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Metastatic Kaposi Sarcoma to a lymph node involved by Nodular lymphocyte predominance Hodgkin lymphoma in an HIV-Negative patient

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Abstract

Although rare, but there are case reports of lymphoproliferative disorders that are associated with human immunodeficiency virus (HIV) negative Kaposi' sarcoma (KS), including Hodgkin lymphoma (HL). The majority of these cases show involvement by lymphoma and KS in different organs. Only 6 cases of concurrent HL and KS within the same lymph node have been documented in previous literature. These cases of HL are predominantly of classic type (cHL), with only one that showed simultaneous Nodular lymphocyte predominance Hodgkin lymphoma (NLPHL) with primary intra-nodal KS (no skin lesions presented).

We report the first case of a 26-year-old HIV negative gentleman with cutaneous KS metastatic to a lymph node primarily involved by NLPHL. Interestingly, in our case, Epstein Barr Virus (EBV) was found to be expressed in cells of both tumours.

Neither EBV nor Human Herpes Virus -8 (HHV-8) were found in association with both KS and HL by itself. EBV has an established role in the pathogenesis of classical HL. Loss of immune surveillance in immunodeficiency states, such as HIV infection, may predispose individuals to the development of EBV-associated cHL. It is possible that EBV infection of a B cell replaces one of the genetic alterations necessary for the development of classical HL.

Keywords: Kaposi sarcoma, NLPHL, HIV, HHV8, EBV

Background

Nodular lymphocyte predominance Hodgkin lymphoma (NLPHL) represents about 5% of Hodgkin lymphoma cases, while classic Hodgkin lymphoma (cHL) represents up to 95%. Patients with NLPHL tend to presentat an early stage with peripheral lymph node involvement with B symptoms in contrast to cHL [1]. Although NLPHL has a favorable course, it might transform into secondary aggressive non-Hodgkin lymphoma in 7-14% of cases [1].

Epstein-Barr virus (EBV) and Human herpesvirus -8 HHV-8 are human viruses that are responsible for the development of a spectrum of haema-tological and non-haematological disorders [2]. Hodgkin lymphoma (HL) is variably associated with EBV infection [3], whereas Kaposi Sarcoma (KS) is consistently associated with HHV-8 infection [4].

The treatment of NLPHL differs according to the stage and whether it is in frontline or in relapsed/refractory settings. Generally it includes: radiotherapy, chemotherapy, combined modality therapy, anti-CD20 agents and watchful waiting. Other agents that were investigated in relapsed settings with promising results include ofatumumab, lenalidomide and bendamustine [5].

Treatment of KS varies according to the form, presence

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of symptoms and extent of disease. Options include: antiretroviral therapy, Local therapies (surgical resection, radiotherapy, cryotherapy, intralesional chemotherapy, and topical therapies as retinoid gel and imiquimod cream), systemic chemotherapy. Other options for refractory/relapsed disease may include bevacizumab, imatinib, interferon, thalidomide [6].

Cytotoxic chemotherapy agents especially Doxorubicin are considered to be effective in treating NLPHL as well as KS. Because of the prevalence of CD 20 expression in NPLHL, anti- CD20 monoclonal antibodies (Rituximab) are considered a treatment option in addition to cytotoxic chemotherapy [1].

There are reported cases of concomitant KS and cHL in the same lymph node [7-11]. However, the occurrence of KS and NLPHL in the same lymph node has only been described once [12].

Case presentation

We present a 26-year-old immunocompetent gentleman who initially presented mid-2017 with bilateral lower limb edema and small itchy papules involving the penis and scrotum for one and half years. He received multiple courses of treatment and antibiotics with no improvement. Six months later, he experienced the appearance of small itchy vesicles on the sole of the left foot and painless inguinal lymph node enlargement with no fever, joint pain or penile discharge. His skin lesions progressed over 2 months to involve the dorsum of both feet.

He presented to us in January 2018, and examination revealed bilateral small purple nodules on both feet accompanied with bilateral pitting edema. No concurrent oral, perianal, scrotal nor penile lesions were identified. The rest of the physical examination was unremarkable showed no significant findings. Chest X-ray, bilateral venous duplex and abdominal ultrasonography. PET-CT scan revealed abdominal and bilateral deep cervical metabolically active lymphadenopathy. In addition, he had a metabolically active left suprarenal lesion, and bilateral diffuse FDG uptake of subcutaneous edema at both legs were detected.

There was no history of sexually transmitted infections, intravenous recreational drug abuse, nor blood transfusion.

HIV testing was negative repeatedly by ELISA antigen and antibodies for HIV-1 and 2. The HIV-1 RNA viral load plasma real-time PCR test was also negative.

An inguinal lymph node excisional biopsy was done. Macroscopically, it measured 4x3 cm with focally hemorrhagic cut surface. The microscopic picture showed a nodular infiltrate by small lymphoid cells with scattered large LH cells. The same lymph node showed involvement by a metastatic tumor formed of proliferating spindle cells entrapping slit-like spaces filled with RBCs with no definite endothelial lining. Anaplasia was mild and mitotic activity was increased (**Figure 1**).

Immunohistochemical tests were performed using the Ventana Benchmark autostainer on formalin fixed paraffin embedded sections with the following antibodies LCA, CD20, CD3, CD34, CD30, CD 15, Bcl-6, EMA, EBV and HHV-8, and revealed positive reaction of the LH cells for LCA, CD20, Bcl-6, EBV, focal positive reaction for CD30 but negative for CD3, CD15 and HHV8. CD3 stained the background reactive T-cells with evident rosetting around the large cells. The spindle cell component was diffusely positive for CD34 and showed positive nuclear reactivity for both EBV and HHV-8 immunostaining (**Figure 1**).

The patient received 2 cycles of ABVD (Doxorubicin 25mg/m2 IV Day 1 and 15, Bleomycin 10units/m2 IV Day 1 and 15, Vinblastine 6mg/m2 IV Day 1 and 15, Dacarbazine 375mg/m2 IV Day 1 and 15) chemotherapy protocol with complete remission (CR). He is planned to finish 4 cycles of ABVD then to be reevaluated by imaging studies.

Discussion and conclusion

Forty five cases of concomitant HL and KS in the same patient have been reported [13,14]. To our knowledge, only 6 cases of simultaneous occurrence of HL and KS in the same lymph node have been reported in previous English language literature [7-12]. Including the present case, they are summarized in **Table 1**.

Table 1. Reported cases of simultaneous of HL and KS in the same lymph node.

Author	Gender	Age	HIV status	HL subtype
Massarelli[4]	Female	43	ND	Nodular sclerosis
Carbone [5]	Male	82	ND	Mixed cellularity
Hayes [6]	Male	NA	Positive	NA
Mitsuyasuand[7]	Male	31	Positive	Mixed cellularity
Ngan &Kuo[8]	Female	61	Negative	Mixed cellularity
Kankaya et al. [9]	Male	57	Negative	NLPHL
Our case	Male	26	Negative	NLPHL

NA: Not Available, ND: Not Documented

EBV was the first virus shown to cause cancer in humans and is associated with malignant neoplasms originating from epithelial cells, lymphocytes and mesenchymal cells [15]. EBV-associated neoplasms affect both immune-competent individuals and immune-compromised patients, post organ transplantation or iatrogenic immune suppression. The development of an EBV-associated neoplasm is largely dependent on environmental factors and genetic susceptibility to viral infection that is associated with genetically prone immune deregulation [16]. EBV is associated with a subset of HL, a subset of diffuse large B-cell lymphoma, endemic Burkitt lymphoma and age-related EBV-positive B-lymphoproliferative diseases [17]. Aggressive NK-cell leukemia and extranodal NK-/T-cell lymphoma are EBV-positive [16]. Nasopharyngeal carcinoma [18] and gastric adenocarcinoma [19] are representative epithelial malignancies associated with EBV.

HHV-8 can cause a spectrum of lymphoproliferative disorders, in addition to KS, which can also involve the lymph nodes. These include HHV8- positive multicentric Castleman disease; HHV8-positive diffuse large B cell lymphoma, primary effusion

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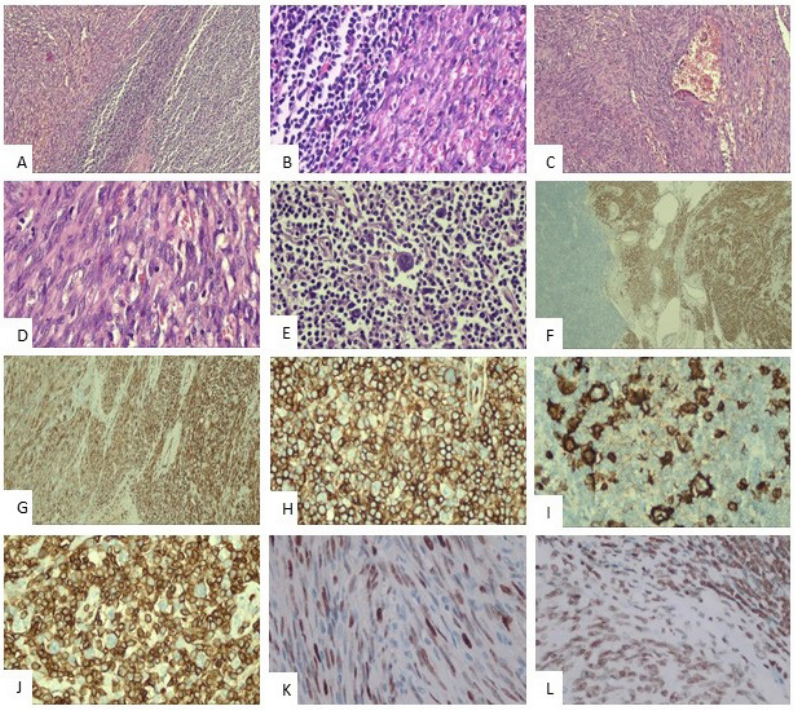

Figure 1: (**A**) H&E stained section showing both KS (Lt) and NLPHL (Rt), original magnification X40. (**B**) H&E stained section of both KS (Rt) and NLPHL (Lt), original magnification X400. (**C**) H&E stained section showing KS original magnification X100. (**D**) H& E stained section of KS, proliferating short spindle cells with slit-like vascular spaces and extravasated RBCs, original magnification X400 (**E**) H&E stained section showing the multilobated HL cells, original magnification X400. (**F**) CD34 immunostained section showing KS cells positive for CD34 (Rt) and lymphoma cells are negative (Lt), original magnification X40. (**G**) CD34 immunostained section showing KS, original magnification X400. (**H**) LCA immunostained NLPHL section, the large cells are LCA positive, original magnification X400. (**I**) CD20 immunostained NLPHL section, the large cells are CD20 positive, original magnification X400. (**J**) CD3 immunostained NLPHL section, the large cells are CD3 negative, surrounded by CD3 positive reactive T-lymphocytes (rosetting), original magnification X400. (**K**) HHV-8 immunostained KS cells, original magnification X400. (**L**) EBV immunostaining in both HL cells and KS cells, original magnification X400.

lymphoma and germinotropic lymphoproliferative disorder [20]. These disorders are most commonly seen in the setting of HIV infection and in HHV-8 endemic areas, but they can also occur in other immune-suppression states [21]. However, there are reported cases of HHV-8 infection in immunocompetent individuals [22,23].

The simultaneous occurrence of KS and HL in the same lymph node has raised questions about a common pathogenic mechanism, however this is not yet proved. Neither EBV nor HHV-8 were found in association with both of these malignancies by itself [12].

EBV has an established role in the pathogenesis of cHL and is found in only a proportion of cases. Loss of immune surveillance in immunodeficiency states, such as HIV infection, may predispose to the development of EBV-associated cHL. It is possible that EBV infection of a B cell replaces one of the genetic alterations necessary for the development of cHL. NLPHL is rarely positive for EBV (<5% of cases) [24].

In our case, HHV-8 was immunohistochemically demonstrated only in the KS cells, however EBV was found in both the LH cells of NLPHL and KS cells. Our case is unique in several aspects. First, our patient is HIV negative, unexpectedly developed KS which metastasized to a lymph node, accidentally discovered to be involved by NLPHL. In addition, the 2 independent tumors showed different types of viral infection. EBV was present both in the HL and KS cells and HHV-8 was identified in the KS.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	NM	HA	NG	AM	MEB
Research concept and design	✓	--	--	--	--
Collection and/or assembly of data	✓	✓	✓	--	--
Data analysis and interpretation	--	--	--	--	--
Writing the article	✓	✓	✓	--	--
Critical revision of the article	--	--	--	✓	✓
Final approval of article	✓	--	--	--	--
Statistical analysis	--	--	--	--	--

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