The importance of co-morbidity in older HIV-infected patients

We read with interest the recent study by Tumbarello et al. [1]. The authors compared a group of HIV-infected older patients (aged > 50 years) with a group of younger patients (aged 20–35 years). All patients received highly active antiretroviral therapy (HAART). The older cohort had a lower mean CD4 cell count than the younger cohort (108 versus 187 cells/mm³). In addition, the older cohort had a significantly higher percentage of co-morbid conditions than controls (44.8 versus 15.5%) as measured by the Charlson co-morbidity index [2]. In univariate analysis, a lower Charlson co-morbidity index (indicating fewer co-morbid illnesses) was associated with a higher chance of immunological success in response to HAART as was the baseline CD4 cell count. In multivariate analysis, after controlling for sex and co-morbid conditions, there was no difference in immunological success in response to HAART. However, as demonstrated by Tumbarello and colleagues [3,4], in clinical practice underlying non-HIV-related co-morbid conditions are present in up to a half of older patients. In the clinic, many older patients will thus have other significant illnesses that may impact their response to HIV treatment.

Several years ago we published the first report on the impact of co-morbidity on survival in older patients with HIV [4]. In a case–control study we compared an older cohort (aged > 55 years) with a matched younger cohort (aged < 45 years). Like Tumbarello et al. [1], we also found that the older cohort had significantly lower CD4 cell counts (205 versus 429 cells/mm³) and a significantly higher Charlson co-morbidity index (39.5 versus 10.5% or 0.907 versus 0.198 points per patient), indicating a high prevalence of non-HIV-related co-morbid conditions in the older cohort. A higher co-morbidity index was a predictor of mortality in our study. Older patients had more hospitalizations and shorter survival than younger patients.

It thus appears that the observations we made 7 years ago regarding lower CD4 cell counts and the importance of co-morbid conditions in older patients remain relevant in the HAART era. We agree that older patients should receive HAART and generally respond well to HAART, but would emphasize the importance of diagnosing older patients as early as possible to prevent immunological decline and to improve the chances of successful HAART. Clinicians should address and treat co-morbid conditions aggressively in order to improve outcome in this group of patients.

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Digoxin toxicity and ritonavir: a drug interaction mediated through p-glycoprotein?

P-glycoprotein is an MDRI gene product that functions as an ATP-dependent drug efflux pump. P-glycoprotein is expressed in the apical membrane of epithelial and endothelial cells of a number of tissues, including the liver, small intestines, kidney and the blood–brain barrier, where it results in reduced absorption, enhanced elimination and the prevention of drug entry into the central nervous system, respectively. Digoxin is a substrate for p-glycoprotein, and given its low therapeutic index its concurrent use with drugs that have a propensity to increase digoxin exposure is of significant concern. Clinically significant drug interactions with digoxin have been associated with itraconazole, quinidine, clarithromycin and verapamil that inhibit intestinal or renal digoxin excretion by inhibiting p-glycoprotein-mediated transport [1]. All protease inhibitors are substrates for p-glycoprotein [2]. The predominant effect of ritonavir on p-glycoprotein expression has been somewhat controversial [3]. A recent pharmacokinetic study in normal volunteers [4] showed...
that ritonavir decreased the renal clearance of digoxin. It is plausible that the mechanism of this is through the inhibition of p-glycoprotein-mediated transport in the renal proximal tubules. We describe a case of digoxin toxicity, which we believe was precipitated by the introduction of ritonavir.

A 61-year-old woman presented to the emergency department with increasing nausea and vomiting 3 days after the addition of ritonavir 200 mg twice a day to lamivudine, indinavir and stavudine. Before this she had been tolerating indinavir 800 mg three times a day, lamivudine 150 mg twice a day and stavudine 40 mg twice a day for the past 3 years. She had been diagnosed as being HIV infected in 1995 after her husband died from AIDS-related complications. The past history was significant for rheumatic heart disease, with valve replacement and permanent pacemaker insertion in 1992. She had been taking a stable dose of digoxin (0.250 mg a day) since developing atrial fibrillation after open-heart surgery 8 years earlier. Other concurrent medications at the time of admission included digoxin, coumadin 5 mg alternating with 10 mg a day and aerosolized pentamidine once a month. The basic laboratory work-up on admission was normal apart from an unconjugated bilirubin level of 129 µmol/l, which was up from 30 µmol/l, probably explained by the increased exposure to indinavir after the introduction of ritonavir. The electrocardiogram showed a paced rhythm. The digoxin level on admission, measured by the CEDIA immunoassay (Roche Diagnosti Systems Inc., Branchburg, NJ, USA), approximately 5 h after her last dose was 7.2 nmol/l (N 1–2.6). Digoxin levels were repeated in duplicate using the Immono1System (Bayer Diagnostics, New York, USA) to rule out any interference with bilirubin. Levels 11, 15 and 27 h after the last dose were 5.5, 4.5 and 2.7 nmol/l. By the second day in hospital she was clinically much improved. Digoxin was permanently discontinued without any sequelae. The original antiretroviral drugs (lamivudine, indinavir and stavudine) were restarted without significant side-effects.

The inhibition of p-glycoprotein-mediated transport by ritonavir may be one mechanism to explain digoxin toxicity in this woman previously on a stable dose of digoxin for several years. A more recent study suggested that ritonavir may be unique among protease inhibitors in its inhibition of p-glycoprotein, and that this may occur in particular at the level of the renal tubules. Although p-glycoprotein is often co-expressed with cytochrome P450 3A4, this case appears to represent drug interaction mediated through p-glycoprotein because digoxin is a substrate for p-glycoprotein but not cytochrome P450 3A4. Of interest is the fact that the patient described had been on a stable dose of indinavir for 3 years without any evidence of toxicity. This is in support of in-vitro data, which suggest that indinavir is not a significant inhibitor of p-glycoprotein-mediated transport. As the HIV population ages the potential for these types of drug interactions will increase with more exposure to drugs such as digoxin. Other factors such as genetic polymorphisms in MDR1 may be important in predicting the likelihood of a clinically significant drug interaction as outlined in a recent study of pharmacokinetic interactions between clarithromycin and digoxin [3,5]. Our case and pharmacokinetic data support the fact that patients who are concurrently treated with ritonavir and digoxin may be at risk of digoxin toxicity and should be closely monitored.

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Alterations in bone mineral metabolism in Brazilian HIV-infected patients

As of March 2002, 237 588 AIDS cases have been officially reported to the Brazilian Ministry of Health, and it is estimated that approximately 600 000 individuals are infected by HIV [1,2]. To face this serious health problem, the Brazilian government has implemented the universal access to retroviral therapy for all AIDS patients.

HIV-infected patients have demonstrated alterations in bone mineral metabolism that appear to be related to
the infection as well as to protease inhibitor therapy [3,4].

This study investigated the influence of HIV infection on osteocalcin plasma levels in Brazilian patients. A cross-sectional study was performed on 69 patients infected with HIV (48 men, 21 women, mean age 33 ± 4 years) before the initiation of antiretroviral therapy. Fifty healthy seronegative adults, matched by age and sex, served as controls. To analyse the relationship between the plasma osteocalcin levels and disease severity, the HIV patients were classified into three groups of 23 patients, according to their CD4 cell counts (group 1 > 500 cells/ml; group 2 500–200 cells/ml; group 3 < 200 cells/ml). Osteocalcin levels were measured using a commercial enzyme immunoassay (Immulate; Osteocalcin-Diagnostic Products Corporation, Los Angeles, CA, USA), following the manufacturer’s recommendations.

The Kruskal–Wallis test was used to test potential differences in the osteocalcin levels of the three groups, and the Mann–Whitney U-test (two-tailed) was used to confirm the differences between each pair of groups. Correlation coefficients were calculated using the Spearman rank test. Data are given as medians and 25th–75th percentiles, unless otherwise noted. Two-sided P values less than 0.05 were considered significant.

Table 1 summarizes the characteristics of the 119 study subjects and the results of the osteocalcin analysis.

Reduced osteocalcin plasma levels were present in 43.5% of HIV-infected patients and in 16% of healthy controls (P = 0.0001; odds ratio 4.04; 95% confidence interval 1.68–9.69).

Although the three groups of HIV-infected patients had differences in CD4 cell counts and viral loads that were significantly different, their osteocalcin levels were not statistically different. The plasma osteocalcin concentration was weakly correlated with the CD4 cell count (r = 0.067; P = 0.587) and negatively correlated with the viral load (r = −0.228; P = 0.06).

Our present results show a marked decrease in osteocalcin plasma levels in HIV-1-infected patients before the initiation of antiretroviral therapy similar to previous reports [5–7]. The hypothesis that the systemic activation of T cells in vivo leads to an osteoprotegerin ligand-mediated increase in osteoclastogenesis and bone loss could explain the interaction of HIV infection and bone mineralization [8].

Indeed, the direct interaction of HIV with cells of the bone marrow microenvironment could induce chronic T-cell activation [8] and abnormal cytokine production affecting osteoblast and osteoclast function, as previously described in HIV-infected patients before the use of antiretroviral therapy [5–7].

Decreased bone mineral density has previously been reported in HIV-infected patients [9], and although the clinical consequences of our findings remain unclear, it is conceivable that if these abnormalities persist over time, they may well lead to clinically significant bone loss.

Taking into account the number of HIV patients in Brazil, most undergoing retroviral therapy, further studies should be performed to assess the magnitude of bone and mineral metabolism alterations in these patients.

Table 1. Patient characteristics and osteocalcin results.

<table>
<thead>
<tr>
<th>HIV-positive/CD4 cell count/mm³</th>
<th>HIV-negative</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>≥ 500</td>
</tr>
<tr>
<td>N</td>
<td>50</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>Median osteocalcin</td>
<td>3.9</td>
</tr>
<tr>
<td>Median CD4 cell count/mm³</td>
<td>NT</td>
</tr>
<tr>
<td>Median viral load</td>
<td>NA</td>
</tr>
<tr>
<td>% of subjects with reduced</td>
<td>16</td>
</tr>
<tr>
<td>osteocalcin levels</td>
<td></td>
</tr>
</tbody>
</table>

NA, Not applicable; NT, not tested.

*aValues are mean ± SD.

*bOsteocalcin levels are expressed in nanograms/ml.

*cViral load = × 10⁴ messenger RNA copies/ml.
Relapse of Kaposi's sarcoma in HIV-infected patients switching from a protease inhibitor to a non-nucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy regimen

Kaposi's sarcoma (KS) is the most common malignancy associated with HIV infection. In recent years, several studies have reported a steady decline in the incidence of KS, coinciding with the increasing use of combination potent antiretroviral agents, such as HIV-1 protease inhibitors (PI) [1]. Furthermore, a number of reports have documented tumour regression after the initiation of highly active antiretroviral therapy (HAART) that includes at least one PI [2,3]. We describe here five patients in whom a relapse of KS was documented a few months after the switch from a PI, to a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART regimen.

The characteristics of the five patients are summarized in Table 1. At the diagnosis of KS, all five patients presented with widespread skin lesions, three also had mucosal involvement, and one had multicentric Castleman's disease. All had been treated with cytotoxic chemotherapy for a median duration of 30 months (range 2–51 months). Three patients had received major chemotherapy such as adriamycin–bleomycin–vincristine and docetaxel. The other two had been treated with bleomycin and radiotherapy or bleomycin alone. Before the switch from a PI to a NNRTI-based HAART regimen, the median duration of complete KS remission was 32 months (range 16–33 months). At the time of the switch, the median duration of the PI-based HAART regimen was 29 months (range 10–37 months). Two patients had received indinavir, two nelfinavir, and one ritonavir. The decision to switch treatment from PI to NNRTI was made because of a

<table>
<thead>
<tr>
<th>Case no. 1</th>
<th>Case no. 2</th>
<th>Case no. 3</th>
<th>Case no. 4</th>
<th>Case no. 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40</td>
<td>39</td>
<td>52</td>
<td>47</td>
</tr>
<tr>
<td>Duration of KS sarcoma remission</td>
<td>33</td>
<td>29</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>between the last KS treatment and the switch to NNRTI (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of PI-based HAART (months)</td>
<td>10</td>
<td>31</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>HIV-RNA copies/ml at the time of the switch from PI to NNRTI</td>
<td>&lt; 20</td>
<td>2800</td>
<td>162 000</td>
<td>7900</td>
</tr>
<tr>
<td>CD4 cells/mm³ at the time of the switch from PI to NNRTI</td>
<td>814</td>
<td>658</td>
<td>511</td>
<td>165</td>
</tr>
<tr>
<td>Duration between the switch from PI to NNRTI, and KS relapse (months)</td>
<td>24</td>
<td>11</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>HIV-RNA copies/ml at onset of KS relapse</td>
<td>&lt; 20</td>
<td>&lt; 20</td>
<td>41 800</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>CD4 cells/mm³ at onset of KS relapse</td>
<td>1032</td>
<td>349</td>
<td>499</td>
<td>157</td>
</tr>
</tbody>
</table>

HAART, Highly active antiretroviral therapy; KS, Kaposi's sarcoma; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
virological failure in three cases and a wish to simplify the regimen in the remaining two cases. All patients received a combination of two nucleoside reverse transcriptase inhibitors and efavirenz (four patients) or nevirapine (one patient). The KS relapse was diagnosed within a median of 11 months (range 4–28 months) after the switch, despite a sustained high CD4 cell count in four cases. Overall, the median CD4 cell count did not change significantly from the time of the switch to the relapse of KS: 658 cells/mm$^3$ (range 165–814 cells/mm$^3$) versus 499 cells/mm$^3$ (range 157–1319 cells/mm$^3$), respectively. The relapse of KS was not associated with virological failure from the new antiretroviral combination. Before the switch, the HIV-RNA level was below 20 copies in two out of five cases, and in four out of five cases after the switch.

Although the precise mechanism by which PI-based HAART modifies the clinical course of KS has not been elucidated, it has been suggested that an improvement in KS is largely caused by the recovery of the immune system [2,3]. However, clinical studies and in-vivo models have indicated a lack of association between the suppression of HIV-1 replication and KS [3,4]. The patients described here presented with a relapse of KS after a switch from PI to NNRTI, despite having a long-term remission of their KS under PI-based HAART. Of significance is the fact that the KS relapse was not explained by the immunological or virological failure of NNRTI-based HAART. Two reports using in-vitro and in-vivo models [4,5] have recently demonstrated that PI, such as ritonavir, indinavir or saquinavir, have direct anti-angiogenic, anti-KS and anti-tumour effects. Notably, PI block angiogenesis mediated by basic fibroblast growth factor and vascular endothelial growth factor, the two key factors for KS lesion formation. PI not only block the development of KS in mice treated with the drugs before KS cell inoculation, but they are also effective when given at the time of cell inoculation [4]. This suggests that PI can both directly prevent the development and induce the regression of KS. These data are in agreement with the observed lower incidence and the regression of KS seen in patients treated with a PI-based HAART regimen. Our case series, therefore, illustrates the fact that KS can relapse after the withdrawal of PI, despite successful antiretroviral therapy. This relapse may be explained by the antineoplastic effects of PI, which are independent of their ability to inhibit HIV protease or induce CD4 cell recovery.

A switch from PI to NNRTI should be performed with caution in patients with a history of KS, even though the new regimen is fully active in maintaining HIV viral suppression and high CD4 cell counts.

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Occult hepatitis B virus infection in HIV/hepatitis C virus co-infected patients

We read with interest the paper by Nuñez et al. [1], in which the authors said that ‘occult HBV infection is not a frequent phenomenon (if it exists at all) among HIV/HCV co-infected individuals’. These conclusions are in contrast with both previous findings and our experience. For instance, in the study reported by the Swiss HIV cohort [2], hepatitis B virus (HBV)-DNA positivity for surface and core genes was detected in serum samples of 62.4% and 59.9% HIV positive, hepatitis B core antibody (HBcAb)–positive but hepatitis B serum antigen (HBsAg)–negative individuals. In the same study the presence of occult HBV infection was associated with higher mean serum alanine aminotransferase (ALT) levels, suggesting that occult HBV could also play a role in liver disease progression in these patients.

In support of the existence of occult B in HIV/hepatitis C virus (HCV) co-infected individuals, we report here a fatal HBV reactivation in a patient with markers of previous exposure to HBV infection. Briefly, the patient was a 37-year-old man first seen in our clinic in 1996 for HCV antibody positivity and hypertransaminasemia. A liver biopsy showed histolog-
In the case reported here the reactivation of occult HBV in HIV/HCV-infected patients does exist. This case report demonstrates that polymerase chain reaction, and was found to be positive for surface gene. This case report demonstrates that polymerase chain reaction, and was found to be positive for surface gene. This case report demonstrates that polymerase chain reaction, and was found to be positive for surface gene. The CD4 cell count was 40 cells/mm^3. At admission, transaminase serum levels were: aspartate aminotransferase 2560 UI/l (normal value < 40 IU/l), ALT 5630 (normal value < 45 UI/l). He died a week after admission with the diagnosis of fulminant hepatitis B with HIV/HCV co-infection. A frozen specimen of the liver biopsy, stored at −80°C 6 years before, was tested for HBV-DNA using a nested polymerase chain reaction, and was found to be positive for surface gene. This case report demonstrates that occult HBV in HIV/HCV-infected patients does exist. In the case reported here the reactivation of occult HBV infection was strongly associated with the CD4 cell depletion.

The lack of the detection of HBV DNA in serum samples could be explained by the different sensitivities of the assays used in the different studies, and by the low levels of viremia in patients with occult HBV. To avoid false-negative results, we suggest that liver biopsies, instead of serum samples, should be tested to assess the real prevalence and significance of occult HBV infection in HIV/HCV co-infected patients.

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Epstein–Barr virus-related plasmablastic lymphomas arising from long-standing sacrococcygeal cysts in immunosuppressed patients

Immunosuppression is associated with an increased risk of cancers, particularly lymphoproliferative syndromes [1]. There are three well-differentiated groups among immunosuppressed patients: those with congenital immunodeficiencies, 10–15% of whom will develop non-Hodgkin’s lymphomas (NHL); those with iatrogenous immunodeficiencies, especially transplant patients [2,3]; and the main group, patients with HIV infection, in whom NHL constitutes the second most common neoplasia, and whose relative risk for the development of this condition is 60 times higher than that of the general population [4].

These opportunistic neoplasias show a high degree of polymorphism, which is probably related to the different pathogenetic patterns. A correct characterization of the different lymphoproliferative syndromes is essential because they have prognostic and therapeutic implications. Here we report two immunosuppressed patients with Epstein–Barr virus (EBV)-related plasmablastic lymphomas arising from chronic sacrococcygeal cysts.

**Patient 1**

A 57-year-old man, who underwent surgery for a chronic sacrococcygeal sinus tract in another facility, was sent to our hospital because histological examination of the surgical specimen suggested plasmacytoma. The patient had been taking cyclosporin A for 4 years since undergoing cardiac transplantation. On admission, the patient was asymptomatic and the physical examination was unremarkable except for an inguinal lymphadenopathy and the sacrococcygeal lesion. Histological study of the lymphadenopathy revealed a large-cell lymphoma with marked plasmablastic differentiation, whose immunohistochemical pattern is shown in Table 1. The immunoglobulin heavy chain (IgH) gene rearrangement showed two amplification bands by polymerase chain reaction, and the rearrangements of bcl-1 and bcl-2 were negative. Immunohistochemical study was negative for EBV-encoded latent membrane protein-1 (LMP-1) and Epstein–Barr nuclear antigen 2 (EBNA-2), but in-situ hybridization demonstrated the presence of EBV-encoded messenger RNA. Cyclosporin A was withheld but the lymphoma progressed involving the bone marrow. He was treated with valacyclovir and two cycles of cyclophosphamide and high-dose methotrexate and, later, with ifosfamide, carboplatin and etoposide for three cycles, without response. He died 6 months after diagnosis.
Patient 2

A 30-year-old man had undergone a surgical intervention 2 years earlier because of a sacrococcygeal cyst with multiple local infections, which relapsed later with the appearance of two sinus tracts. Eleven weeks before admission he developed *Pneumocystis carinii* pneumonia, and was found to be HIV seropositive. The CD4 cell count was 30 cells/μl and the viral load was 529,826 RNA copies/ml. Four weeks later he began antiretroviral therapy with didanosine, stavudine, nevirapine and nelfinavir. The patient was admitted because of a necrotic and painful perianal mass involving the sinus tracts that had appeared 2 weeks earlier. Otherwise the patient was asymptomatic. The mass was surgically removed and the histopathological study revealed a large-cell lymphoma with substantial plasmablastic differentiation (Table 1). Rearrangement of the IgH gene showed three amplification bands, and the rearrangements of bcl-1 and bcl-2 were negative. As with the previous patient, EBV-encoded mRNA was positive and LMP-1 and EBNA-2 were negative. Extension studies failed to find other sites of involvement, and the patient was treated with standard-dose cyclophosphamide, doxorubicin, vincristine and prednisone for six cycles. Forty months after diagnosis the patient remains asymptomatic and in complete remission.

There are multiple factors involved in the pathogenesis of lymphoproliferative syndromes in immunocompromised patients, such as immunosuppression, virus-mediated oncogenesis, polyclonal B cell activation, the aberrant regulation of B cells, as well as oncogenes and tumour suppressing genes. Infection or reactivation of latent EBV is particularly important in the pathogenesis of lymphoproliferative syndromes. In fact, genomic sequences of EBV have been identified in 40% of systemic lymphomas of AIDS patients, and in the vast majority of both NHL in transplanted patients and primary lymphomas of the central nervous system [5]. In immunocompetent EBV-infected patients, the infection is mainly controlled by the cytotoxic T cell response. Its alteration in immunocompromised patients can lead to the immortalization and proliferation of the infected B cells. This proliferation is initially polyclonal, later oligoclonal and, finally, monoclonal. Similarly, sequences of herpesvirus 8 DNA have been identified in most body cavity-based lymphomas of HIV-infected patients [6]. Regarding the role of HIV itself, there is no evidence of its direct involvement in the malignant transformation of B lymphocytes as no genomic sequences have been found in NHL cells.

The vast majority of lymphoproliferative syndromes in immunosuppressed patients corresponds to the B phenotype. In HIV-infected patients, 80–90% are disseminated lymphomas, two-thirds of which are of the large cell type (diffuse large cell and immunoblastic), and the remainder are small non-cleaved cell (Burkitt or not) [7,8]. Less common are primary lymphomas of the central nervous system and body cavity-based lymphomas. Recently, plasmablastic lymphomas, mainly involving the oral cavity, have been described, which differs from other large cell lymphomas in that it does not express most of the B antigens [9–14]. The common occurrence of extranodal involvement is characteristic in HIV-infected patients, as well as the presentation in advanced stages and the presence of constitutional symptoms.

We believe that the NHL of our two immunosuppressed patients share some characteristics that suggest that they constitute a peculiar form of EBV-induced lymphomas. First, both arose from long-standing sacrococcygeal cysts, an atypical location not reported to date according to a Medline search. Second, the histopathological picture corresponded to large-cell immunoblastic lymphomas with marked plasmablastic differentiation and an immunological phenotype (Table 1) very similar to that described in plasmablastic lymphomas. In addition, the rearrangement of the IgH gene showed an oligoclonal pattern in both patients. Finally, the finding of EBV-encoded nuclear RNA transcripts in the absence of expression of LMP-1 and EBNA-2 is characteristic of a latency type I, unusual for large-cell lymphomas in immunosuppressed patients, which has been described in some plasmablastic lymphomas [9,15].

The lymphoproliferative syndromes in immunosuppressed patients are highly polymorphic. We believe that our two cases can be considered plasmablastic lymphomas arising in a location not described so far. This location cannot be considered casual because phenomena of lymphoid stimulation occur in chronic infectious and inflammatory conditions, as is the case of sacrococcygeal cysts. A persistent immunological stimu-

Table 1. Immunohistochemical phenotype of the patients’ malignant cells.

<table>
<thead>
<tr>
<th>Patient</th>
<th>CD 79a</th>
<th>CD 138</th>
<th>CD 56</th>
<th>CD 38</th>
<th>CD 10</th>
<th>CD 20</th>
<th>sIg</th>
<th>EMA</th>
<th>MUM-1</th>
<th>CD 3</th>
<th>Cyclin D-1</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>±</td>
<td>±</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>±</td>
<td>+</td>
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<td>–</td>
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<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
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</tbody>
</table>

EMA, Epithelial membrane antigen; MUM-1, multiple myeloma-1; +, expression of the antigen on many cells; ±, expression of the antigen on occasional cells; −, absence of expression of the antigen.
lation, along with the reactivation of EBV infection in severely immunosuppressed patients, seems to be able to trigger the oncogenic process with the final result of an aggressive B cell lymphoma.

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