Epstein–Barr virus-positive plasmacytoma in immunocompetent patients

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Aims: Extramedullary plasmacytomas are often localized, clinically indolent neoplasms, and affected patients usually respond to radiation therapy or limited cycles of chemotherapy. In contrast, plasmablastic lymphomas are clinically aggressive neoplasms composed of immunoblastic or plasmablastic cells and associated with more mature plasma cells in some cases. Patients with plasmablastic lymphoma usually have a poor prognosis despite aggressive chemotherapy. Evidence of Epstein–Barr virus (EBV) infection is uncommon in plasmacytoma, but common in plasmablastic lymphoma, and is therefore helpful in differential diagnosis. The aim of this study is to describe four cases of plasmacytoma arising in immunocompetent individuals that were diffusely positive for Epstein–Barr virus-encoded small RNA as shown by in-situ hybridization.

Methods and results: We describe the clinicopathological and immunophenotypic findings of four EBV-positive plasmacytomas arising in immunocompetent patients. These tumours were characterized by diffuse proliferation of mature-appearing plasma cells intermixed with a briskly reactive, CD8-positive, TIA-1-positive cytotoxic T-cell infiltrate. Long-term follow-up was available for all patients, and all were alive and free of disease at last follow-up (median 43.4 months).

Conclusions: We suggest the term EBV-positive plasmacytoma in immunocompetent patients for these lesions. It is essential to distinguish these tumours from plasmablastic lymphoma, as the latter diagnosis is associated with a much poorer prognosis, and patients require much more aggressive therapy.

Keywords: CD8-positive T cells, Epstein–Barr virus, plasmablastic lymphoma, plasmacytoma

Introduction
Plasmacytomas are monoclonal neoplasms of plasma cells that present as a localized mass that can involve bones or extramedullary sites. Solitary plasmacytoma of bone is frequently associated with plasma cell myeloma, either at initial diagnosis or subsequently. In contrast, patients with extramedullary plasmacytoma infrequently develop plasma cell myeloma.1 As a result, the prognosis of patients with extramedullary plasmacytoma is usually much better than that of patients with solitary plasmacytoma of bone. Patients with extramedullary plasmacytoma can usually be treated successfully with radiation therapy or limited cycles of chemotherapy.2

Although rare tumours were described in the past that, in retrospect, had features suggestive of plasmablastic lymphoma (PBL),3 PBL as an entity was first described by Delecluse et al.4 in the oral cavity of patients with human immunodeficiency virus (HIV) infection. The clinicopathological spectrum of this entity was subsequently expanded to include patients with autoimmune diseases being treated with immunomodulatory or immunosuppressive therapy,5 organ transplant recipients,6 and elderly patients with...
presumed age-related immunodeficiency. Approximately one-third of patients with PBL have no apparent immunodeficiency. PBL is a clinically aggressive neoplasm, and most affected patients succumb to their disease within 2 years following diagnosis. PBL is recognized as a distinctive entity in the current World Health Organization classification.

Epstein–Barr virus (EBV) infection is common in PBL, occurring in approximately 60–70% of patients, and has been implicated as a factor contributing to pathogenesis. Evidence of EBV infection can be used to support the diagnosis of PBL, and can be helpful in the differential diagnosis of PBL from either plasma cell neoplasms or diffuse large B-cell lymphoma, not otherwise specified, with overlapping morphological features with PBL. This differential diagnosis is obviously important, as the therapies for plasma cell tumours, diffuse large B-cell lymphoma and PBL differ greatly.

In this study, we describe four patients with EBV-positive plasmacytoma. These tumours were distinctive in that they were composed of mature plasma cells associated with a prominent CD8-positive cytotoxic (TIA-1-positive) small T-cell infiltrate in the background. All four patients had a benign clinical course, including one patient who underwent surgical excision alone. We suggest the term EBV-positive plasmacytoma in immunocompetent patients (EPIC) for these lesions. It is important to distinguish EPIC from PBL, as the prognostic and treatment implications differ greatly.

Materials and methods

This study was approved by the Institutional review Board at The University of Texas, MD Anderson Cancer Center. We identified four cases of EBV-positive plasmacytoma in our departmental files. Clinical data were obtained by chart review.

Haematoxylin and eosin-stained sections were prepared from formalin-fixed paraffin-embedded tissue blocks. Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded tissue sections with an automated immunostainer and according to the manufacturer’s instructions. The antibodies used, their dilutions and the respective vendors were as follows: anti-ALK-1 (1:50) (Cell Signaling Technology, Beverly, MA, USA); anti-CD3 (1:100), anti-CD20 (1:1400), anti-CD45 (1:300), anti-CD79a (1:50), anti-CD138 (1:600), anti-EBV latent membrane protein (LMP) type 1 (1:1000), anti-kappa (1:20 000), anti-lambda (1:20 000), anti-Ki67 (1:100), and anti-MUM1/IRF-4 (1:35) (Dako, Carpinteria, CA, USA); anti-CD4 (1:80), anti-CD38 (1:75), and anti-human herpes virus 8 (HHV-8) (1:50) (Leica Biosystems, Buffalo Grove, IL, USA); anti-CD8 (1:20) (Fisher Scientific, Pittsburgh, PA, USA); anti-CD30 (1:80) (Covance, San Diego, CA, USA); anti-CD56 (1:600) (Dako, Carpinteria, CA, USA); anti-CD56 (1:35) (BD Biosciences, San Jose, CA, USA); anti-CD56 (1:50) (Ventana, Tucson, AZ, USA); and anti-TIA-1 (1:300) (Immunotech, Swanton, VT, USA). Some immunohistochemical studies were performed at the referring institutions, and we reviewed the results as part of the diagnostic work-up and for the purpose of this study.

In-situ hybridization analysis to determine the presence of EBV-encoded RNA (EBER) was performed on formalin-fixed, paraffin-embedded tissue sections with the Ventana ISH kit, according to the manufacturer’s instructions, with appropriate positive and negative controls.

Fluorescence in-situ hybridization was performed on formalin-fixed, paraffin-embedded tissue sections with the Vysis LSI MYC dual-colour, breakapart rearrangement probe (Abbott Molecular, Des Plaines, IL, USA), according to methods described previously. The probe hybridizes to band 8q24.2 (spectrum orange on the centromeric side and spectrum green on the telomeric side of the MYC gene).

Results

Clinical features and laboratory findings

The salient clinical features for the four patients are summarized in Table 1. The patients were three (75%) men and one (25%) woman, with a median age of 55 years (range, 26–73 years). All patients were Caucasian. None of the patients had a history or evidence of immunodeficiency. Three of four patients were tested for HIV and were seronegative. HIV testing was attempted in patient 1, but the results were unsatisfactory for technical reasons. Patient 1 was simultaneously diagnosed with eosinophilic oesophagitis, on the basis of histological examination of biopsy specimens obtained from multiple areas of the oesophagus. This patient had not received any immunosuppressive therapy for this condition prior to his tumour diagnosis. Patient 3 had a history of coronary artery disease. The remaining patients had no other significant illnesses.
The sites of the plasmacytomas included the nasal cavity \( (n = 2) \), distal oesophagus \( (n = 1) \), and mediastinum \( (n = 1) \). Three patients presented with a localized mass and associated symptoms, and patient 3 had a localized mediastinal mass that was identified incidentally during cardiac surgery.

The laboratory data and results of imaging studies at the time of diagnosis are summarized in Table 2. Serum lactate dehydrogenase levels were within the normal range or slightly below normal in all three patients with available data. One patient (patient 1) had mild anaemia. Serum creatinine, calcium and immunoglobulin levels were within normal limits, and there was no evidence of a serum paraprotein or paraproteinuria. Staging bone marrow examination gave negative results in all patients.

### HISTOPATHOLOGICAL FEATURES

All four cases showed similar histological features. The neoplasms had a diffuse growth pattern, and were composed of sheets of predominantly mature-appearing plasma cells with round nuclei, clock-face chromatin, and abundant amorphophilic cytoplasm; a subset of cells in some cases had recognizable but not prominent nucleoli. Occasional Dutcher bodies and Russell bodies were identified. A common feature was the presence of binucleated and multinucleated plasma cells. Mitotic figures were present, but not frequent. In case 2, apoptotic cells were common, and mitotic figures were more frequent than in the other four cases. Only occasional apoptotic cells were noted in the other cases. There was no evidence of a starry sky pattern or coagulative tumour necrosis in all four cases (Figures 1A–C and 2A–C). All cases had a moderately dense, small lymphocytic infiltrate intermixed with the neoplastic plasma cells (Figures 1B,C, 2B,C, and 3).

### IMMUNOPHENOTYPIC ANALYSIS AND IN-SITU HYBRIDIZATION

The results of the immunohistochemical studies are summarized in Table 3. Plasmacytic differentiation was confirmed by expression of at least one plasma cell-associated marker in every case. The neoplastic plasma cells were positive for CD138 and monotypic cytoplasmic light chain (lambda 3 and kappa 1). MUM1/IRF4 \( (n = 2) \) and CD38 \( (n = 1) \) were expressed in all cases assessed. CD56 was positive in two of three cases analysed. CD45 expression was evaluated in three cases; the neoplastic cells showed partial expression in one case, and were negative in the other two cases. The median Ki67 proliferation index was 25% (range, 5–40%) (Figures 1F and 2F). CD20 \( (n = 3) \), HHV-8 \( (n = 4) \), EBV LMP1 \( (n = 3) \), MYC \( (n = 2) \) (Figure 1G) and ALK-1 \( (n = 4) \) were negative in all cases assessed. The intermixed small reactive lymphocytes in all cases were T cells, with a marked predominance of CD8-positive over CD4-positive cells \( (n = 4) \). The T cells were also positive for CD3 \( (n = 3) \) and TIA-1 \( (n = 4) \), supporting a cytotoxic immunophenotype (Figure 3A–F).

### Table 1. Clinical features of patients with Epstein–Barr virus-positive plasmacytoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Race</th>
<th>Sex</th>
<th>Age (years)</th>
<th>History</th>
<th>Presentation</th>
<th>Tumour site</th>
<th>Therapy</th>
<th>FU length (months)</th>
<th>Status at last FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C</td>
<td>M</td>
<td>49</td>
<td>Eosinophilic oesophagitis</td>
<td>Dysphagia</td>
<td>Oesophagus</td>
<td>Resection</td>
<td>14.7</td>
<td>ANED</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>F</td>
<td>26</td>
<td>None</td>
<td>Stuffy nose</td>
<td>Nasal cavity</td>
<td>Hyper-CVAD x3 and XRT</td>
<td>59.9</td>
<td>ANED</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>M</td>
<td>73</td>
<td>CAD</td>
<td>Incidentally identified during cardiac surgery</td>
<td>Mediastinum</td>
<td>NA</td>
<td>42.6</td>
<td>ANED</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>M</td>
<td>61</td>
<td>NA</td>
<td>Epistaxis</td>
<td>Right nasal septum</td>
<td>XRT</td>
<td>44.8</td>
<td>ANED</td>
</tr>
</tbody>
</table>

ANED, alive with no evidence of disease; C, Caucasian; CAD, coronary artery disease; F, female; FU, follow-up; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; M, male; NA, not available; XRT, radiation therapy.

Table 2. Laboratory and imaging findings in patients with Epstein–Barr virus-positive plasmacytoma at the time of diagnosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>LDH (IU/l) (313–618)*</th>
<th>β₂-Microglobulin (mg/l) (0.8–2.3)*</th>
<th>Hb (g/dl) (14–18 male; 12–16 female)*</th>
<th>Serum Cr (mg/dl) (0.70–1.30)*</th>
<th>Serum Ca (mg/dl) (8.4–10.2)*</th>
<th>Free kappa/lambda (0.26–1.65)*</th>
<th>SPEP</th>
<th>Serum IF</th>
<th>UPEP</th>
<th>Urine IF</th>
<th>Bone survey</th>
<th>Additional PET-positive lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>304 ↓</td>
<td>1.3</td>
<td>13.7 ↓</td>
<td>0.94</td>
<td>9</td>
<td>1.09</td>
<td>Normal pattern</td>
<td>Negative</td>
<td>Normal pattern</td>
<td>NA</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>426</td>
<td>1.3</td>
<td>13.6</td>
<td>0.8</td>
<td>9.3</td>
<td>0.95</td>
<td>Normal pattern</td>
<td>Negative</td>
<td>NA</td>
<td>NA</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.2</td>
<td>9.3</td>
<td>NA</td>
<td>Normal pattern</td>
<td>NA</td>
<td>Normal pattern</td>
<td>NA</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>514</td>
<td>1.7</td>
<td>17.6</td>
<td>0.79</td>
<td>9.2</td>
<td>15.5</td>
<td>Normal pattern</td>
<td>Negative</td>
<td>Normal pattern</td>
<td>Negative</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Ca, calcium; Cr, Creatinine; Hb, haemoglobin; IF, immunofixation; LDH, lactate dehydrogenase; NA, not available; PET, positron emission tomography; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

*Reference ranges for the parameters are provided in parentheses.
In-situ hybridization analysis for EBER showed that the neoplastic cells were diffusely positive in all four cases (Figures 1H and 2G). Fluorescence in-situ hybridization analysis was negative for MYC gene rearrangement in two cases (patients 1 and 2) assessed (Figure 4).

Figure 1. A. Oesophageal tumour from patient 1 demonstrating an expansile, well-circumscribed mass within the submucosa [haematoxylin and eosin (H&E)] composed of sheets of mature-appearing plasma cells intermixed with numerous small lymphocytes. B. Features of plasmablastic lymphoma, such as a starry sky appearance, are not seen (H&E). C. Occasional large binucleated plasma cells are present (H&E). D,E. Immunohistochemical analysis showed that the neoplastic plasma cells are positive for CD38 (D) and lambda light chain (E), and negative for kappa light chain (not shown). F,G. The Ki67 proliferation index is ~30% (F) and there is no evidence of MYC overexpression (G). H. The neoplastic cells are diffusely positive for Epstein–Barr virus-encoded RNA (EBER) by in-situ hybridization.

Figure 2. Nasal mass from patient 2. A–C. The neoplasm has a diffuse growth pattern [A, haematoxylin and eosin (H&E)] and is composed of sheets of neoplastic plasma cells, some with visible nucleoli, intermixed with numerous small lymphocytes (B,C, H&E). D,E. Immunohistochemical analysis showed that the neoplastic plasma cells are positive for CD138 (D) and lambda light chain (E), and negative for kappa light chain (not shown). F. The Ki67 proliferation index is ~40%. G. The neoplastic cells are diffusely positive for Epstein–Barr virus-encoded RNA (EBER) by in-situ hybridization.
THERAPY AND OUTCOMES

A summary of therapeutic regimens and follow-up information for all patients is shown in Table 1. The median length of follow-up was 43.4 months (range, 14.7–59.9 months). All patients were alive and free of disease at last follow-up. Patients were treated with various therapeutic modalities. Patient 1 was treated with surgical excision with clear margins and no adjuvant chemotherapy or radiation. He had no evidence of disease at last follow-up (14.7 months). Patient 4 was treated with radiation therapy alone and had no evidence of disease at 44.8 months. Patient 2 was initially diagnosed as having PBL on the basis of the presence of EBV and a proliferation rate of 40%. This patient received hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone for three cycles, followed by radiation therapy. She had no evidence of disease at last follow-up (59.9 months). The details of therapy for patient 3 were not available to us.

Discussion

Plasmacytomas are monoclonal proliferations of plasma cells characterized by expression of one or more plasma cell-associated markers, and usually cytoplasmic monotypic immunoglobulin light chain expression. Although most extramedullary plasmacytomas involve the head and neck area, a region rich in EBV-associated tumours, these tumours are seldom positive for EBV, especially in immunocompetent hosts. In this study, we describe four patients with EBV-positive extramedullary plasmacytoma. Clinically, the patients had no obvious signs, symptoms or laboratory evidence of immunodeficiency, and sites of involvement included the nasal cavity (n = 2), distal oesophagus, and mediastinum. Histologically, all tumours were composed of diffuse sheets of mature-appearing plasma cells, including scattered binucleated and multinucleated forms. Mitotic figures were observed, but were not frequent, and a starry sky pattern was not present. One case had a moderate proliferation rate of 40%, and the other cases had a lower proliferation rate. The plasmacytic proliferation was associated with an infiltrate of small CD8-positive T cells that expressed TIA-1. The patients were variably treated with approaches ranging from surgical excision alone to multiagent chemotherapy. Clinical follow-up was benign for all four patients.

Although the histological and immunophenotypic features of these four cases of EBV-positive plasmacytoma are distinctive, the pathogenesis of these lesions is not understood. The presence of EBV, however, a highly unusual finding in plasmacytoma, suggests that EBV infection is involved in pathogenesis. During latent infection, EBV expresses a constellation of antigens that aid the virus in effectively maintaining its genome and escaping host cell immune surveillance. EBV latency patterns can be defined according to the differential expression of these latent genes. In type I latency, EBV expresses nuclear antigen 1 (EBNA-1) and small non-coding RNAs (EBER), but lacks expression of the other nuclear antigens, such as EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C, and EBNA-LP, as well
as LMP1, LMP2A, and LMP2B. EBNA-1 is consistently expressed in all EBV-associated neoplasms, and is necessary for replication and persistence of episomes in EBV-infected tumours, leading to B-cell immortalization. In contrast, LMP1 is expressed in a type II latency pattern, and almost all EBV proteins are expressed in a type III latency pattern.

The neoplastic cells in these four cases of plasmacytoma showed an EBV type I latency pattern of infection, as the neoplasms were positive for EBER but negative for EBV LMP1 in all three cases assessed. This pattern is in contrast to that of EBV-positive lymphoproliferative disorders that arise in the setting of immunodeficiency, including PBL, which usually show EBV latency type II and III patterns of infection. The type I latency pattern seen in EPIC, associated with a lack of EBNA-2 and EBNA-3C expression, is in concordance with the lack of MYC expression observed with immunohistochemistry. The EBNA-2 and EBNA-3C latent antigens observed in type III latency are implicated in MYC up-regulation and MYC stabilization, respectively, in EBV-infected tumour cells. In contrast, cases of PBL often show up-regulation of MYC and MYC gene alterations.

The presence of numerous reactive CD8-positive, TIA-1-positive T lymphocytes in these neoplasms is likely to be related to EBV infection. EBV is known to induce an immune response characterized by cytotoxic T cells. CD8-positive memory T cells are also known to play a substantial role in controlling the reactivation of EBV in asymptomatic carriers. In fact, in primary EBV infection there is a striking expansion of peripheral blood CD8-positive T cells. Increased numbers of CD8-positive T cells have been shown to confer a favourable prognosis in non-haematolymphoid tumours with EBV infection. On the basis of these reports, it seems reasonable to sug-

Table 3. Summary of immunophenotypic features of neoplastic cells in Epstein-Barr virus (EBV)-positive plasmacytoma*

<table>
<thead>
<tr>
<th>Case</th>
<th>CD138</th>
<th>CD38</th>
<th>CD79a</th>
<th>CD45</th>
<th>CD56</th>
<th>MUM1</th>
<th>CD20</th>
<th>PAX5</th>
<th>Kappa</th>
<th>Lambda</th>
<th>ALK1</th>
<th>Cyclin D1</th>
<th>HHV8</th>
<th>EBV LMP1</th>
<th>MYC (%)</th>
<th>Ki67 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</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>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</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>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
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<td>ND</td>
</tr>
</tbody>
</table>

*In all cases, the neoplastic plasma cells were diffusely positive for EBV-encoded RNA by in-situ hybridization.

†Weakly, in a small subset of neoplastic cells.

HHV8, human herpes virus 8; LMP1, latent membrane protein type 1; ND, not done.

Figure 4. Nasal mass from patient 2. There no evidence of MYC rearrangement or amplification by fluorescence in-situ hybridization.
gest that the CD8-positive cytotoxic T cells in the four cases of EPIC that we report here may contribute to better control of disease and the favourable clinical outcome in these patients.

Nagafuchi et al. have reported a case of EBV-positive plasmacytoma involving the femoral bone. During the course of this study we encountered a similar patient (not included in the study group) who had EBV-positive plasmacytoma and presented with three lytic lesions involving the pelvis, humerus, and rib bones, but otherwise did not meet the criteria for plasma cell myeloma; the patient had moderate anaemia but no other laboratory findings to support the diagnosis of plasma cell myeloma, and staging bone marrow examination was negative for plasma cell myeloma. Our patient was treated with three cycles of cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone, followed by lenalidomide, dexamethasone and radiation therapy, and did well, being alive with no evidence of disease 86.5 months later. This case suggests that there may be a ‘grey zone’ between EPIC and PBL. It is of note that the patient reported by Nagafuchi et al. had chronic active EBV infection and received recombinant human interleukin-2. EBV serology was not performed in the patient with bone lesions who we encountered. In addition, none of the four patients included in this study had signs or symptoms of chronic active EBV infection, such as fever, generalized lymphadenopathy, hepatosplenomegaly, cytopenias, or liver function abnormalities.

EBV-positive plasmacytomas in immunocompetent hosts have been described in the literature, and are summarized in Table 4. Including the four cases that we report here, a total of 11 cases of EBV-positive plasmacytoma have been reported. There was a male predominance, all patients were adults, and all patients with available data were apparently immunocompetent. The head and neck and the gastrointestinal tract were the most common sites. Little information is available in the literature regarding therapy, follow-up, or survival, with the exceptions of a case reported by Saito et al. and the cases that we report here. Notably, Saito et al. described focal features compatible with PBL, such as ‘plasmablast-like cells and mitotic figures’. The tumour illustrated in the photomicrographs of their publication closely resembles the four cases that we report here, including the presence of a moderately dense lymphocytic infiltrate; however, Saito et al. reported a Ki67 proliferation index of 80–90%.

Although EBV infection is a confounding variable, the distinction between plasmacytoma and PBL can be made on the basis of histopathological examination. In general, plasmacytoma is composed of mature plasma cells with minimal atypia and low

Table 4. Summary of literature reporting Epstein-Barr virus-positive plasmacytomas in immunocompetent patients

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Race (no.)</th>
<th>M/F ratio</th>
<th>Age range (years)</th>
<th>Immune status</th>
<th>Tumour site (no.)</th>
<th>Therapy (no.)</th>
<th>Median FU length (months)</th>
<th>Status at last FU (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguilera et al. (1995)</td>
<td>3</td>
<td>NS</td>
<td>NS NS NS NS*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS NS NS NS</td>
</tr>
<tr>
<td>Tomita et al. (1998)</td>
<td>2</td>
<td>NS†</td>
<td>1:1</td>
<td>46–49</td>
<td>Competent</td>
<td>Ileum (1) Stomach (1)</td>
<td>NS</td>
<td>NS</td>
<td>NS NS</td>
</tr>
<tr>
<td>Yan et al. (2011)</td>
<td>1</td>
<td>NS</td>
<td>1:0</td>
<td>78</td>
<td>Competent</td>
<td>Submandibular gland</td>
<td>NS</td>
<td>NS</td>
<td>NS NS</td>
</tr>
<tr>
<td>Saito et al. (2012)</td>
<td>1</td>
<td>A</td>
<td>1:0</td>
<td>34</td>
<td>Competent</td>
<td>Ileocaecal, lymph nodes</td>
<td>Excision, R-CHOP</td>
<td>90</td>
<td>ANED</td>
</tr>
<tr>
<td>Loghavi et al. (2015; current study)</td>
<td>4</td>
<td>C (4)</td>
<td>3:1</td>
<td>26–73</td>
<td>Competent</td>
<td>Nasal cavity (2) Mediastinum (1) Oesophagus (1)</td>
<td>Excision (1) XRT (1) Chemotherapy (1) NA (1)</td>
<td>43.4</td>
<td>ANED (4)</td>
</tr>
</tbody>
</table>

ANED, alive with no evidence of disease; A, Asian; C, Caucasian; F, female; FU, follow-up; M, male; NA, not available; NS, not specified; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; XRT, radiation therapy.

*Although immunodeficiency was not specifically mentioned, the authors do not describe any signs or symptoms of immunodeficiency in these patients.
†Race was not specified by the authors; however, the study was based in Korea.
mitotic and proliferation rates, although a subset of cases can show more atypia and mitotic figures. The few cases of plasmacytoma reported with a starry sky pattern and a very high proliferation rate were often the initial manifestation of plasma cell myeloma, or were better classified as PBL. Usually, cases of plasmacytoma are not associated with a history of immunodeficiency, and the frequency of EBV infection in plasmacytomas is very low.

In contrast to the patients described in this study, PBL commonly affects immunodeficient patients, although approximately one-third of patients have no apparent evidence of immunodeficiency. Morphologically, PBL is characterized by diffuse proliferation of large cells with cytological features ranging from those closely resembling the features of immunoblasts to more prominent plasmacytoid differentiation. In some cases, a subset of the neoplastic cells are more mature plasma cells. The presence of frequent mitotic figures and tingible body macrophages imparts a so-called ‘starry sky’ appearance in most cases. The proliferation rate as assessed by the Ki67 proliferation index is usually high, being >70% in most cases and >90% in a subset of tumours. Approximately 60–70% of cases of PBL are EBV-positive.

We propose the designation EPIC for these cases, which we believe have been under-recognized and under-reported in the literature. We also suggest that these lesions complicate the differential diagnosis of plasmacytoma versus PBL, an obviously important differential diagnosis, as these two diseases have very different clinical and therapeutic implications. Plasmacytoma is managed with definitive radiation therapy and surgical excision, when feasible, and patients usually have excellent long-term survival. In contrast, patients with PBL require aggressive multiagent chemotherapy, and, despite therapy, the overall prognosis for patients with PBL is poor, with a reported overall survival of <2 years. In a recent large meta-analysis of 277 patients by Morscio et al.,10 immunocompetent patients with EBV-positive PBL had a median survival of 11 months. However, there are data to indicate that patients with early-stage (stage I) PBL may have longer overall survival.10

In summary, we describe four cases of EPIC with characteristic histopathological features. Distinguishing such lesions from PBL is particularly important because, in our experience, patients with EPIC have benign outcomes, even with conservative therapy. The cases of EPIC in this study showed less nuclear atypia than PBL, and, unlike PBL, lacked a starry sky pattern, lacked overexpression of MYC and MYC gene rearrangement, and generally had a low proliferation rate as assessed by the Ki67 proliferation index. One case of EPIC, however, had a proliferation rate of ~40%. Another helpful feature that may aid in the recognition of EPIC is the presence of a reactive CD8-positive, TIA-1-positive T-cell infiltrate.

Author contributions
S. Loghavi: conception and design of the study, data collection and analysis, and manuscript preparation. J. D. Khoury: data analysis and manuscript preparation. L. J. Medeiros: conception and design of the study, data collection and analysis, and manuscript preparation.

Conflicts of interest
The authors have no conflicts of interests or sources of funding to disclose.

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