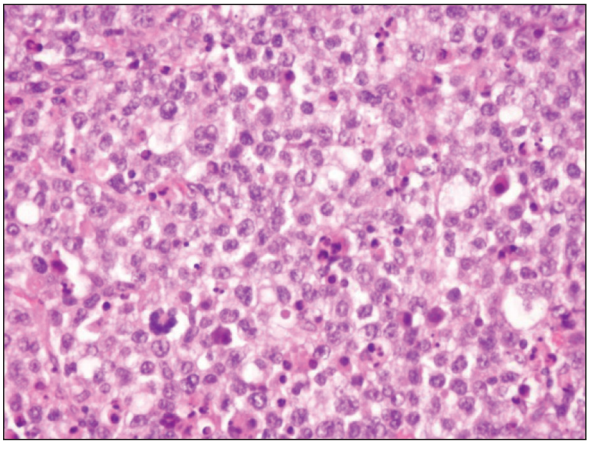

FIGURE 2: Neoplastic lymphoid cells on low power (HE, x40).

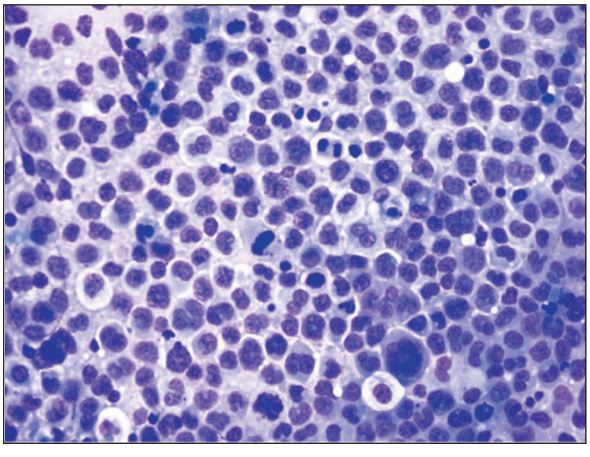

FIGURE 3: Neoplastic cells in tissue imprint preparations (Giemsa, x40).

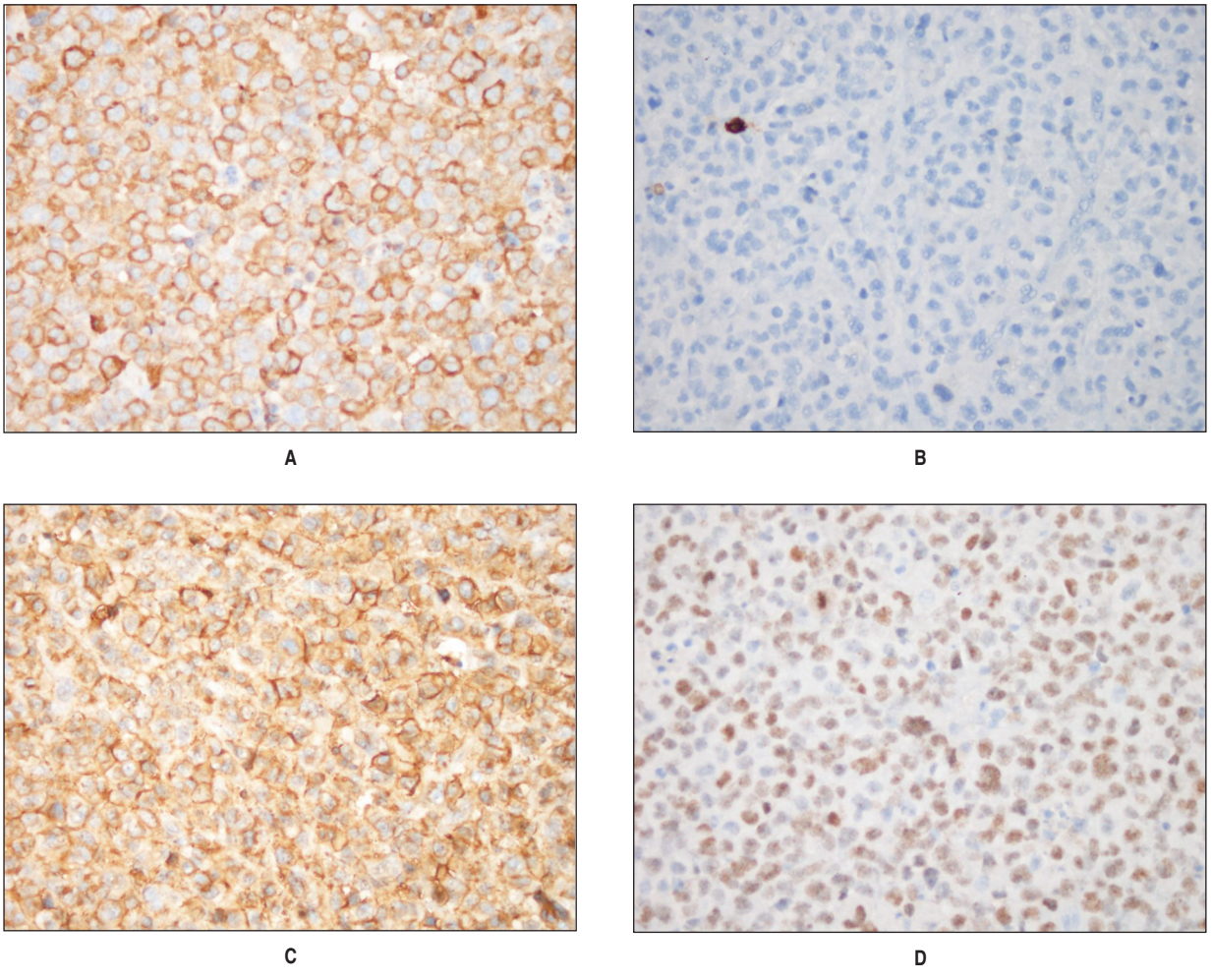

FIGURE 4: On immunohistochemical staining, **A:** CD3 positivity (DAB, x40), **B)** CD20 negativity (DAB, x40), **C)** CD138 positivity (DAB, x40), **D)** HHV-8 positivity (DAB, x40).

sinus and nasal cavity, which was the reason of her new complaints. Also, punch biopsy of nasal cavity supported the diagnosis of PEL, extracavitary/solid variant and lumber puncture sitology was malignant. Immediately cranial radiotherapy and systemic chemotherapy started. She received 2 cycles of ESHAP (methylprednisolone, cisplatin, etoposide, cytarabine) protocol. Simultaneously, systemic low dose cidofovir (1 mg/kg) was administered per week in the first two weeks, and than once in every two weeks (total of 4 doses). Although she clinically responded well to treatment, her lesions rapidly enlarged at the end of the cycle. CODOX-M (cyclophosphamide, methotrexate, vincristine, calcium leucovorin) protocol with intrathecal ARA-C 100 mg was initiated. Her neurological status and tumor

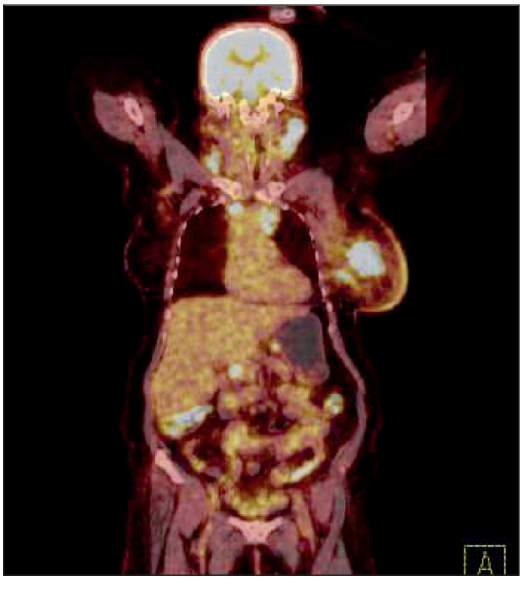

FIGURE 5: Positron emission tomography for staging PEL.

masses did not respond to drugs and rapid clinical deterioration began. Her family decided to stop medical support and she was discharged from the hospital. A few weeks after discharge, she died because of progressive disease.

Informed consent was obtained from the patient for publication of the paper during her treatment period.

DISCUSSION

Primary effusion lymphoma (PEL) is generally associated with immunosuppressive states and accounts for about 4% of HIV- associated non-Hodgkin lymphomas.[5] A significant number of PEL patients have history of other HHV-8-related diseases such as KS and MCD. Primary effusion lymphoma generally arises in body cavities such as pleural, pericardial, and peritoneal spaces, but there is also a rare solid variant. Extracavitary/solid variant presents with solid masses or lymphadenopathy. Both classic and solid variant exhibit similar morphology, immunophenotype, and genetic features. Although PEL is a B-cell lymphoma, cells fail to express neither B- nor T-cell immunophenotype. They are usually positive for CD45, CD30, and CD138, resembling plasmablastic differentiation.[4]

Due to rarity of the disease, there is no consensus on the treatment of PEL.[6] Boulanger et al. reported a series of 28 HIV positive patients with PEL. Majority of the patients received CHOP-like regimens, some of them additionally had etoposide and methotrexate. Other patients had only interferon or interferon plus cidofovir, mini-CHOP, or no treatment. Overall median survival was found to be 6.2 months and 1-year disease-free survival rate 78.6%.[7] The efficacy of high dose chemotherapy with autologous stem cell transplantation is not clear, because there are few conflicting results available in the literature.[8,9] Antiviral therapy in PEL has gained success especially by intracavitary cidofovir administration, but systemic cidofovir treatment remains to be elucidated.[4]

Our patient was tested for HIV infection several times during the course and was found to be negative. She had no other immunosuppressive states. Her pre-existing HHV-8-related diseases are consistent with literature, but she is the only immunocompetent patient with solitary variant PEL and the only one who had all three diseases related to HHV-8. She was resistant to all chemotherapy protocols, therefore we had to switch the treatment to a more comprehensive and aggressive level. She had progressive disease despite autologous stem cell transplantation. When she received the diagnoses of PEL, blood HHV-8 viral load was not measured, but because of HHV-8 positivity of neoplastic cells by immunohistochemistry, systemic cidofovir treatment was administered. Resistance of the disease may be explained by aggressive behavior of the tumor, patient's past chemotherapy burden, and her low performance status. Maybe there is an unknown immunosuppressive state, which could not be recognized with classical clinical approach. We need more data in such kind of rare diseases.

Our patient is the only immunocompetent case in the literature who had all three of the HHV-8 related malignancies, KS, MCD, and PEL, to the best of our knowledge. Furthermore, she is one of the very few PEL patients undergone autologous stem cell transplantation and received systemic antiviral treatment. We expect that our case report will contribute to the literature and help to expand knowledge regarding HHV-8-related malignancies.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Eren Arslan Davulcu, Yusuf Ulusoy, Hale Bülbül, Derya Demir, Mine Hekimgil, Mahmut Töbü;* ***Design:*** *Eren*

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