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# High incidence of Kaposi sarcoma-associated herpesvirus infection in HIV-related solid immunoblastic/plasmablastic diffuse large B-cell lymphoma

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**Kaposi sarcoma-associated herpesvirus (KSHV) is known to be associated with two distinct lymphoproliferative disorders: primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD)/MCD-associated plasmablastic lymphoma. We here report a high incidence of KSHV infection in solid HIV-associated immunoblastic/plasmablastic non-Hodgkin's lymphomas (NHLs), in patients lacking effusions and without evidence of (prior) MCD. Within a cohort of 99 HIV-related NHLs, 10 cases were found to be KSHV positive on the basis of immunostaining for KSHV LNA-1 as well as KSHV-specific polymerase chain reaction. All but one of the tumors coexpressed Epstein–Barr virus. Interestingly, all KSHV-positive cases belonged to a distinctive subgroup of 26 diffuse large B-cell lymphomas characterized by the expression of CD138 (syndecan-1) and plasmablastic/immunoblastic morphology. These KSHV-positive lymphomas were preceded by Kaposi sarcoma in 60% of the patients and involved the gastrointestinal tract in 80%. Our results indicate that KSHV infection is not restricted to PEL and MCD; it is also common (38%) in HIV-related solid immunoblastic/plasmablastic lymphomas.**
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## Introduction

Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV8), was discovered in AIDS-related Kaposi sarcoma and plays a major role in the pathogenesis of all forms of Kaposi sarcoma.[1–3] Subsequently, the virus has also been identified in two rare B-cell lymphoproliferative disorders, primary effusion lymphoma (PEL)[4–7] and multicentric Castleman disease (MCD)/MCD-associated plasmablastic lymphoma.[8–14] PEL occurs predominantly in HIV-infected individuals and presents as a lymphomatous effusion in the pleural, peritoneal, or pericardial cavity without a contiguous tumor mass. In the vast majority of cases, the tumor cells are coinfected with KSHV and Epstein–Barr virus (EBV).[15] The transformed cells of PEL generally harbor somatically mutated immunoglobulin (Ig) variable region (V) genes, implying a postgerminal center B-cell origin, and they have an immunophenotype and gene expression profile similar to plasma cells/plasmablasts.[16–18] MCD is characterized by lymphadenopathy with angiofollicular hyperplasia and plasma cell infiltration. The KSHV-positive plasmablasts in MCD show monotypic expression of IgM$\lambda$ but, intriguingly, are usually multiclonal, are not coinfected with EBV, and do not contain somatic mutations in their IgV genes.[13,14] Hence, unlike the malignant cells in PEL, the MCD plasmablasts originate from naïve B cells.

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Although KSHV association in lymphoproliferative disease is currently regarded to be restricted to PEL and MCD, a small number of KSHV-positive lymphomas without effusions have been described in the literature, usually as anecdotal case reports.[19–28] These tumors, which usually arise in the context of HIV infection, have been proposed to represent 'extracavitary PELs' and are believed to be decidedly rare.[22] However, systematic studies exploring the incidence of KSHV infection in solid HIV-related lymphomas are lacking. We therefore studied the incidence of KSHV infection in a cohort of patients with HIV-related non-Hodgkin's lymphomas (NHLs).

## Materials and methods

### *Patients and tissue samples*

The study group consists of a cohort of 99 patients with HIV-related NHL from the lymphoma registry of the Departments of Pathology and Hematology of the Academic Medical Center (AMC), Amsterdam, The Netherlands, which is the main referral center for the treatment of HIV infection and AIDS in the Netherlands. All patients with an HIV-related NHL diagnosed between 1988 and 2003, of whom adequate histological material and clinical information, were available were included. The tumors were reviewed and classified according to the WHO classification. Clinical parameters retrieved included: age, sex, stage, lymphoma localization, presence or absence of effusions, and previous history of Kaposi sarcoma or MCD (Table 1). Statistical analysis was performed using a Pearson $\chi^2$ test (SPSS11.5 for Windows); $P<0.05$ was considered significant.

### *Immunohistochemistry and EBV small RNA (EBER) in situ hybridization*

Sections (5 $\mu$m) were cut from formalin-fixed and paraffin-embedded tissue and immunohistochemical studies were performed, using the biotin-free Power Vision+ Poly-Hrp-Anti-Ms/Rb IgG histostaining method (Lab Vision Corporation, Freemont, CA, USA). Antibodies used were: LN53, against KSHV LNA-1 (LANA) (Advanced Biotechnologies, Maryland, USA); anti-CD138 (IQ-Products, Groningen, The Netherlands); and anti-CD3, anti-CD20, anti-CD10, anti-BCL-6, anti-CD30, anti-Ig$\kappa$, anti-Ig$\lambda$, and anti-PAX5 (all from Dako, Glostrup, Denmark). *In situ* hybridization for EBER was carried out with an oligonucleotide probe labeled with fluorescein, followed by immunohistochemical detection using the Power Vision histostaining method, as mentioned above.

**Table 1** Clinical, immunohistochemical and PCR findings in patients with HIV-related solid immunoblastic/plasmablastic (CD138-positive) B-cell NHLs

| *Patient* | *Sex/age (years)* | *Primary site of diagnosis* | *Ann Arbor Stage* | *Other sites involved* | *KS (years before/ after lymphoma diagnosis* | *KSHV-PCR* | *KSHV-IHC* | *EBER-ISH* | *clg LC* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M/36 | Stomach | IV | Lung, LN abd and tx, spleen | Yes (2 years before) | + | + | + | – |
| 2 | M/41 | Colon | IV | Small bowel, retroperitoneum | No | + | + | + | – |
| 3 | M/54 | LN | IV | Small bowel, LN cervical | Yes (1 year before) | + | + | + | $\lambda$ |
| 4 | M/46 | Stomach | IV | Lung, skin, CSF | Yes (1 year before) | + | + | + | – |
| 5 | M/44 | LN abd | IV | Liver, spleen, colon | Yes (2 years before) | + | + | + | $\kappa$ |
| 6 | M/35 | LN inguin | IV | Skin | Yes (2 years before) | + | + | + | – |
| 7 | M/38 | LN axil | IV | Colon, small bowel, skin | No | + | + | + | $\lambda$ |
| 8 | M/54 | LN supraclav | IV | Liver, spleen, LN inguin and tx | No | + | + | + | – |
| 9 | M/41 | Stomach | IV | Lung, colon, kidney | Yes (same year) | + | + | – | – |
| 10 | M/44 | Cecum | IIE | LN mesenterial | No | + | + | + | $\kappa$ |
| 11 | M/28 | LN inguin | IV | Liver | Yes (1 year after) | – | – | – | ND |
| 12 | M/23 | LN abdom, tx, inguin | IV | BM, liver, kidney | No | – | – | – | ND |
| 13 | M/57 | LN para-iliac | IV | Colon, spleen, pericard., prost. | No | – | – | + | ND |
| 14 | M/40 | BM | IV | Testis, liver, spleen, CNS | No | – | – | + | $\kappa$ |
| 15 | M/29 | Stomach | IV | – | No | – | – | ND | – |
| 16 | F/24 | CNS | IE | | No | – | – | + | – |
| 17 | M/48 | Nasoph | IV | Skin | No | – | – | – | ND |
| 18 | M/45 | Small bowel | IV | | No | – | – | + | – |
| 19 | M/33 | Skin | IIE | Anal, LN inguin | Yes (same year) | – | – | ND | – |
| 20 | M/39 | Tonsil | IE | – | No | – | – | ND | – |
| 21 | F/56 | LN inguin | IV | Colon, stomach, retroperitoneum | No | – | – | + | – |
| 22 | M/39 | Oral | IE | – | No | – | – | + | – |
| 23 | M/33 | Colon | IV | BM, LN abd | No | – | – | + | – |
| 24 | M/32 | Oral | IV | LN abd | No | – | – | – | ND |
| 25 | M/29 | Anus | IV | LN abd | No | + | – | + | $\kappa$ |
| 26 | M/55 | Testis (left) | IV | Testis (right) | No | – | – | + | $\kappa$ |

M = male; F = female; IHC = immunohistochemistry; ISH = *in situ* hybridization; LN = lymph node; abd = abdominal; tx = thoracal; axil = axillary; prost = prostate; inguin = inguinal; CNS = central nervous system; CSF = cerebrospinal fluid; nasoph = nasopharynx; BM = bone marrow; para-iliac = para-iliacal; supraclav = supraclavicular; ND = not done; clg = cytoplasmic immunoglobulin; KS = Kaposi sarcoma.

### *Polymerase chain reaction (PCR) detection of KSHV*

Detection of KSHV sequences was performed on extracted DNA using primer sets and PCR amplification as described previously.[29]

## Results

All 99 patients with HIV-related NHL included in this study presented with solid lymphomas. Of these tumors, 95 were B-lineage lymphomas classified as either Burkitt lymphoma or diffuse large B-cell lymphomas (DLBCL), whereas four lymphomas were of T-cell origin. Immunohistochemical staining for KSHV LNA-1 was positive in 10 of these lymphomas, with distinct nuclear staining of the vast majority of the tumor cells (Figure 1). KSHV infection was confirmed by DNA PCR in all these immunohistochemically positive tumors. Interestingly, all KSHV-positive lymphomas belonged to a distinctive subgroup of 26 DLBCL characterized by an immunoblastic/plasmablastic morphology and by expression of CD138 (syndecan-1) (Table 1, Figure 1). The relation of these KSHV-positive tumors to terminally differentiated B cells was confirmed by their immunophenotypical profile, showing the absence or low expression of the B-cell markers CD20, CD79a, and PAX5, often accompanied by the expression of CD30 (Table 2). Importantly, none of the patients with KSHV-positive lymphomas showed effusions at presentation or had a history of MCD, and only one patient developed a malignant effusion in the course of the disease. The development of a KSHV-positive lymphoma was preceded by Kaposi sarcoma in six of 10 (60%) patients, whereas a history of Kaposi sarcoma was present in only two of 16 (12.5%) patients with a CD138-positive KSHV-negative DLBCL (Pearson $\chi^2$, $t=6.5$, 1 df, $P=0.011$). All KSHV-positive lymphomas showed extranodal dissemination, most often (8/10) involving the gastrointestinal tract, whereas only five of 16 KSHV-negative lymphomas displayed gastrointestinal involvement (Pearson $\chi^2$, $t=5.8$, 1 df, $P=0.016$). All but one of the KSHV-positive lymphomas was coinfected with EBV.

## Discussion

Our cohort study shows that KSHV infection is common (38%) in HIV-related lymphomas with an immunoblastic/plasmablastic phenotype, which represent a distinctive subtype of HIV-related DLBCL.[30] This observation contradicts the notion that KSHV infection in solid lymphomas is rare.[22] Notably, during the whole study period, only a single case of PEL was diagnosed, indicating that, at least in our patient population, KSHV-positive solid lymphomas greatly outnumber PELs. The solid immunoblastic/plasmablastic lymphomas (SIPLs) reported here are clearly distinct from MCD-related lymphoproliferations,[13,14] since they do not show monotypic expression of Ig$\lambda$ and since the vast majority is coinfected with EBV.[16,17] Although SIPLs share important features with PELs, including a strong association with EBV and an immunophenotype implying a common origin from plasma cells/plasmablasts, there are also features suggesting pathogenetic differences. For example, the distinctive clinical presentation of SIPL and PEL implies the existence of

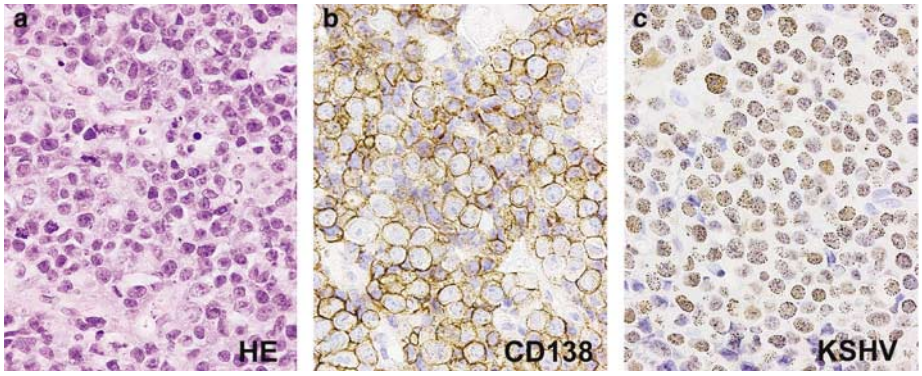


**Figure 1** KSHV-positive solid immunoblastic/plasmablastic lymphoma, representative case. (a) Characteristic morphology of tumor cells (hematoxylin and eosin, original magnification × 400). (b) Immunohistochemical staining with antibody B-B4 against CD-138 (syndecan-1) shows strong membranous expression. (c) Immunohistochemical staining with antibody LN53 against LNA-1 protein of KSHV shows strong stippled nuclear expression.

**Table 2** Immunophenotypical features of KSHV-positive solid immunoblastic/plasmablastic diffuse large B-cell lymphoma

| | *CD138* | *CD45* | *CD79a* | *CD20* | *Pax-5* | *CD30* | *clg kappa* | *clg lambda* |
|---|---|---|---|---|---|---|---|---|
| Case 1 | + | ± | ± | − | − | − | − | − |
| Case 2 | + | − | − | − | − | − | − | − |
| Case 3 | + | − | − | − | − | − | − | + |
| Case 4 | + | − | − | − | − | + | − | − |
| Case 5 | + | − | − | − | − | − | + | − |
| Case 6 | + | + | − | − | − | + | − | − |
| Case 7 | + | ± | + | − | − | + | − | + |
| Case 8 | + | − | − | − | − | − | − | − |
| Case 9 | + | + | − | − | − | ± | − | − |
| Case 10 | + | − | ± | + | − | − | + | − |

clg = cytoplasmic immunoglobulin.

**Table 3** Summary of KSHV-positive solid immunoblastic/plasmablastic DLBCL without effusions reported in the literature

| *Ref.* | *Sex/age* | *Primary site* | *Other sites* | *KS* | *KSHV PCR* | *KSHV IHC* | *EBV* | *CD20* | *CD138* | *Other plasma cell markers* |
|---|---|---|---|---|---|---|---|---|---|---|
| 19 | M/44 | Cecum | NS | NS | ± | + | + | − | + | CD30 |
| 19 | M/41 | LN | Skin, rectum | NS | + | + | + | − | − | CD30 |
| 20 | M/48 | LN | NS | + | − | + | + | + | NS | CD38 |
| 20 | M/48 | Soft tissue | NS | + | − | + | + | − | NS | CD38 |
| 20 | M/41 | Spleen | NS | + | − | + | − | − | NS | CD38 |
| 21 | M/59 | Lung | − | + | + | + | − | − | − | CD30 |
| 22 | M/44 | Inguin LN | Spleen, LN | − | + | + | + | − | + | CD30 |
| 22 | M/40 | Axillary LN | NS | − | + | + | + | − | ND | CD30 |
| 22 | M/49 | Chest wall | NS | − | + | + | ND | − | ND | ND |
| 22 | M/27 | LN | NS | − | + | + | + | − | ND | CD30 |
| 22 | M/51 | Axillary LN | Chest, pelvic and abd LN | − | + | + | + | − | − | − |
| 22 | M/37 | Hilar LN | Dissem.+skin | + | + | + | + | − | + | CD30 |
| 22 | M/40 | LN | Dissem. | + | + | + | + | + | − | − |
| 22 | M/39 | Cervical LN | Dissem+stomach, bowel | − | + | + | + | − | + | CD30 |
| 23 | M/23 | Gingiva | NS | NS | + | + | − | + | NS | NS |
| 23 | M/NS | Oral cavity | NS | NS | + | + | + | − | NS | VS38 |
| 23 | M/31 | Oral cavity | NS | NS | + | + | + | − | NS | VS38 |
| 23 | M/51 | Or phar | NS | NS | + | + | + | − | NS | VS38 |
| 23 | M/34 | Nasoph | NS | NS | + | + | + | − | NS | VS38 |
| 24 | M/51 | Cerebell | Skin, abd LN | NS | NS | + | + | − | NS | NS |

Ref. = reference; KS = Kaposi sarcoma; IHC = immunohistochemistry; M = male; NS = not stated; ND = not done; LN = lymph node; inguin = inguinal; or phar = oropharynx; nasoph = nasopharynx; dissem = disseminated; abd = abdominal; cerebell = cerebellum.

profound differences in the expression of molecules that mediate homing of the tumor cells including adhesion molecules and chemokines/chemokine receptors.[18,31] Furthermore, although both SIPL and PEL are associated with KSHV, the KSHV association in PEL is much stronger, that is, is close to 100%, suggesting a distinct pathogenetic role of the virus. Whereas KSHV infection could represent an early event in the pathogenesis of PEL, involved in transformation, KSHV infection in SIPL might represent a secondary event in patients with an already high viral load. Our finding that 60% of the KSHV-positive SIPL patients had prior Kaposi sarcoma is consistent with this scenario. The observation that all KSHV-positive lymphomas in our cohort expressed the heparan sulfate proteoglycans (HSPGs) syndecan-1 (CD138), a molecule that is also expressed by PELs,[13] is intriguing. Since HSPGs have been shown to function as receptors for KSHV,[32] syndecan-1 could be instrumental in the viral entry into the lymphoma cells or their precursors.

In the literature, a limited number ($n = 24$) of KSHV-positive solid lymphomas without effusions have thus far been reported, all in HIV-infected individuals.[19–28] In contrast to our systematic cohort study, all these studies represent (extended) case reports. As a consequence, they do not allow conclusions concerning the incidence of KSHV infection in HIV-related solid lymphomas. In four of the reported cases, KSHV infection was established by PCR analysis alone.[25–28] In view of the high seroprevalence of KSHV and the frequent presence of Kaposi sarcoma in HIV patients, this approach provides insufficient evidence for KSHV infection of the lymphoma and requires confirmation by immunohistochemistry. The main characteristics of the 20 reported cases in which KSHV infection of the lymphoma has been documented by immunohistochemistry, mostly in combination with PCR, are listed in Table 3. Although the clinical and pathological data of most cases are incomplete, their overall characteristics are strikingly similar to that of the lymphomas reported in our current study. These characteristics include an immunoblastic/plasmablastic morphology and immunophenotype (ie expression of CD138/CD30/CD38/VS38 and absence of CD20/PAX5), coinfection with EBV, frequent Kaposi sarcoma, and gastrointestinal tract involvement.

In conclusion, our results indicate that KSHV infection is not restricted to PEL and MCD; it is also common in HIV-related solid lymphomas with an immunoblastic/plasmablastic phenotype, characterized by the expression of CD138 and the absence of B-cell markers. These KSHV-positive SIPLs are often preceded by Kaposi sarcoma and preferentially involve the gastrointestinal tract. Since our cohort study suggests that KSHV-positive SIPLs are considerably more common than PELs and only seldomly give rise to effusions, our data do not support the proposal by Chadburn *et al* to classify these tumors as extracavitary (or solid) PELs.

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