Epstein - Barr virus (EBV) association with plasma cell neoplasms

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Summary. Aims. Epstein-Barr virus (EBV) expression has been reported in several hematopoietic and non-hematopoietic disorders but its expression in plasma cell neoplasms has been largely limited to immunodeficiency-related cases such as in the setting of post-organ transplantation or human immunodeficiency virus (HIV) infection. The aim of this study is to evaluate the association of EBV with plasma cell neoplasms, mainly in immunocompetent patients. Methods and results. We retrospectively studied 147 cases of patients with different plasma cell neoplasms (109 plasma cell myelomas, 22 plasmacytomas, and 16 monoclonal gammopathy cases). Six patients were immunocompromised. EBV was positive in 6 cases; 3 immunocompromised (2 patients with HIV infection and 1 patient was post-renal transplant) and 3 immunocompetent patients with plasmacytoma and variable plasmablastic features. Conclusions. Our data shows that EBV was negative in all plasma cell myeloma cases in immunocompetent patients and has an overall low association with the different plasma cell neoplasms in the immunocompetent setting. When expressed, it is usually associated with variable plasmablastic features.

Key words: Plasma cell neoplasms (PCN), Epstein-Barr virus (EBV), Plasma cell myeloma, Plasmacytoma, Plasmablastic

Introduction

Plasma cell neoplasms (PCN) encompass a spectrum of plasma cell disorders that include non-IgM monoclonal gammopathy of undetermined significance (MGUS), plasmacytoma, plasma cell myeloma and variants, monoclonal immunoglobulin deposition disease and plasma cell neoplasms associated with paraneoplastic syndrome, according to the 2016 World Health Organization (WHO) classification (McKenna et al., 2008). They result from expansion of a clone of plasma cells that usually represents post germinal center, terminally-differentiated, B lymphocytes and secrete a monoclonal immunoglobulin or paraprotein (McKenna et al., 2008; Lorsbach et al., 2011). Epstein-Barr virus (EBV) is a member of the human herpes virus family with double stranded DNA. It was the first known oncogenic virus and more than 90% of the adult population worldwide is estimated to be infected by the virus. It has been linked to many human neoplasms including hematopoietic, epithelial, and mesenchymal tumors (Rezk and Weiss, 2007).

True plasma cell neoplasms have been rarely reported to be associated with EBV expression, except in the setting of immunodeficiency (Rezk et al., 2018). Plasmablastic lymphoma, a subtype of diffuse large B-cell lymphoma with near-identical immunophenotype to

plasma cell neoplasms, has been reported to show EBV expression in about two thirds of the cases and near 100% expression in the oral mucosa subtype (Vega et al., 2005). Post-transplant and severely immunocompromised patients, especially those with established human immunodeficiency virus (HIV) infection, have been reported to have slightly increased incidence of EBV-positive plasma cell neoplasms (Engels et al., 2013; Ouedraogo et al., 2013). The morphologic features of the neoplastic cells in such cases have been mainly described as plasmablastic or anaplastic (Chang et al., 2007; McKenna et al., 2008). Plasmablastic features are defined as plasma cells having larger concentrically-placed nucleus with little or no cytoplasmic hof and exhibiting open or coarse chromatin, prominent nucleoli (usually central), and less abundant cytoplasm (Greipp et al., 1985). Few studies have examined the association of EBV expression with PCN but they lacked the sample size or the ethnic diversity (Sadeghian et al., 2011; Pipatsakulroj et al., 2013). The aim of this study is to evaluate the association of EBV with PCNs in both immunocompromised and immunocompetent patients with a main focus on the immunocompetent setting.

Materials and methods

A search of the pathology files at University of California Irvine Medical Center (UCIMC) from 2000-2016 identified 200 formalin-fixed, paraffin-embedded (FFPE) tissue samples with different plasma cell neoplasms. Of these cases, only 147 cases met the inclusion criteria for our study. The inclusion criteria included: presence of a clot biopsy with a plasma cell infiltrate in plasma cell myeloma cases to avoid possible RNA degradation by the decalcification process performed on the core biopsy sections (however, 11 core biopsies after brief decalcification with diffuse strong Poly T RNA probe positivity were used), no frozen section or bony tissue with decalcification, minimum of 3% clonal plasma cells, final diagnosis based on the WHO classification, and available clinical, imaging, and other laboratory data for correlation purposes. Of the selected 147 cases, 109 cases represented plasma cell myeloma, 22 cases represented plasmacytoma (osseous or extraosseous), and 16 cases represented MGUS (Table 1). Bone marrow biopsy data including aspirate smears, clot, touch imprints, and trephine biopsy sections were available for all MGUS and plasma cell myeloma cases; it was available in 16 out of 22 plasmacytoma cases. All the MGUS cases showed 3-10% bone marrow involvement by monoclonal plasma cells. Overall survival was calculated from the date of pathologic diagnosis to the date of last follow-up or expiration. In addition, 14 cases with reactive plasmacytosis (5-10% polyclonal plasma cells) and 10 normal bone marrow cases (performed mainly for lymphoma staging) were included in our study as a control group and were assessed for EBV expression.

The hematoxylin and eosin (H&E)-stained sections were performed on formalin-fixed paraffin-embedded tissue blocks to evaluate the morphology of cases and make the diagnosis. Based on previously reported studies (Greipp et al., 1985; Sailer et al., 1995; Fujino, 2018), plasmablastic morphology on H&E-stained sections was defined as plasma cells that have high nuclear/cytoplasm ratio, large prominent nucleus, centrally located nucleoli, and lack of perinuclear "hof". Moreover, the percentage of plasmablastic cells in tissue sections has to be equal or greater than 30% for the designation of plasmablastic PCN.

Immunohistochemical staining was performed on FFPE 4 μm-thick tissue sections using an automated Ventana BenchMark ULTRA immunostainer and according to the manufacturer's protocol. The antigen-retrieval was applied as needed for each antibody. All antibodies were pre-diluted and ready to use (RTU) by the manufacturer. The manufacturer information for each used antibody (Clone, Vendor and City) is as follow: CD138 (B-A38, Cell Marque, Rocklin, CA), Cyclin-D1(SP4, Cell Marque, Rocklin, CA), human herpesvirus 8-latency-associated nuclear antigen (HHV-8) (13B10, Cell Marque, Rocklin, CA), EBV latent membrane protein 1(LMP-1) (CS1-4, Cell Marque, Rocklin, CA), MUM-1/IRF-4 (MRQ-43, Cell Marque, Rocklin, CA), CD20 (L26, Ventana, Tucson, AZ), CD56 (123C3, Ventana, Tucson, AZ), PAX-5 (SP34, Ventana, Tucson, AZ), kappa (Polyclonal, Ventana, Tucson, AZ), lambda (Polyclonal, Ventana, Tucson, AZ), and Ki-67 (30-9, Ventana, Tucson, AZ). Appropriate positive control samples were used for all immunohistochemical stains.

Table 1. Plasma cell neoplasm cases.

Cases (total number)	Age[a]	Male	Female	EBV-Status[b]	EBV-Status in Immunocompromised cases		EBV-Status in Immunocompetent cases	
					Positive*	Negative	Positive*	Negative
MGUS (16)	39 to 85 (67.8)	9	7	0/16	0 (0%)	1	0 (0%)	15
PC (22)	21 to 78 (50.9)	19	3	4/22	1 (100%)	0	3 (14%)	18
PCM (109)	30 to 90 (61.7)	60	49	2/109	2 (50%)	2	0 (0%)	105

*The p-value of Fisher's exact test was 0.0039. BM, bone marrow; MGUS, monoclonal gammopathy of undetermined significance; PC, plasmacytoma; PCM, plasma cell myeloma; [a]: The age range in years with mean; [b]: EBV-status based on EBER-ISH result.

Epstein-Barr encoding region by in situ hybridization (EBER-ISH) analysis was performed on FFPE tissue for all cases on 4-um tissue sections using the Ventana ISH kit (EBER1, Analyte Specific Reagent/RTU, Ventana, Tucson, AZ) according to the manufacturer's protocol with appropriate positive and negative controls. PolyT probe (U6 DNP, Analyte Specific Reagent/RTU, Ventana, Tucson, AZ) was used for all cases as a control for RNA preservation.

Table 2. Ethnic origin of plasma cell neoplasms cases.

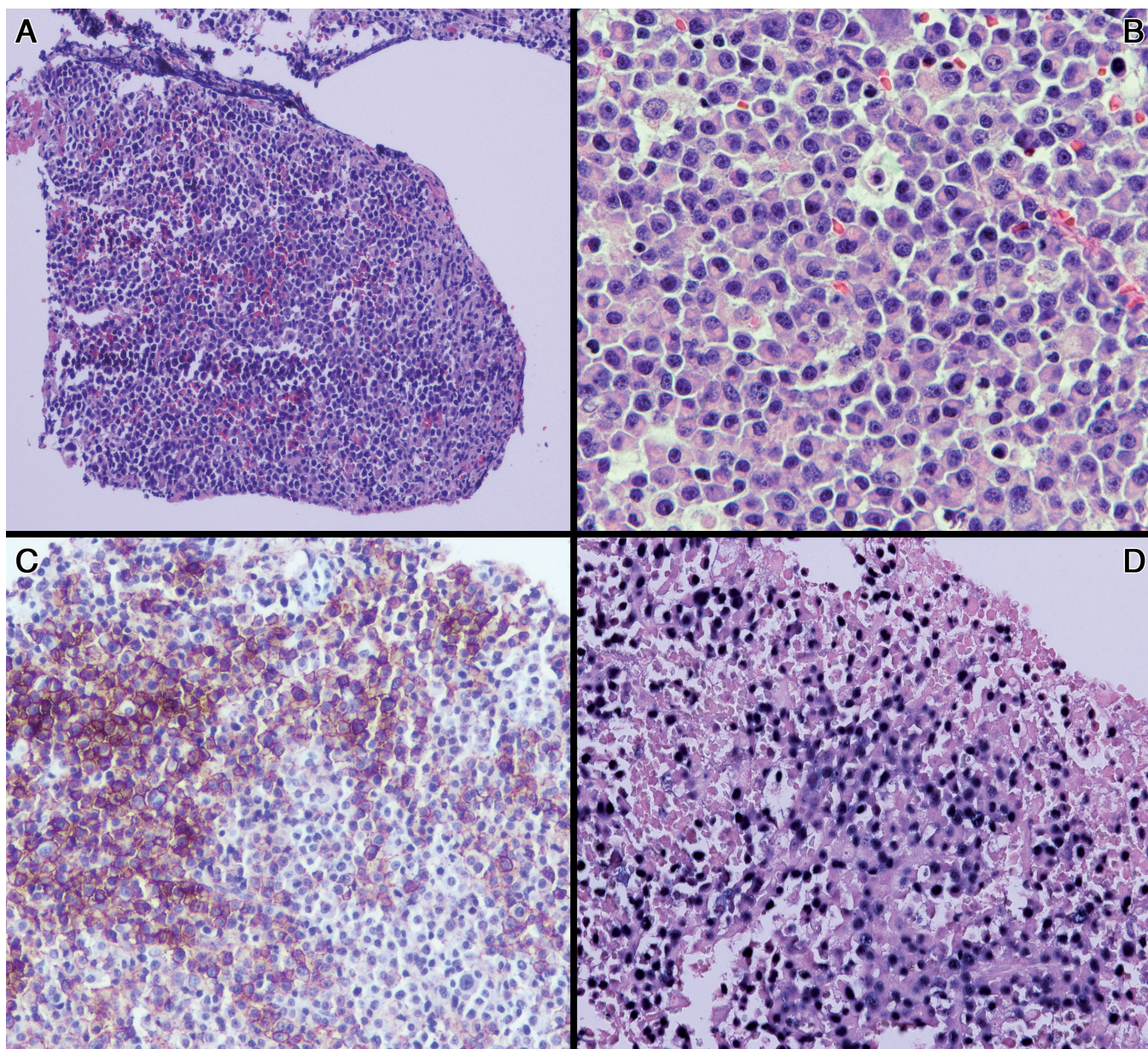| Ethnicity	Plasma cell myeloma	Plasmacytoma	MGUS	Total
Caucasian	51	11	8	70
Hispanic	29	7	3	39
Asian	13	4	4	21
African American	3	0	0	3
Middle Eastern	3	0	0	3
Unknown	10	0	1	11

Fig. 1. The composite picture is from case 1 in table 3 and represents nasal involvement by extramedullary plasmacytoma. Most of the cells show unremarkable morphology except for few intermixed cells with plasmablastic features (prominent nuclei, high N/C ratio, and lack of prominent hof), mainly seen in the upper right and lower right quadrants. **A.** Low-power magnification of the plasma cells. **B.** High-power magnification. **C.** Partial CD138 expression by the plasma cells. **D.** EBER expression. A, C, D, x 10; B, x 40.

Results

Out of 147 cases, 109 cases represented plasma cell myeloma, 22 cases represented plasmacytoma, and 16 cases represented MGUS (Table 1). The cases represented true ethnic diversity, where 70 patients were Caucasian, 39 patients were Hispanic, 22 patients were Asian, 3 patients were African-American, 3 patients were Middle Eastern, and 11 patient had undocumented ethnicity (Table 2). A total of 6 cases represented immunocompromised patients including 3 HIV-positive patients and 3 patients who were post solid organ transplant. The rest of the patients were immunocompetent per history and clinical data. The 3 HIV positive patients had different plasma cell neoplasms; 1 with a diagnosis of MGUS, 1 with a diagnosis of plasmacytoma, and the third patient had a diagnosis of plasma cell myeloma. All 3 post-transplant patients had a diagnosis of plasma cell myeloma.

A total of 6 cases were EBV positive by in-situ hybridization (Table 3). Four of these cases were part of previous cohorts that was reported previously by our

Table 3. Review of EBV positive plasma cell neoplasms.

#	Cases	Age[a]	Sex	Race and Clinical Presentation	Site of involvement	SPEP/UPEP	Immune Status	EBV Status	Morphology[b]	Immunophenotype	Cytogenetic results	Follow up[a]
1	PC	38	M	Caucasian with altered mental status and epistaxis	Nasal cavity extending into frontal lobe and no BM involvement	IgG kappa	Intact	EBER-ISH: Positive LMP1: Negative	Plasmablastic PC	Positive: CD138 (partial), kappa and Ki-67 of 40-50% Negative: CD56, BCL-1, HHV-8 and CD20	Normal karyotyping No MYC amplification	Lost follow up after poor initial response to Chemotherapy and Radiotherapy
2	PCM	39	F	Hispanic with abdominal distention and pain	Liver, ovaries, BM and multiple bony lesions	IgG kappa and IgA kappa	HIV positive	EBER-ISH: Positive LMP1: Negative	Plasmablastic PCM	Positive: CD138, CD56, kappa and Ki-67 of 50-60% Negative: BCL-1, HHV-8 and CD20	Normal karyotyping No MYC amplification	Died after 2 month
3	PC	39	M	Hispanic with severe back pain and leg numbness	Skull, cervical, thoracic and lumbar spine, but no BM involvement	IgA kappa	Intact	EBER-ISH: Positive LMP1: Positive	Mature plasma cells with focal area of plasmablastic morphology	Positive: CD138, kappa and Ki-67 of 10-20% Negative: CD56, BCL-1, HHV-8, PAX-5 and CD20	Normal karyotyping No MYC amplification	Alive after 3.5 year with good response to BM transplant and maintenance treatment
4	PC	40	M	Hispanic with altered mental status	Multiple Frontal gyrus mass but no BM involvement	Negative	HIV positive	EBER-ISH: Positive LMP1: Negative	Mature plasma cells with focal area of plasmablastic morphology	Positive: CD138, kappa and Ki-67 of 50-60% Negative: CD20, PAX5, HHV-8, CD56 and BCL-1	Normal karyotyping No MYC amplification	Transferred to hospice care after 10 weeks due to severe mental status deterioration
5	PCM	56	M	Hispanic with ESRD due to MM	Kidney and BM	Lambda free light chain	Post-renal transplant	EBER-ISH: Positive LMP1: Negative	Mature plasma cells and scattered immature plasma cells with plasmablastic features	Positive: CD138, lambda, CD 56 and Ki67 of 90% Negative: BCL-1, HHV-8, PAX-5 and CD20 Not available	Not available	Died in 6 months
6	PC	70	M	Caucasian with abdominal pain	Pancreas	Not available	Intact	EBER-ISH: Positive LMP1: Negative	Mature plasma cells with no plasmablastic features	Positive: CD138, lambda and Ki-67 of 70-80% Negative: CD56, BCL-1, HHV-8, PAX-5 and CD20	Not available	Not available

BM, bone marrow; EBER-ISH, Epstein-Barr virus-encoded RNA in situ hybridization; ESRD, end stage renal disease; HHV-8, human herpesvirus 8-latency-associated nuclear antigen; HIV, human immunodeficiency virus; LMP-1, EBV Latent membrane protein 1; PC; plasmacytoma; PCM, plasma cell myeloma; a Age and follow-up in years at or from time of presentation; b Plasmablastic morphology was defined as presence of >30% plasmablasts.

group (Pasch et al., 2013; Wu et al., 2013). Two patients were HIV positive (1 patient had plasmacytoma and 1 patient had plasma cell myeloma). One patient was post-renal transplant with plasma cell myeloma. Three patients were immunocompetent with plasmacytoma. LMP-1 immunohistochemical stain was positive in one of the 6 positive cases. Partial loss of CD138 expression was seen in one of the positive cases (Fig. 1). Morphologic evaluation of the EBER-positive cases showed at least focal area of plasmablastic morphology in 5 out of the 6 cases (Fig. 1). However, frank plasmablastic morphology in at least 30% of the cells to be consistent with plasmablastic myeloma was only noted in the 2 HIV positive cases (Fig. 2), one of which had obvious plasmablastic morphology (case 2) mimicking plasmablastic lymphoma. In these 2 cases, the presence of positive serum protein electrophoresis, lytic bone lesions, CD56 expression, and bone marrow involvement prompted the diagnosis of plasma cell myeloma with plasmablastic features rather than plasmablastic lymphoma. All 3 immunocompromised EBER-positive cases had an aggressive clinical course with overall survival of less than 6 months.

For the immunocompetent patients with positive EBER, one showed poor initial response to treatment, one is alive with no evidence of disease for 3.5 years after bone marrow transplant and maintenance therapy, while follow-up data was not available for the third patient. Based on the available data within the immunocompetent group, 14% (3/21) of plasmacytoma cases showed a positive EBV result, while none of the MGUS (0/15) or plasma cell myeloma (0/105) cases showed positive EBV results. The p-value of Fisher's exact test was 0.0039 which indicates statistically significant differences in the percentages of positive EBV status among the three types of PCN cases (Table 1). The 24 cases in the control group (10 normal bone marrows and 14 cases with reactive plasmacytosis) were all negative for EBV expression.

Discussion

EBV, a member of the human herpes virus family with double stranded DNA, has been linked to many human neoplasms including hematopoietic, epithelial, and mesenchymal tumors. However, it has a main predilection for B-cells as they serve as the virus's reservoir (Rezk and Weiss, 2007). EBV has both a lytic (productive) stage and a latent (non-productive) stage that makes it capable of evading immune clearance and
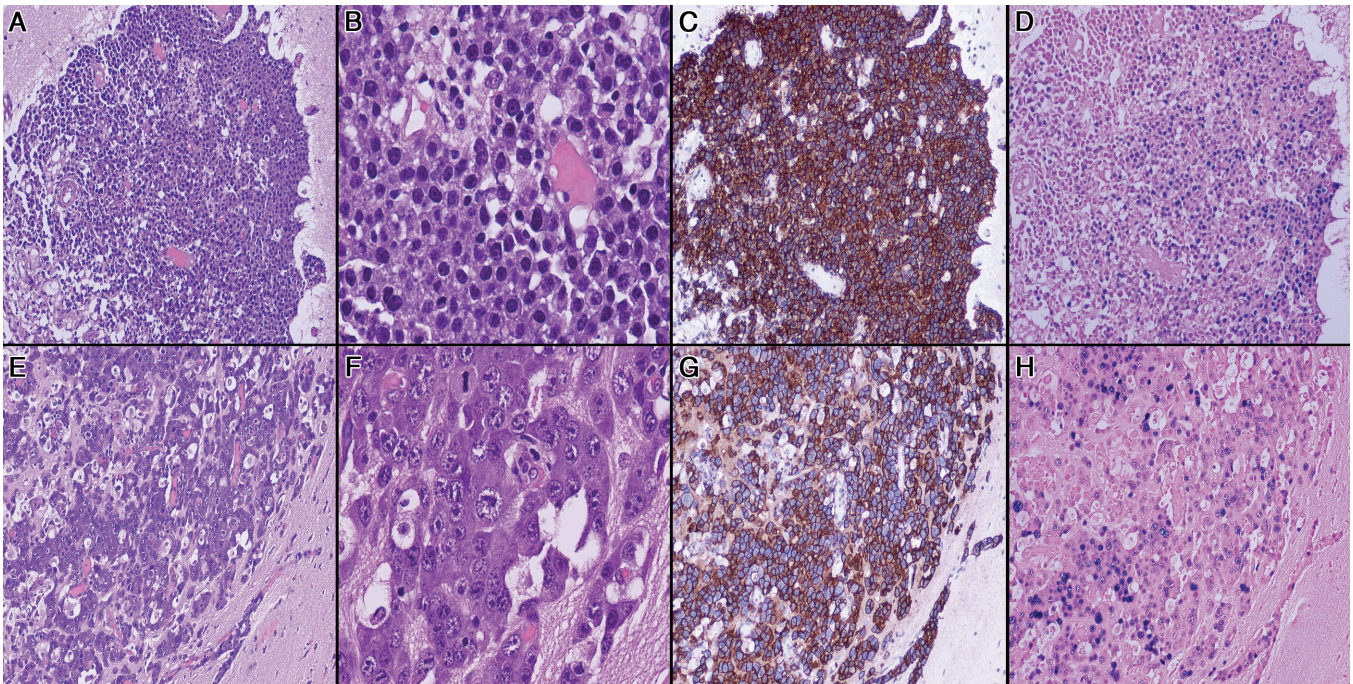

Fig. 2. The composite picture is from case 4 in table 3 and represents brain involvement by extramedullary plasmacytoma with one distinct focal area showing evident plasmablastic features. The picture represents 2 different fields; the upper half shows sheets of neoplastic plasma cells that show no atypical features, which is representative of the majority plasma cells seen in this case. **A.** Low-power magnification of the plasma cells. **B.** High-power magnification. **C.** CD138 expression by the plasma cells. **D.** EBER expression (EBV by in situ hybridization). The lower half of the composite picture shows clusters of plasma cells with atypical and plasmablastic features and a high proliferative activity, which represents one focal area within the entire specimen. **E.** low-power magnification of the atypical plasma cells. **F.** High-power magnification. **G.** CD138 expression by the atypical plasma cells. **H.** EBER expression. A, C-E, G, H, x 10; B, F, x 40.

persists for the entire life of the host. Both stages have pathogenic importance for cell transformation and growth of EBV-associated malignancies. EBV LMP-1 is the main oncogenic latent viral protein and is essential for tumorigenesis as it activates many downstream pathways, which results in the induction of anti-apoptotic proteins and cytokines, contributing to growth and differentiation of infected B-cells (Chen, 2011). Recent studies showed that LMP-1 activates human telomerase reverse transcriptase (hTERT) at the transcriptional level through nuclear factor kappa B (NF-κB) and MAPK/ERK1/2 pathways (Terrin et al., 2008). hTERT is the catalytic component of the telomerase complex, which is crucial for acquiring unlimited replicative potential and neoplastic transformation (Giunco et al., 2013).

In healthy individuals that are seropositive for EBV, terminal differentiation of EBV-infected memory B-cells into plasma cells has been reported to be associated with viral replication and initiation of the EBV lytic cycle (Laichalk and Thorley-Lawson, 2005; Anastasiadou et al., 2009). In contrast, individuals with plasmacytic tumors frequently associated with EBV such as primary effusion lymphoma (PEL) or plasmablastic lymphoma have been shown to establish a latent cycle and exhibit a restrictive EBV latency pattern (Latency I/II) (Laichalk and Thorley-Lawson, 2005; Rezk and Weiss, 2007). In addition, a strong reduction in plasma cell associated markers such as CD38 and CD138, and a regression to a less mature B-cell phenotype was observed in the EBV-infected plasmacytic tumor cells as well as in few plasma cell myeloma cell lines examined *in vitro* (Laichalk and Thorley-Lawson, 2005). As such, plasma cell myeloma or plasmacytoma cases that express EBV, whether as a result of an associated immunodeficiency or for unknown reasons, may follow the same path as plasmablastic lymphoma and exhibit a latent cycle, increase proliferation, and exhibit plasmablastic cytologic features starting in focal areas and eventually progressing to diffuse pattern as in plasmablastic lymphoma. Moreover, other investigators have reported that plasma cells in EBV-positive plasmacytoma cases in immunocompetent patients exhibited plasmablastic morphology. They concluded that these neoplasms may have been driven by EBV to gain the plasmablastic morphologic features and a higher proliferation rate (Chang et al., 2007; Sasaki et al., 2011; Wu et al., 2013). Other studies did not report such an association with EBV and plasmablastic features, where Loghavi et al. reported 4 immunocompetent EBV-positive plasmacytoma cases that did not show any plasmablastic morphology (Loghavi et al., 2015).

Several studies have examined a potential role that infectious agents such as HIV, EBV, hepatitis C virus and HHV-8 may play in the pathogenesis of plasma cell neoplasms (Gold et al., 1990; Montella et al., 2000; Beksac et al., 2001). EBV association with plasma cell neoplasms in immunocompromised patients, particularly in the setting of established HIV infection or in post solid organ transplant patients, is well documented (Tcheng et al., 2006; Zhang et al., 2012; Engels et al., 2013; Ouedraogo et al., 2013). Both EBV and HHV-8 were reported to induce interleukin-6 (IL-6) production in the setting of immunosuppression, which is a potent growth factor for plasma cells (Chen et al., 2003). Only few studies though have evaluated EBV association in immunocompetent patients. Chang et al. evaluated 58 immunocompetent patients with plasma cell neoplasms, where they found 3 EBV positive myeloma cases and 1 EBV positive plasmacytoma case (overall 7%) (Chang et al., 2007). Aguilera et al. showed 3 EBV positive cases out of 20 plasmacytoma cases with unknown immune status in the head and neck region (15% association) (Aguilera et al., 1995). Sadeghian et al. showed 10 EBV positive cases out of 30 immunocompetent patients with myeloma (33%) but these results may not be truly representative of the incidence given the small sample size and the biased ethnicity of the patient population (Sadeghian et al., 2011). In that study, 3 EBV positive cases were detected out of 30 normal control cases, which indicates a high incidence rate of EBV in their population (10% positivity in the control group) (Sadeghian et al., 2011). Pipatsakulroj et al. found only one EBV positive plasmacytoma case after evaluating 37 PCN cases; however, this positive case was from an HIV positive patient, indicating 0% EBV association with PCNs in immunocompetent patients in that study (Pipatsakulroj et al., 2013). Another recent study detected 10% (4 out of 46 cases) EBV positive expression in their immunocompetent plasmacytoma patient cohort. They reported no association with plasmablastic features, no difference in overall survival time, but an increased likelihood of disease relapse/progression to plasma cell myeloma than in their EBV-negative patients (Yan et al., 2017). In our study, progression to plasma cell myeloma was not seen in these 3 cases; however, 2 cases had a short follow-up period (one patient lost to follow-up and the other patient was sent to hospice due to poor response to treatment and mental status deterioration).

To our knowledge, our series is the largest study to examine the association of EBV with plasma cell neoplasms in a population with diverse ethnicity. The 24 cases in our control group were all negative for EBV expression. Our data confirms the previously reported data regarding the increased association between EBV and plasma cell neoplasms in the immunocompromised setting (3/6; 50%). In immunocompetent patients, EBV has an overall low association with plasma cell neoplasms (3/141; 2.1%). None of our MGUS or plasma cell myeloma cases showed EBV expression and while it is a small sample, EBV has a relatively increased association rate in plasmacytoma cases, where 3 out of 21 cases (14.2%) showed positive expression. The EBV positive cases showed increased proliferation rate and variable plasmablastic features (focal in 2 cases). No specific clinical/laboratory/radiological association was seen in the EBV positive cases other than partial loss of

CD138 in one of the cases. A larger multicenter study focused on evaluating plasmacytoma cases may shed more light on the EBV association.

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