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The unholy trinity of human herpesvirus 8-associated malignancy in a person living with HIV-1

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To the editor,

We report the case of a 45-year-old homosexual man who was diagnosed with HIV-1 infection (nadir CD4 count 138 cells/ μ l) upon presentation with Kaposi's sarcoma (KS, ACTG stage T0 I1 S0, Fig. 1A). KS lesions resolved following initiation of combination antiretroviral therapy (ART) with tenofovir, emtricitabine and efavirenz combined with local radiotherapy for cosmesis. Persistent generalised lymphadenopathy was also noted at presentation, but biopsy of an axillary lymph node was benign. The patient had an appropriate response to ART, achieving complete viral suppression and immune reconstitution (CD4 334 cells/ μ l) within 6 months.

Eight months later he presented with nephrotic-range proteinuria (serum albumin 26 mg/dl, urine protein 14 g/l) secondary to histologically proven membranous glomerulonephritis, in association with fever, systemic upset and elevated inflammatory markers. Serology for hepatitis B, C and syphilis was negative and tenofovir was switched to abacavir. A repeat groin lymph node biopsy revealed Castleman's disease (Fig. 1B), and quantitative polymerase chain reaction (qPCR) for human herpes virus 8 (HHV8) DNA was 47,000 copies/ml. He was treated initially with valganciclovir 900mg b.d. for 3 months with minimal impact on HHV8 replication, and rituximab (750mg weekly for one month then monthly for 3 months) was introduced.

There was a clinical response with resolution of proteinuria and reduction of lymphadenopathy, however HHV8 replication, anaemia and elevated C-reactive protein persisted. Surveillance imaging approximately 6 months later showed further improvement with complete resolution of adenopathy but identified a new 15mm liver lesion. Histological examination of this lesion revealed an extracavitary primary effusion lymphoma (PEL, Fig. 1C). No additional foci were observed by ¹⁸-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT)

and cerebrospinal fluid cytological examination was normal. He was treated with six cycles of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy with intrathecal methotrexate, resulting in a complete response and no recurrence of HHV-8 viral replication in blood up to 3 years later (Fig. 1D).

This case neatly illustrates the spectrum of HHV-8-associated malignancy that manifests in patients with HIV-1, and raises some interesting points regarding diagnosis and management. Surprisingly, this is the first published report of metachronous KS, MCD and PEL in a person living with HIV, although the coexistence of KS and MCD [1] or MCD and PEL [2] is not unusual. These disorders are aetiologically linked to the gamma herpes virus HHV8 (previously known as Kaposi sarcoma-associated herpesvirus, KSHV). MCD and PEL are associated with lytic replication, higher levels of the virus detected in plasma, and the paracrine effects of oncogenic viral proteins homologous to interleukin-6, Bcl-2 and several others [3]. KS, MCD and PEL occur at considerably higher frequency in patients with HIV-1 although they have an inconsistent relationship with immunosuppression: KS and PEL are associated with low CD4 counts; MCD, which follows a relapsing-remitting course with episodes of systemic inflammation, is unrelated to the degree of immunosuppression and often develops following ART initiation [4]. Thus while the incidence of KS in the post-ART era has fallen dramatically, the incidence of MCD is stable or increasing [3].

Quantification of HHV8 replication by qPCR in plasma or mononuclear cells has an important role in diagnosis, prognosis and monitoring of treatment response in HHV-8-associated malignancies in HIV, particularly MCD. For example, the presence of high plasma HHV8 DNA levels in patients with KS should prompt a diagnostic search for synchronous MCD [5]. HHV-8 DNA > 40,000 copies/ml was associated with risk of death in an HIV-MCD cohort [6], and a rising HHV8 level appeared to predict the occurrence of symptomatic episodes [7]. The role of HHV8 monitoring in PEL is unclear [3]. As demonstrated here, valganciclovir has only a modest impact on HHV8

replication kinetics *in vivo* [3], and remission rates in MCD are inferior to the anti-CD20 monoclonal antibody (mAb) rituximab [3] – which remains the mainstay of therapy, with 5 year relapse-free survival of 82% (CI 72-92%) [8]. Tocilizumab, an interleukin-6 receptor specific mAb, has shown promise [9, 10], but no randomised trial evidence is available. An association between MCD and nephrotic syndrome has been reported previously [11-13] and warrants further investigation.

Although the metachronous presentation might suggest an unusually oncogenic strain of HHV8, no material was available for viral sequencing. Moreover, we have not yet explored whether an additional host defect of innate or adaptive antiviral immunity may be involved. Nevertheless, this case serves to illustrate the range of HHV8-associated pathology in the context of HIV, underscoring the importance of quantifying HHV8 viral load in KS patients where additional HHV8-associated lymphoproliferative disorders are suspected, and in assessing response to therapy in MCD/PEL.

Conflict of interest and funding:

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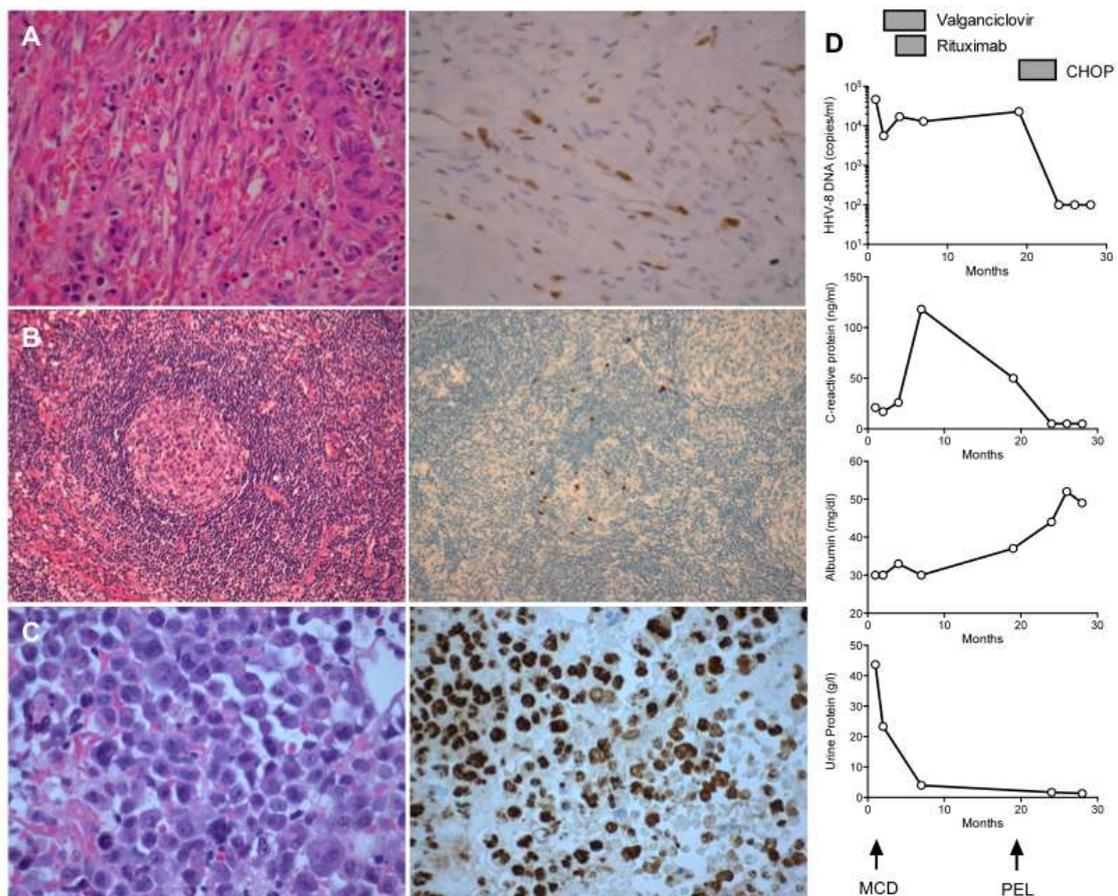


Figure 1

Haematoxylin & eosin (left panels) and human herpes virus 8 (HHV8) immunostain (right panels) of: A) skin biopsy demonstrating Kaposi sarcoma; B) Lymph node biopsy demonstrating multicentric Castleman's disease (MCD); C) Liver lesion biopsy demonstrating extracavitary primary effusion lymphoma (PEL). D) Time-course of laboratory parameters relative to treatment regimen (filled blocks). CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone with intrathecal methotrexate chemotherapy.

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