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Original Article

Epstein-Barr virus-positive plasmacytoma in immunocompetent patients: a diagnostic dilemma

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Abstract: By literature review, plasmacytomas arising in immunocompetent patients are rarely associated with Epstein-Barr virus (EBV) infection. EBV-positive plasmacytoma can cause a diagnostic dilemma as it may morphologically and phenotypically overlap with a clinically aggressive plasmablastic lymphoma (PBL). We reported the clinicopathologic and immunophenotypic findings of four patients with EBV-positive plasmacytomas (three cases of extramedullary plasmacytomas, one case of solitary plasmacytoma of bone) with immunocompetent status. These tumors were characterized by a diffuse proliferation of mature appearing plasma cells, which were diffusely positive for EBV encoded RNA (EBER) by in situ hybridization. All the four patients were alive with no evidence of disease at last follow-up.

Keywords: Epstein-Barr virus, plasmacytoma, plasmablastic lymphoma, immunocompetent

Introduction

The plasmacytomas are mature monoclonal plasma cell neoplasms including solitary plasmacytoma of bone (SPB) and extraosseous (extramedullary) plasmacytoma (EMP) [1]. Plasmacytomas usually present as a localized mass involving bones or extramedullary sites. Epstein-Barr virus (EBV)-related plasmacytomas are rarely reported. On the other hand, plasmablastic lymphomas (PBLs), which are typically EBV positive, are clinically aggressive B-cell neoplasms usually expressing plasma cell markers but lacking B-cell markers [2]. PBL frequently occurs in human immunodeficiency virus (HIV)-positive individuals and patients in other immunocompromised states [1]. Only a handful of PBL cases in immunocompetent individuals have been reported to date [3]. Considering EBV-positive plasmacytomas may morphologically and phenotypically resemble PBL, this could cause a diagnostic dilemma in differentiating the two malignancies.

Materials and methods

Four cases of EBV-positive plasmacytoma were retrospectively reviewed in this study followed at the Affiliated Hospital of Nanjing University, Nanjing Drum Tower Hospital between January 2008 and September 2018. All the patients provided informed consent. This study was approved by Institutional Review Board of our hospital. All cases were pathologically confirmed as plasmacytoma according to 2016 World Health Organization (WHO) classification of Tumors of Hematopoietic and Lymphoid Tissues. We reviewed the available ancillary studies including pre-existing H&E-stained tissue sections, immunohistochemistry, in situ hybridization, molecular analysis, radiologic findings, and laboratory results upon diagnosis.

Results

Clinical characteristics and outcome

The baseline characteristics of all 4 patients with plasmacytoma are shown in **Table 1**. The patients consisted of 3 (75%) men and 1 (25%) woman with a median age of 54.5 years (range: 26-69 years) at diagnosis. They all denied any immunodeficiency history, or use of immunosuppressive agents. All the patients presented with a localized mass and associated symptoms. The lesion sites included thoracic verte-

Table 1. Clinical characteristics and outcomes of all 4 patients with plasmacytoma

Case	Age (y)	Gender	Site	Symptoms	Radiologic findings	Bone lesions	IG rearrangement	FISH	BM	IE	Therapy	Outcome (months)
1	45	M	Thoracic vertebra	Backache, weakness of lower extremities, urination defecation difficulties	bursting fracture of thoracic vertebra	+	IGκ-VJ rearrangement	Amplication: 1q21, 13q14 (RB1), 13q14.3 (D13S319), IGH	Plasma cells (1.5%)	Polyimmuno-globulin	Lenalidomide +DXMS	Alive (37)
2	69	F	Left nasal cavity	Inhale with difficulty, nasal obstruction with mild rhinorrhagia	mass in nasal cavity	-	ND	ND	-	NA	CT+RT	Alive (18)
3	26	M	Inferior nasal concha	Dry eyes	maxillary sinusitis	-	ND	ND	-	NA	RT	Alive (71)
4	64	M	Left nasal cavity	Mild rhinorrhagia	mass in nasal cavity	-	ND	ND	ND	ND	Extensive resection of the nasal neoplasm	Alive (2)

M, male; F, female; ND, not done; NA, not acquired; RT: radiotherapy; IE: Immunofixation electrophoresis.

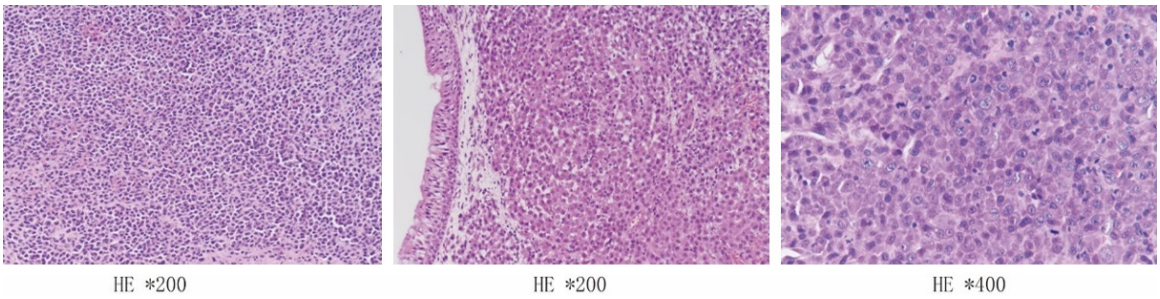

Figure 1. Diffuse proliferation of mature appearing plasma cells in these tumors. (H&E ×200, H&E ×400).

Table 2. Immunophenotypic findings of neoplastic cells in 4 patients with plasmacytoma

Case	Diagnosis	CD20	PAX-5	CD79α	CD138	CD38	Ki67	Light chain	EBER
1	SP of bone	-	ND	+	+	+	2%	κ (-), λ (-)	+
2	EMP	ND	-	+	+	+	20%	κ (-), λ (+)	+
3	EMP	ND	-	-	+	+	15%	κ (+++), λ (-)	+
4	EMP	ND	ND	+	+	+	20%-60%	ND	+

SP, solitary plasmacytoma; EMP, extramedullary plasmacytoma; ND, not done; NA, not available.

bra (n=1), nasal cavity (n=2), and inferior nasal concha (n=1). Staging bone marrow examination was negative in patient 2 and 3. Although plasma cells (1.5%) were seen in bone marrow examination of patient 1, it did not meet the diagnostic criteria of plasma cell myeloma. Epstein-Barr virus serology was not performed in all four patients. Case 1 was treated with lenalidomide and dexamethasone, case 2 with chemotherapy following radiotherapy, case 3 with radiotherapy alone and case 4 with extensive resection of the nasal neoplasm. By the last follow-up, none of them were dead or suffered disease progression. The mean length of follow-up was 32 months (range, 2-71 months).

Histopathologic findings

Microscopically, these tumors were characterized by proliferation of mature differentiated plasma cells in a diffuse and sheet-like pattern (**Figure 1**). In patient 1, the neoplastic plasma cells were medium-sized in relatively uniform morphology with perinuclear halos, eccentric cartwheel nuclei, and sparse basophilic cytoplasm. Nucleoli were inconspicuous and mitotic figures were present, but not frequent (about 1-2/10HPF). Bone trabeculae were destroyed focally. In the remaining patients, the tumor cells were relatively large with abundant cytoplasm, irregular nuclear contours and severe atypia. Conspicuous nucleoli and mitotic figures (about 8-10/10HPF) could be seen in the three cases. In addition, the stroma was intermingled with plenty of lymphocytes infiltrate in patient 3.

Immunophenotypic analysis, Epstein-Barr virus encoded RNA (EBER) in situ hybridization, and molecular analysis

Immunophenotypic findings were summarized in **Table 2**. PAX5 (n=2) was negative in both cases assessed. CD20 expression was evaluated in patient 1 without positive staining. The neoplastic cells showed expression of CD79a in 3 cases (**Figure 2**) and were negative in the other case. The neoplastic plasma cells were positive for CD138 (**Figure 2**) and CD38 while Ki67 proliferation index ranged from 2%-60%. The plasma cells were clonal and exhibited light chain restriction on immunohistochemical staining for kappa and lambda light chains.

In all cases, the neoplastic plasma cells were diffusely positive for Epstein-Barr virus encoded RNA (EBER) by in situ hybridization (**Figure 2**). Additionally, neither *MYC* translocation nor *MYD88* mutation was detected.

Discussion

Solitary plasmacytomas are single localized tumors consisting of monoclonal plasma cell myeloma (PCM) and no physical or radiographic evidence of additional plasma cell tumors [1].

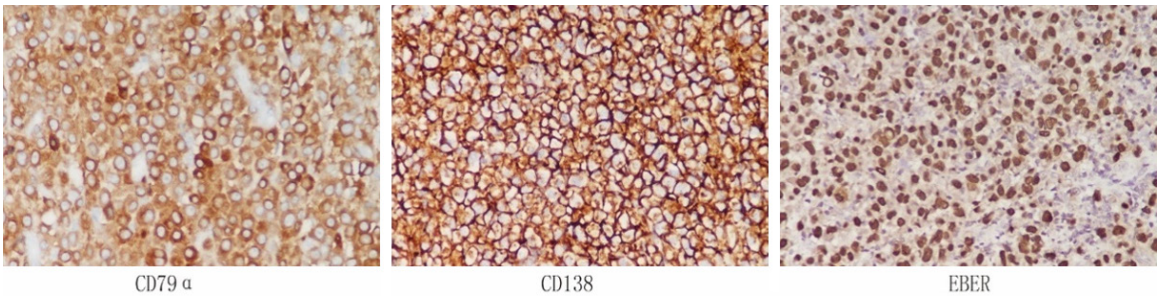

Figure 2. Expression of CD79a, CD138 by immunochemistry (×400) and EBER *in situ hybridization*.

There are two types of plasmacytoma: solitary plasmacytoma of bone (SPB) and extraosseous (extramedullary) plasmacytoma (EMP). SPB constitutes 1-2% of plasma cell neoplasms, while EMP accounts for 1%. There is a male predominance. The median patient age at diagnosis is about 55 years old [1]. SPB is composed of monomorphic, well-differentiated, or atypical neoplastic plasma cells that are indistinguishable from PBL. Bones are the most commonly involved sites, including the vertebrae, ribs, skull, pelvis, femora, clavicles, and scapulae. EMPs typically involve the upper respiratory tract of immunocompetent individuals and usually respond to radiation therapy or limited cycles of chemotherapy [4]. By literature review, EBV-positive plasmacytomas in immunocompetent hosts have been reported occasionally [5-8]. Loghavi et al. recently proposed the designation EBV-positive plasmacytoma in immunocompetent patients (EPIC) for the lesions [4].

PBLs are clinically aggressive B-cell neoplasms, which usually lack B-cell markers but express plasma cell markers [2, 3]. PBL typically occurs in immunocompromised patients, although PBL in immunocompetent individuals have been described infrequently. Unlike plasmacytomas, PBL generally has a high Ki67 proliferative index (often >60%) [9]. Approximately 75-100% of PBL are positive for EBER. Patients with PBL often show *MYC* abnormalities. In this present study, no *MYC* rearrangement was detected.

Since EBV-positive plasmacytoma may morphologically and phenotypically mirror PBL, especially anaplastic plasmacytoma, it is challenging for a pathologist to establish an accurate diagnosis. EBV infection status is no longer enough to help determine the type, other helpful but not determinant diagnostic clues include a relatively low Ki67 proliferative index (usually <20%), MYC aberrations in plasmacytoma, as well as an immunodeficiency history. In fact, the genetics of plasmacytomas have not been extensively studied so far [1], probably due to the small sample size in a single center. On the other hand, data are limited regarding differences of EBV-positive plasmacytomas and EBV-negative plasmacytomas. According to our experience at our institution, EBV-positive plasmacytoma seems more likely to occur in males and the nasal cavity is a common site. Anaplastic features are often seen. However, it still remains unclear whether the two groups are distinctive in clinicopathologic characteristics, genetic profiling, biologic behavior, and prognosis. Is there a possibility that they belong to different entities? EBV is found to be associated with high expression of PD-L1 in some malignancies such as EBV-associated gastric cancer and EBV-positive diffuse large B-cell lymphoma [10, 11]. It is still unknown whether EBV-positive plasmacytomas share similar patterns of immune escape with them. Further larger-scale multicenter studies are warranted to deepen our understanding of EBV-positive plasmacytomas and explore more hallmarks to better distinguish between EBV-positive plasmacytomas and PBL.

In conclusion, EBV-positive plasmacytomas in immunocompetent patients can have much-morphologic and phenotypic overlap with PBL. Comprehensive clinical findings, morphologic and phenotypic investigations may contribute to a specific diagnosis.

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Chen and Xiangshan Fan designed the research study; Lu He and Zhiwen Li performed the research; Qianyun Shi and Hongyan Wu contributed essential reagents or tools; Lu He wrote the paper.

Disclosure of conflict of interest

None.

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