CD20-negative large-cell lymphoma with plasmablastic features: a clinically heterogenous spectrum in both HIV-positive and -negative patients

J. Teruya-Feldstein¹*, E. Chiao², D. A. Filippa¹, O. Lin¹, R. Comenzo², M. Coleman³, C. Portlock² & A. Noy²

Departments of ¹Pathology and ²Medicine, Memorial Sloan-Kettering Cancer Center, NY; ³Department of Medicine, New York Presbyterian Hospital–Weill Cornell Center, New York, NY, USA

Received 16 April 2004; revised 3 June 2004; accepted 15 June 2004

Background: Plasmablastic lymphoma (PBL) has been described as a rapidly progressive and almost invariably fatal CD20– VS38c+ diffuse large-cell lymphoma with plasmablastic features, almost exclusively involving the jaw and oral mucosa in HIV-positive patients.

Methods: From 2001 to 2003 we evaluated 12 men with PBL, and report the pathology, clinical findings, treatment and outcome. Six of 12 were HIV-positive while among the others, one was post-renal transplant, one had ulcerative colitis and four had no known immunodeficiency.

Results: Tumor growth pattern, in general, showed cohesiveness and a starry-sky pattern; the morphology varied from typical plasmablastic to centroblastic cells. Partial immunophenotypes were (+/total): CD138, 11 of 12 (91.7%); MIB1 10 of 11 (4+, range 75–95%); p63/VS38c, nine of 10 (90%); EBV, eight of 11 (73%); LCA(CD45), two of 12 (16.7%); HHV8/LANA, zero of 10; ALK, zero of seven; and CD20, zero of 12. Three had stage IE and nine stage IV disease. Nine of 12 had an intermediate/high International Prognostic Index or high-risk disease. Computed tomography and positron emission tomography scan in four of 12 revealed extensive bone metastases. Seven of 12 patients are alive with no evidence of disease at a median follow-up of 15 months (range 7–27+). Of the HIV-positive patients, five of six are alive with a median follow-up of 17 months.

Conclusions: It appears that PBL are heterogenous in terms of clinical presentation and morphology. The outcome presented here is superior to that originally reported.

Key words: EBV-positive, HIV-positive/negative patients, plasmablastic lymphoma

Introduction

Plasmablastic lymphomas (PBLs) were originally described in patients with HIV as a subtype of diffuse large-cell lymphoma, presenting almost exclusively with jaw and oral mucosa involvement [1]. Morphologically, cells were described as large and centroblastic or immunoblastic, but were CD20- and CD45-negative and expressed plasma cell-related antigens such as CD138, P63 and variable CD79A with heavy or light chain restriction. A subset of cases was negative for Epstein–Barr virus (EBV) and the Kaposi sarcoma herpes virus 8 latent nuclear antigen (HHV8/LANA). Since then, the disease clinical spectrum has been expanding, with a number of single case reports in HIV-negative patients and a series of four cases in HIV-positive patients with extraoral sites [2–9]. We document a series of consecutive patients in order to characterize better the clinical and histopathological features of PBL.

Materials and methods

Study population

The study cohort comprised 12 patients whose pathology slides were reviewed at the Memorial Sloan-Kettering Cancer Center (MSKCC) between 2001 and 2003. All biopsies were obtained at diagnosis. The initial histological diagnosis was based on hematoxylin–eosin (H&E) staining and immunophenotyping results. Patient anonymity was insured and the study received a waiver from the Institutional Review Board following the guidelines for experimental investigation with human subjects for a review of archival material and clinical information. H&E sections were reviewed and morphological findings were summarized. Immunohistochemical stains were performed with an extensive panel of antibodies. CD138 (DAKO, Carpenteria, CA, USA; 1:200 dilution), P63 (DAKO; 1:200), Kappa and Lambda (DAKO; 1:40 000) and BCL6

*Correspondence to: Dr J. Teruya-Feldstein, Department of Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA. Tel: +1-212-639-2130; Fax: +1-212-717-3203; E-mail: feldstej@mskcc.org

© 2004 European Society for Medical Oncology
(Santa Cruz Biotechnology, Santa Cruz, CA, USA; 1:200) were used, microwaved for antigen retrieval with citrate buffer, pH 6.0, and used according to the Ventana manufacturer’s instructions. p53, MIB1, LCA, EMA, IgG, CD30, CD10, CD56, CD79A, CD20, CD3, CAM5.2, BCL2, ALK1, LMP1, Cyclin D1 and CD31 were pre-diluted and used according to the Ventana manufacturer’s instructions.

The medical charts were reviewed and the following clinical characteristics recorded: age at biopsy, gender, HIV status, other immunodeficiency in HIV-negative patients, bone marrow (BM) involvement, clinical stage according to Ann Arbor classification, radiological studies including computed tomography (CT), bone and/or positron emission tomography (PET) scans, cerebrospinal fluid (CSF) involvement, initial treatment, intrathecal therapy, and treatment for relapsed disease. CD4 cell counts and HIV viral loads were reviewed in HIV-positive patients. Laboratory values including serum and urine electrophoresis and immunofixation, as well as free light chain analysis, were also reviewed. Clinical information was updated through January 2004.

Patients were treated at the discretion of the attending physician. Eleven of 12 patients were treated at MSKCC and one at its affiliate, New York Presbyterian Hospital. Complete remission was defined as the disappearance of all clinical evidence of disease and the normalization of clinical symptoms, laboratory values, radiographs, CT scans and BM biopsy (if initially involved) after treatment. Patients were followed up at regular intervals. During follow-up, patients underwent physical examinations, chest X-ray, repeat CT scans, PET scans and repeat BM biopsy as indicated, in addition to routine peripheral blood count and chemistry studies.

Survival analysis
Survival curves were generated using the Kaplan–Meier method [10]. Overall survival was calculated based on the date of initial diagnosis.

Results
Pathology findings
Cases were selected based on immunophenotype demonstrating CD20 negativity and either VS38c+ or CD138+. There was a range of tumor morphology (Figure 1), most commonly demonstrating typical plasmablastic or immunoblastic cells with abundant basophilic cytoplasm with prominent central nuclei and Golgi hof (seven cases) to centroblastic cells with peripheral based nuclei (four cases). One case showed scattered large cells with central nuclei and prominent cytoplasmic retraction, most likely representing a histological processing artifact. The tumor growth pattern showed cohesiveness (10 cases), with a focal to prominent starry-sky pattern (nine cases) (Figure 2A). Two cases were infiltrative into the bowel wall and omentum and one case was a cytology block only.

Immunophenotyping (Figure 2) is summarized as follows (Table 1; partial panel included) (+/total): p53, nine of nine (100%); CD138, 11 of 12 (91.7%); MIB1 10 of 11 (4+, range 75–95%, with one 3+, showing a range 30–80%); p63/VS38c, nine of 10 (90%); LCA (CD45), two of 12 (16.7%); EMA, three of four (75%); IgG, six of eight (75%); Kappa, eight of 11 (72.7%); Lambda, four of 11(36.4%); EBER1, six of 10 (60%); LMP1, two of nine (22%); CD30, three of 10 (30%); CD10, one of six (16.7%); CD56, one of eight (12.5%); and CD79A, one of 12 (8.3%). No staining was seen for: HHV8/LANA, zero of 10; CD20 and CD3, zero of 12; BCL6, zero of nine; CAM5.2, zero of four; BCL2, zero of six; ALK1, zero of five; or CD31, zero of one. In general, cases showed positivity for CD138 and/or p63, with a high proliferative growth fraction by MIB1, and EBER1-positive tumor cells (Figure 2). Figure 2 shows the pathology of the testicular orchiectomy specimen of patient 4 (Tables 1 and 2) and characteristic positive immunohistochemical stains, in general, representative of the case series.

PCR was performed for IgH (2+/3) and EBV (2+/3), while negative for T-cell receptor (TCR)-gamma (zero of two) and BCL2 (zero of one). Seven of eight BMs showed no increase in plasma cells. In one case the BM aspirate was positive at diagnosis and had complex cytogenetics including 1q, 7, del(8q), add(14q), del(17p) and t(8; 14) (Table 1). Morphology showed large anaplastic cells distinct from multiple myeloma. The patient was HIV-positive, and tumor cells from the rectal resection showed similar large plasmablastic cells with

![Figure 1](link-to-image)  
**Figure 1.** Tumor morphology ranged from: (A–D) commonly, typical plasmablastic cells: abundant basophilic cytoplasm with prominent central nuclei and Golgi hof; (E) centroblastic cells with peripheral-based nuclei; (F) one case with small cells with prominent nuclei with cytoplasmic retraction.
eccentric nuclei, perinuclear hof and abundant amphophilic cytoplasm.

Clinical findings

The median age of the 12 patients was 39.5 years (range 23–73). All were male. Six (50%) were HIV-negative, including one post-renal transplant patient and one with a history of ulcerative colitis. Nine (75%) presented with stage IV disease. Five of six HIV-negative patients presented with stage IV disease. The remaining three patients presented with stage IE disease. Nine of 12 had intermediate/high or high-risk disease, and three of 12 had low/intermediate or low-risk disease by International Prognostic Index (IPI) score. Biopsy or resection sites included: lower gastrointestinal tract (three), mandible (one), neck (one), testis (one), stomach and testis (one), lung (one), sternum (one), forehead and rectum (one), anus (one), and skin (one). Bone marrow biopsies were negative in six of seven patients despite extensive bone metastases by CT and PET. CSF cytology was negative in eight of eight cases at diagnosis. Oral involvement presenting as lesions within the mandible was present in only two of 12 patients, both of whom were HIV-positive.

The characteristics of the six HIV-positive patients are delineated in Table 1. Two of six HIV-positive patients presented with stage IE disease. Four of six presented with stage IV disease.

Table 1. Patient clinical, tumor immunohistochemical, EBV and BM status characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>HIV status</th>
<th>Primary site(s)</th>
<th>CD20</th>
<th>CD45</th>
<th>CD79A</th>
<th>CD138</th>
<th>P63</th>
<th>MIB1</th>
<th>EBV</th>
<th>Cyclin D1</th>
<th>CD56</th>
<th>BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 *</td>
<td>40</td>
<td>M</td>
<td>+</td>
<td>Anal canal</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+/4+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>M</td>
<td>+</td>
<td>Scrotum</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+/4+</td>
<td>ND</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>M</td>
<td>+</td>
<td>Rectum/bone</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/4-</td>
<td>–</td>
<td>ND</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>M</td>
<td>+</td>
<td>Stomach</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+/4+</td>
<td>ND</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>M</td>
<td>+</td>
<td>Bone/rectum</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4/+</td>
<td>ND</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>M</td>
<td>+</td>
<td>Mandible</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>4/+</td>
<td>ND</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>M</td>
<td>–</td>
<td>Sigmoid colon</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+/4+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>M</td>
<td>–</td>
<td>Neck mass, bony destruction of sinuses</td>
<td>–</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>3+</td>
<td>ND</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9 b</td>
<td>29</td>
<td>M</td>
<td>–</td>
<td>Colon</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
<td>+</td>
<td>ND</td>
<td>4/+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10 c</td>
<td>73</td>
<td>M</td>
<td>ND</td>
<td>Skin (leg)</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>4/+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>11</td>
<td>49</td>
<td>M</td>
<td>–</td>
<td>Multiple bone</td>
<td>–</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>3/+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>12</td>
<td>61</td>
<td>M</td>
<td>–</td>
<td>Lung, liver</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Patient was diagnosed coincidentally with squamous carcinoma of anal canal. After treatment for squamous carcinoma of anal canal was completed, pathological diagnosis was later amended to reflect the presence of plasmablastic lymphoma. There was no evidence of residual disease after 5-fluorouracil/mitomycin, radiotherapy and chemotherapy were completed.

b Patient with history of ulcerative colitis.

c Patient is 4 years status-post living unrelated donor renal transplant.

EBV, Epstein–Barr virus; BM, bone marrow; M, male; ND, not determined.
Table 2. Patient clinical, treatment, and survival characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>HIV status</th>
<th>Primary site(s)</th>
<th>Stage at diagnosis</th>
<th>CD4 count at diagnosis (cells/μl)</th>
<th>HIV viral load at diagnosis (copies/ml)</th>
<th>Antiretroviral therapy at diagnosis</th>
<th>Treatment regimen</th>
<th>Outcome</th>
<th>Overall survival at last follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>M</td>
<td>+</td>
<td>Anal canal</td>
<td>IE</td>
<td>336</td>
<td>20 749</td>
<td>Yes</td>
<td>Fulguration, radiation 5-FU, mitomycin*</td>
<td>NED</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>M</td>
<td>+</td>
<td>Scrotum</td>
<td>unknown</td>
<td>10</td>
<td>Unknown</td>
<td>No</td>
<td>CHOP × 4 cycles</td>
<td>NED</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>M</td>
<td>+</td>
<td>Rectum</td>
<td>IV</td>
<td>450</td>
<td>15 000</td>
<td>Yes</td>
<td>CODOX/M-IVAC</td>
<td>Died (refused therapy during cycle 1)</td>
<td>4 (died)</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>M</td>
<td>+</td>
<td>Stomach</td>
<td>IV</td>
<td>167 (at relapse)</td>
<td>98 (at relapse)</td>
<td>Yes</td>
<td>CHOP × 8 at relapse: auto PBSCT with Bu/Cy</td>
<td>NED</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>M</td>
<td>+</td>
<td>Bone/rectum</td>
<td>IV</td>
<td>93</td>
<td>233 000</td>
<td>Yes</td>
<td>CODOX/M-IVAC</td>
<td>NED</td>
<td>9 (died)</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>M</td>
<td>+</td>
<td>Mandible</td>
<td>IV</td>
<td>19</td>
<td>404 713</td>
<td>No</td>
<td>CODOX/M-IVAC</td>
<td>NED</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>M</td>
<td>–</td>
<td>Sigmoid colon</td>
<td>IV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CODOX/M-IVAC</td>
<td>Died (treatment related)</td>
<td>3 (died)</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>M</td>
<td>–</td>
<td>Neck mass, bony destruction of sinuses</td>
<td>IV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>HyperCVAD × 2 but POD: IVAC × 3 auto PBSCT with BEAM</td>
<td>Died of disease</td>
<td>12 (died)</td>
</tr>
<tr>
<td>9b</td>
<td>29</td>
<td>M</td>
<td>–</td>
<td>Colon</td>
<td>IV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Surgical resection, COPP/BLAM × 2 cycles, CHOP × 4 cycles</td>
<td>NED</td>
<td>15</td>
</tr>
<tr>
<td>10c</td>
<td>73</td>
<td>M</td>
<td>ND</td>
<td>Skin (leg)</td>
<td>IE</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>RCHOP × 6 cycles</td>
<td>On treatment</td>
<td>7</td>
</tr>
<tr>
<td>11</td>
<td>49</td>
<td>M</td>
<td>–</td>
<td>Multiple bone</td>
<td>IV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CHOP × 6 cycles</td>
<td>Relapsed, on treatment</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>61</td>
<td>M</td>
<td>–</td>
<td>Lung, liver</td>
<td>IV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CODOX/M-IVAC</td>
<td>Died of disease</td>
<td>1 (died)</td>
</tr>
</tbody>
</table>

*Patient was diagnosed coincidentally with squamous carcinoma of anal canal. After treatment for squamous carcinoma of anal canal was completed, pathologic diagnosis was later amended to reflect the presence of plasmablastic lymphoma. There was no evidence of residual disease after 5-FU/mitomycin, radiotherapy and chemotherapy were completed.

bPatient with history of ulcerative colitis.

cPatient is 4 years status-post living unrelated donor renal transplant.

M, male; 5-FU, 5-fluorouracil; NED, no evidence of disease; PBSCT, peripheral blood stem cell transplant; NA, not applicable; ND, not determined.
disease, and mandibular involvement was present in two of six HIV-positive patients. Four of the six had intermediate/high or high-risk disease and two of six had intermediate/low or low-risk disease by the IPI score. The median T-cell count was 130 cells/µl (range 10–450) and two of the patients were not previously known to be HIV-positive. The other four had been diagnosed with HIV infection 12–20 years prior to the diagnosis of PBL. HIV viral loads in five of six patients ranged from 98 to 404,713 copies/µl, with a median of 20,749 copies/µl, while none were undetectable. All patients with previously known HIV infection were receiving highly active antiretroviral therapy (HAART) at the time of diagnosis. The two patients with previously undiagnosed HIV infection were started on HAART at the time of the concurrent HIV and PBL diagnosis. Only one of the patients had an undetectable viral load, but no significant change in the CD4 cell count after 6 months of HAART. The other four of the six did not achieve undetectable viral loads, but had higher CD4 counts and improved HIV viral loads at 6 months to 1 year after their PBL diagnosis while on HAART. The median increase in CD4 count was 54.5 and the median decrease in viral load was 126,333.5 for these four patients. All five patients were still living at the time of follow-up. The sixth HIV-positive patient discontinued HAART soon after his diagnosis, which was followed by a significant decrease in his CD4 count with a corresponding increase in his viral load. This patient also refused further chemotherapy and subsequently died.

Initial treatment regimens were not standardized and were at the discretion of the treating physician. They included: CHOP (four), CODOX/M-IVAC (five), Hyper CVAD (one), COPP-BLAM (one) and none (one). Patients who were HIV-positive were treated irrespective of their HIV status and were thus not excluded from the more aggressive regimens. Of note, eight of 12 patients were found to have negative CSF at the time of diagnoses, and all eight of these patients received intrathecal prophylaxis, including five of six of those who were HIV-positive. The patient who subsequently relapsed with leptomeningeal disease was among the eight who received intrathecal prophylaxis.

One patient who was HIV-positive was not treated because PBL was only diagnosed in retrospect as an incidental finding in a surgical resection of anal squamous cell carcinoma. The extent of involvement was limited to the anal canal. This patient underwent fulguration, radiation and 5-fluorouracil/mitomycin, all directed at the squamous cell carcinoma. He remains without evidence of PBL. Of note, HIV was poorly controlled at the time of his diagnosis, with a CD4 count 336 cells/µl, but a viral load of 20,749. The antiretroviral regimen was subsequently changed and, after 12 months, the viral load decreased to 170 copies/µl, and the CD4 count was 335 cells/µl. This patient remains without evidence of PBL 25 months after diagnosis.

One patient had primary refractory disease (HIV-negative) and three relapsed (one HIV-positive and two HIV-negative). One HIV-negative patient has just started second-line therapy with ICE, while the other received IVAC followed by high-dose BEAM and stem cell support. He relapsed 5 months post-stem cell infusion with BM and leptomeningeal disease. The HIV-positive patient had a chemotherapy sensitive relapse to DHAP and was transplanted on an AIDS Malignancy Consortium protocol with BCNU/cyclophosphamide conditioning and remains in remission 12 months post-stem cell infusion.

The median survival of all 12 patients has not yet been reached. The survival ranges from 1 to 27 months (Table 2).
The median survival of HIV-negative patients is 12 months (range 1–15). Median survival of HIV-positive patients has not been reached. The range is 2–27 months with a median follow-up of 22 months.

Seven of 12 patients are alive with no evidence of disease at a median follow-up of 15 months (range 7–27+); one patient relapsed and is receiving salvage therapy. All four patients who died presented with stage IV disease and intermediate/high or high-risk disease by IPI score. Two patients died of treatment-related mortality while receiving CODOX/M-IVAC, although one may have had concurrent progressive disease. Consent for post mortem examination was not obtained. A third patient died from relapsed disease with BM and leptomeningeal involvement post-high-dose therapy for primary refractory disease, while the fourth patient refused therapy in the setting of other co-morbidities and poorly controlled HIV.

**Discussion and conclusions**

We report on 12 patients with PBL seen at Memorial Hospital, a series that expands the clinical spectrum of PBL compared with the original report by Delecluse et al. in 1997 [1]. Findings similar to ours have been documented in a number of case reports and one series of four patients [2–9]. Important clinicopathological characteristiques that underline our series include: an exclusive predilection to the male gender, constant extra-nodal localization, frequent association to EBV and immunodeficiency, a cohesive tumor growth pattern with a focal to prominent stary-sky pattern at low-power, with tumor cells that are immunoblastic, plasmablastic or centroblastic negative for CD20, positive for CD138 and/or p63 with a high proliferative growth fraction with MIB1.

It is tempting to speculate on whether our HIV-negative population was immunocompromised, leading to a diagnosis almost exclusively noted in the context of HIV previously. One patient in our series was a recipient of a renal allograft in October 1999 with localization of his PBL to the skin of his left leg [11]. Another patient had ulcerative colitis and lengthy treatment with azathioprine, and developed PBL in association with an ileal conduit. EBV-associated Hodkgin’s disease [12, 13], T-cell lymphoma [13] and B-cell lymphomas [14] have been reported in association with Crohn’s disease.

By morphology alone, the differential diagnosis of these tumors includes poorly differentiated carcinoma, lymphoblastic lymphoma, anaplastic plasmacytoma, Burkitt’s lymphoma (plasmablastic variant), ALK1-positive large B-cell lymphoma [15–18] and HHV8-associated PBL [19–22]. In our series, the tumor morphology ranged from typical plasmablastic to centroblastic cells, with one atypical case showing small cells with prominent nucleoli and cytoplasmic retraction; however, this could represent histological processing artifact. Immunophenotyping was by definition CD20-negative, with all cases staining positive for either p63/VS38c [nine of 10 (90%)] and/or CD138 [11 of 12 (91.7%)]. In general, our cases were EBV-associated [total eight of 11(73%): EBER1, six of 10 (60%); LMP1, two of nine (22%); EBV PCR, two of three (25%)]. None of the seven cases tested with available tissue sections were ALK1-positive, and 10 cases were HHV8/LANA-negative. Two of the three cases that were EBV-positive by PCR were both negative by EBV LMP1 immunohistochemistry, and one case showed positive tumor cells and one showed negative tumor cells by EBER1 in situ hybridization. EBV positivity was determined by the EBER1 status by in situ hybridization, despite the result obtained by EBV PCR (Table 1). Although the physiopathology remains unclear, it is known that EBV induces a plasma cell differentiation of B-cells in vitro.

Distinguishing these tumors from anaplastic plasmacytoma or myeloma is the most difficult, yet the most important, distinction for clinical management. Unlike myeloma, CT and PET scans displayed extensive bone metastases, yet all but one patient initially had negative BM biopsies. The only positive BM biopsy at diagnosis showed large anaplastic cells morphologically distinct from multiple myeloma. Cytogenetics in this case were complex, as noted overall in our series, tumor cells were immunoreactive for CD138, p63, p53 and EBV, with an MIB1 proliferative index ranging from 75% to 95% in all but one case. Notably, the proliferative fraction highlighted by MIB1 is much higher in PBLs (ranging from 75% to 100%) compared with anaplastic plasmacytomas (up to 60%) [1] and myelomas (5%) (J. Teruya-Feldstein and D. A. Filippa, personal observation, data not shown). Furthermore, unlike multiple myeloma, six of 12 (50%) had minimal IgG M-spikes, while the remaining six (50%) had no detectable IgG M-spike. Free light chain and Bence–Jones proteins were negative in two of two patients tested. In addition, stains for CD56 and cyclin D1 may prove to be positive in plasma cell myelomas and extramedullary plasmacytomas, but negative in PBL [23].

Patients 3, 5, 8 and 11 (Table 1), with extensive bone involvement and features resembling multiple myeloma, were indeed negative for cyclin D1 and CD56. In addition, these cases raise the point that PBLs can rarely involve the BM, but perhaps more commonly present as diffuse bony metastases with hypermetabolic disease on [18F]Fluoroexyglucose (FDG) PET scan, showing avid uptake, as shown in Figure 3. The forehead biopsy on patient 5 represented direct extension of the bony metastases and stained negative for plasma cell myeloma markers such as cyclin D1, CD56 and CD31. Therefore, the combined clinical, morphological, immunophenotypic and laboratory data support a diagnosis of an aggressive lymphoma with plasmablastic features over blastic transformation of a plasma cell neoplasm.

Although there were treatment failures, the outcome of the HIV-positive patients presented here is superior to the majority of reports in the literature, with a wide range of treatments. In the original report by Delecluse et al. [1], 10 of 12 patients with available follow-up died, nearly all within 12 months of diagnosis. Others have also reported very short survival [24, 25], with the exception of one outlier alive 3.5 years after diagnosis [4]. The median survival of the HIV-positive patients reported here has not been reached, with a median follow-up of 22 months. The median survival of
the HIV-negative patients was 12 months. Given the small sample size, this may merely reflect the fact that two HIV-negative patients presented with very advanced disease and died within their first cycle of therapy.

All six HIV patients were either on HAART prior to diagnosis, or were placed on HAART shortly after diagnosis. The median and overall survival in this current report appears to be similar to AIDS-related lymphoma survival in the HAART era reported elsewhere [26, 27]. The reason for improved outcome in our series compared with historical reports may relate to better HIV control in those who were HIV-positive. It is also interesting to speculate that more intensive therapy, such as CODOX/M-IVAC, may have made an impact in this tumor with a proliferative index similar to Burkitt’s lymphoma, but this cannot be proven with the current data.

Although, in general, the tumors show plasmablastic morphology, express plasma cell antigens, show a high proliferative fraction and are EBV-associated, it appears that PBL are heterogenous with respect to clinical presentation. There is also some variation in morphology and immunophenotype. Recognition of this pathological entity, more aggressive chemotherapy and better management of HIV may account for better outcome than previously reported.

Acknowledgements

We sincerely thank Drs Amy Chadburn, Ethel Cesman, Marc Ladanyi and Suresh Jhanwar for their laboratory assistance for the HHV8, EBER1, molecular and cytogenetics assays, and Drs Qianxun Xiao and Louis Sussman for controls and pathology assistance. We also thank Dr Susan Krown for her clinical expertise.

References