Case Report
Low-grade Epstein-Barr virus positive plasma cell proliferations of precursor plasma cell origin: report of two cases

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Abstract: B cell lymphoproliferative disorders with plasmacytic differentiation are a spectrum of neoplasms arising from B cells in different stages of maturation, which include marginal zone lymphoma, plasmablastic lymphoma, ALK-positive diffuse large B cell lymphoma, primary effusion lymphoma, and plasma cell neoplasms. Within this group, Epstein-Barr virus (EBV) is mostly linked to plasmablastic lymphoma and primary effusion lymphoma. EBV has only rarely been associated with the remaining entities and occurs almost exclusively in immunocompromised patients. We report two cases of EBV positive, mature appearing plasma cell proliferations without previously identified immunodeficiency. The proliferating plasma cells showed co-expression of CD19, CD38, and CD138 with monoclonal surface light chain expression suggesting a plasmablastic origin. The neoplastic plasma cells were positive for EBV RNA by in situ hybridization (EBER) in both cases, and showed a low proliferation index (Ki-67 10-20%). Such lesions could be easily mistaken for plasmacytomas and low grade B cell non-Hodgkin lymphomas with extensive plasmacytic differentiation without detailed immunophenotyping and EBV studies, if the diagnosis is solely based on the morphologic features and the low proliferation index. Increased awareness of this rare or under recognized entity is necessary to better characterize this group of neoplasms and determine the best treatment approach for these patients.

Keywords: EBV, plasma cell, indolent, plasmablast, plasmacytoma

Introduction

B cell lymphoproliferative disorders with plasmacytic differentiation are a spectrum of diseases arising from plasma cells in different stages of maturation. This spectrum includes small B cell lymphomas with extensive plasmacytic differentiation (most commonly marginal zone lymphomas), large cell non-Hodgkin lymphomas including diffuse large B cell lymphomas, and lymphomas with so called plasmablastic features (such as plasmablastic lymphoma, ALK-positive DLBCL, and primary effusion lymphoma). Additionally, plasma cell neoplasms including plasmacytoma, plasma cell myeloma, and monoclonal gammapathy of undetermined significance are within this disease group. The combined interpretation of histological, immunophenotypic, cytogenetic/molecular, and clinical-radiological data can lead to the most accurate diagnosis.

Pellat-Deceunynck, et al. [1] characterized the development of human plasma cells from B lymphocytes and concluded that the stage of maturation can be determined based on the immunophenotype. Precursor plasma cells have normal CD45 expression, along with CD38 and CD138 positivity and loss of CD20 expression. Unfortunately, further immunophenotypic details were not reported on this cell population. This precursor plasma cell immunophenotype can be detected in reactive plasmacytosis. The work also described the immunophenotype of the terminally differentiated plasma cells, which are mostly present in the bone marrow and mucosal lamina propria in small numbers. These mature, fully differentiated plasma cells are the cell of origin for plasma cell neoplasms with a typically CD19 negative and dim-to-negative CD45 immunophenotype [1].
Epstein-Barr virus (EBV) positive mature appearing plasma cell proliferations are rare. EBV is a common oncogenic virus that affects about 90% of the population worldwide. Recently, 4 cases of EBV positive plasmacytoma in immunocompetent (EPIC) hosts were reported, increasing the number of published cases to 11 [2]. Histologically, these lesions were comprised of plasma cell sheets with occasional mitotic figures, but overall low-to-moderate proliferation rate (5-40% by Ki-67). No flow cytometric or cytogenetic data was published for these cases.

Plasmacytic differentiation may also be found in approximately one third of MALT lymphoma cases. Some of these may present with plasmacytoma-like morphologic features [3]. EBV, however, is rarely detected in marginal zone lymphomas, and almost exclusively in immunocompromised patients, mostly in the post-transplant setting.

In the evaluation of EBV positive plasma cell proliferations, plasmablastic lymphoma (PBL) should also be considered in the differential diagnosis [2, 4]. Patients are typically immunocompromised, but PBL may occur in immunocompetent patients as well [5]. These neoplasms typically demonstrate high grade morphologic features with high proliferation index, with a dismal prognosis.

Here, we describe two patients without known immunodeficiency, both of whom presented with an EBV positive, mature appearing plasma cell neoplasm with low proliferation index. The immunophenotypic pattern of the aberrant population was most suggestive of precursor plasma cell origin.

Case 1

The first case involved an immunocompetent 42 year-old female who presented for increased pain at the site of a recurring clavicular mass, which had slowly been increasing in size for about a year. She additionally reported unintentional twenty pound weight loss. Laboratory studies at the time of workup were significant for normocytic anemia (hemoglobin 9.7 mg/dL, hematocrit 30.3%). Serum protein electrophoresis (SPEP) showed a monoclonal peak in the gamma region, identified by immunofixation as IgG kappa at a concentration of 3.98 g/dL. Renal function was normal, with a creatinine of 0.6 mg/dL and urine protein was not elevated (0.12 grams/day). Beta 2 microglobulin (2 ng/mL) and lactate dehydrogenase (134 U/L) were within normal limits. Serum free kappa light
chain was elevated at 12.90 mg/L with an increased Kappa-to-lambda ratio of 16.97. Testing for HIV and hepatitis C was negative. A skeletal survey was negative, while CT imaging of the chest showed an expansile, lytic 7.7 cm soft tissue mass at the manubrium of the sternum with associated cortical/osseous destruction and a second lytic focus within the anterior T3 vertebral body. Fine needle aspiration of the sternal mass was performed, with cell block preparation and submission to flow cytometry. Smears and cell block showed sheets of mature appearing plasma cells, positive for CD138 and CD79a by immunohistochemistry, and negative for CD20, PAX5, CD56, Cyclin D1, and ALK-1 (Figure 1). The cells were diffusely positive for EBV encoded RNA by in-situ hybridization (EBER). A Ki-67 proliferation index was low, at 10-20% (Figure 1). Flow cytometry showed a kappa surface light chain-restricted population with coexpression of CD19, CD38, and monotypic surface light chain, but negative for CD20. Case 1 exhibits surface kappa light chain-restriction (A), while, Case 2 shows surface lambda light chain restriction (B).

Figure 2. Cases 1 (A) and 2 (B) flow cytometry dot plots. For both cases, an aberrant B-cell population with plasmacytic differentiation is identified in the lymphocyte gate, with coexpression of CD19, CD38, and monotypic surface light chain, but negative for CD20. Case 1 exhibits surface kappa light chain-restriction (A), while, Case 2 shows surface lambda light chain restriction (B).

an additional biopsy for diagnostic clarification prior to initiating therapy, but was subsequently lost to follow-up at one year.

Case 2

The second case involved an 87-year-old male with a past medical history of insulin dependent diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and a 50 pack year smoking history who initially presented to his primary care physician with pain at the site of a developing mass on his anterior chest. The initial work-up was significant for a normocytic anemia (hemoglobin 10.2 g/dL, hematocrit 34.2%), elevated serum IgG of 3280 mg/dl and elevated serum free lambda light chain of 291.13 mg/L with a decreased serum kappa-to-lambda ratio 0.07. SPEP revealed a monoclonal peak in the beta region, identified as IgG lambda by immunofixation at a concentration of 2.87 g/dL. No renal dysfunction was evident with a creatinine of 1.2 mg/dL; urine protein electrophoresis was not pursued. Lactate dehydrogenase was not elevated (174 U/L). CT imaging revealed a 5.3×3.7×3.6 cm right anterior pleural mass extending into the anterior 3rd and 4th rib and sternum, as well as a smaller lesion.
involving the left 9 and 10 ribs. MRI of the brain showed bilateral parietal calvarial lesions suspicious for metastatic disease as well as suspicious enhancing lesions in the upper cervical spine at C3 and C4. Fine needle aspiration and needle core biopsy of the mass was performed with material submitted for flow cytometry. Smears and sections showed sheets of mature-appearing plasma cells positive for CD138 and negative for CD20, CD20, CD117, ALK-1, HHV-8, Cyclin D1, and EBV-LMP1 by immunohistochemistry (Figure 3). The cells were diffusely positive for EBV encoded RNA by in-situ hybridization (EBER), and lambda restricted by in-situ hybridization. A Ki-67 proliferation index was low, at 10-20% (Figure 3). Flow cytometry showed an aberrant population of B cell lineage, intermediate to large cell size, with coexpression of CD45 (dim), CD19, CD38, surface and cytoplasmic lambda, and negative for CD20, CD22, CD56, and kappa light chain (surface and cytoplasmic) (Figure 2B). Due to the diagnostic difficulty and treatment dilemma, a repeat biopsy was performed three and a half months later and showed a more aggressive appearing plasma cell neoplasm with high-grade features including significant cytoplasmic atypia (intermediate to large cell size, increased nuclear to cytoplasmic ratio, prominent central nucleoli) and a higher Ki-67 proliferation index of 60-70%, the cumulative features compatible with transformation to plasmablastic lymphoma. Cytogenetics and fluorescent in situ hybridization for a myeloma panel was attempted, but failed due to growth failure and insufficient material, respectively. A chest CT performed around this time showed a significant increase in the size of the main mass (10.4 cm in greatest dimension) and the smaller lesions, but no new lesions. Four months following initial diagnosis, the patient presented to the emergency department with bilateral lower extremity weakness and urinary incontinence and was found to have a new extradural mass at T6-T8 on MRI concerning for spinal cord compression. Localized radiation therapy was initiated; nevertheless the patient expired a few days later.

Discussion

Plasma cell or plasmacytoid morphology corresponds to a spectrum of immunophenotypes based on the stage of maturation from mature B cells to fully mature plasma cells. During this process the cells gradually lose typical B cell markers, such as CD20, and surface immunoglobulin light chain expression. Additionally, the cells acquire markers associated with plasma
Indolent EBV positive preplasma cell proliferations

Table 1. Summary of key pathologic features of the current cases

<table>
<thead>
<tr>
<th></th>
<th>Mature plasma cell morphology</th>
<th>Precursor plasma cell immunophenotype</th>
<th>EBV Proliferation index (Ki-67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current cases</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>EPIC</td>
<td>Yes</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td>MZL with EPD</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>PBL</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
</tr>
</tbody>
</table>

EPIC, EBV positive plasmacytoma in immunocompetent patient; MZL with EPD, marginal zone lymphoma with extreme plasmacytic differentiation; PBL, plasmablastic lymphoma; NA, not available.

cell differentiation, including CD138 and CD38. Loss of surface, but acquisition of cytoplasmic immunoglobulin light chain expression also characterizes this process [1]. Based on these changes, the cells can be categorized into different stages of maturation: B-cells, precursor plasma cells (plasmablasts, pre-plasma cells), and mature, fully differentiated plasma cells. Neoplastic proliferations may arise from cells at each of these differentiation stages.

Meyerson, et al. [6] suggested that marginal zone B cell lymphomas with extensive plasmacytic differentiation are precursor plasma cell neoplasms with a characteristic CD19+/CD38+/CD45+ immunophenotype and variable expression of CD138 similar to the previously reported precursor plasma cell immunophenotype (by Pallat et al. [1]). Flow cytometric characterization in 5 cases of marginal zone lymphomas with extensive plasmacytic differentiation found that 4 out of the 5 cases were CD19+/CD38+/CD45+, variably expressed CD20, and surface immunoglobulin light chains, but were negative for CD138 by flow cytometry (by Meyerson et al. [6]). It was proposed that the absence of CD138 expression may be related to the small sample size, or it could be a true feature of this neoplasm group. The precursor plasma cell stage was classified by CD19, CD38 positivity and variable expression of CD138 and CD45. EBV status, molecular or cytogenetic data of these neoplasms were not reported. The fifth case in this study was considered a marginal zone lymphoma with extensive plasmacytic differentiation/extramedullary plasmacytoma based on the immunophenotype.

EBV positive plasmacytomas in immunocompetent patients are extremely rare, or under-diagnosed. These neoplasms show a wide age range at presentation (26-78 years), with male predominance. As for the 4 most recent cases, histological examination revealed sheets of mature appearing plasma cells with occasional mitotic figures, but overall low-to-moderate proliferation rate (5-40% by Ki-67). Plasmacytic differentiation was confirmed with at least one plasma cell-associated marker in each case, with CD138, CD38, and MUM1 positivity, respectively. All samples were CD20 negative. EBER was diffusely positive [2]. A cytotoxic CD8+ T cell infiltrate was associated with these lesions; likely related to the EBV infection as highlighted in the article [2]. Flow cytometry and cytogenetics were not performed. These EBV positive plasmacytomas in immunocompetent patients were presumed to be originating from mature plasma cells based on the employed nomenclature. All patients were alive and free of disease at their last follow-up with a median length of follow-up of 43.3 months (range, 14.7-59.9). Treatment modalities included surgical excision, XRT, or chemotherapy [2].

The third entity to be considered is PBL, which is thought to be of precursor plasma cell origin with a typical CD138+/CD38+/MUM1+ immunophenotype, and loss of expression of mature B cell markers, such as CD20 [7]. Histopathologic features include large cells with immunoblastic or plasmablastic morphology, characterized by round-to-oval centrally or eccentrically located nuclei, dispersed chromatin, and prominent single nucleolus. Apoptotic cells with accompanying tingible body macrophages may be seen, lending to a starry-sky appearance. Mitotic figures are readily seen with a Ki67 proliferation index of typically greater than 90% [4]. PBL carries a poor prognosis, with an average overall survival of 11 months in a treated, HIV-negative immunocompetent patient [8]. No standard of care exists currently, given the general inefficacy of current chemotherapeutic agents [5, 8].

Our two cases are similar in terms of mature plasma cell morphology, precursor plasma cell immunophenotype, presence of EBV in the neoplastic cells, and a relatively low proliferation index. Importantly, these 2 cases also showed several overlaps with the above described, seemingly separate entities. 1. Mature plasma
cell morphology, similarly to the cases of marginal zone lymphoma with extensive plasmacytic differentiation, and EBV plasmacytoma. 2. Precursor plasma cell immunophenotype, also described in marginal zone lymphoma with extensive plasmacytic differentiation as well as in plasmablastic lymphoma. 3. The presence of EBV similarly to EPIC and PBL. 4. Relatively low proliferation index as described in EPIC and in marginal zone lymphoma with EPD (Table 1). Based on these overlapping findings and the limited information in the literature on EBV plasmacytic malignancies with seemingly mature plasma cell morphology, we propose that these neoplasms represent a spectrum of diseases arising from precursor plasma cells.

The precise determination of the cell of origin in these neoplasms can have significant therapeutic consequences and can provide prognostic value. Our findings in the reported 2 cases indicate that the origin of these specific neoplasms is of precursor plasma cells using the schematics highlighted by Pellat-Deceunynck et al. [1]. The transformation of the indolent appearing plasma cell proliferation to a high grade plasmablastic lymphoma in one of our patients further supports the precursor plasma cell origin of this initially low grade lesion. Indeed, the transformation of plasma cell proliferation to plasmablastic lymphoma has been previously proposed in the literature [9, 10].

Based on the morphologic and immunophenotypic features of the two described EBV positive plasma cell proliferations along with the published literature, we suggest that low grade EBV-positive plasma cell proliferations are of precursor plasma cell origin. Awareness of this rare or under recognized entity would help to collect more data including molecular/cytogenetic/gene expression profiling to accurately characterize these neoplasms and find the best treatment approach for these patients.

Disclosure of conflict of interest

None.

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References