Case Study

EBV-positive gastric plasmablastic lymphoma in an HIV-negative adult

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Abstract: Plasmablastic lymphoma (PBL) is a rare B-cell lymphoma most commonly observed in the oral mucosae of HIV-positive patients, with increasing recognition of cases occurring in HIV-negative individuals. There is a noted association between PBL and Epstein-Barr virus (EBV), and chromosomal rearrangements involving *c-MYC* have been implicated in oncogenesis. There have been eight previously described cases of PBL involving the stomach in HIV-negative patients. This report details the first known case of EBV- positive gastric PBL, which was identified in an 82-year-old HIV-negative man. The patient was treated with CHOP-based chemotherapy followed by radiation, and expired eleven months after the initial diagnosis. PBL may be an under recognized entity when it presents in HIV-negative individuals, and should be considered in the differential diagnosis of high-grade lymphomas with plasmacytic or plasmablastic differentiation. Further studies are required to elucidate the pathogenesis of this neoplasm and define optimal treatment strategies.

Keywords: Plasmablastic lymphoma, PBL, Epstein-Barr virus, EBV, gastrointestinal lymphoma

Introduction

Plasmablastic lymphoma (PBL) is a rare, aggressive type of mature B-cell lymphoma that is recognized within the 2008 World Health Organization (WHO) classification [1]. Originally considered a morphologic variant of diffuse large B-cell lymphoma (DLBCL), PBL is now considered a distinct entity, composed of B-cells that morphologically resemble immunoblasts but display the immunophenotypic characteristics of plasma cells. PBL first became well recognized as a human immunodeficiency virus (HIV)-associated lymphoma with strong predilection for the oral cavity, although it has now been described in a wide variety of anatomic sites and patient populations [2–4].

Although the pathogenesis of PBL has yet to be elucidated, Epstein-Barr virus (EBV) has been detected in 66% of PBL biopsies, suggesting this virus may play a role in tumor development and/or progression [4]. In HIV-negative individuals, EBV-driven oncogenesis may be fomented by immunosuppressive therapy or age-related immune senescence. Rearrangements involving *c-MYC* have also been commonly observed, and are associated with aggressive disease and a worse prognosis [4, 5]. Clinically, PBL carries an overall poor prognosis with no standard chemotherapy or radiation regimen in use.

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PBL involving the stomach of HIV-negative patients has been rarely reported in the literature, with a total of eight well described cases to date [6–13]. Notably, six of the cases have been published within the last four years, suggesting the possibility that this entity has been under-diagnosed. EBV-status was assessed by in situ hybridization in five the cases and was found to be negative in each one. Here we report an instance of an EBV-positive gastric PBL that occurred in an 82-year-old HIV-negative man. The patient presented at early stage disease and had a relatively extended course following treatment.

Case Report

An 82-year-old man with a history of gastroesophageal reflux disease (GERD), hypertension, and coronary artery disease was referred for upper gastrointestinal endoscopy, which revealed a lesion in the cardiac/fundic region that was suspicious for malignancy. Superficial mucosal biopsies were taken, which showed a prominent infiltrate of malignant plasmacytoid cells within the lamina propria [Figure 1]. The cells displayed eccentrically placed oval nuclei, finely clumped chromatin, conspicuous central nucleoli, and moderate pink cytoplasm with perinuclear hof. Immunohistochemical stains showed the malignant cells were positive for CD19, CD45, CD79a, CD138 (variable), and MUM1. They were negative for CD3, CD20, CD56, EMA, and ALK-1. Stains for IgG, IgA, and IgM were not interpretable due to high background reactivity. The Ki-67 proliferation index ranged up to 80% in the most active regions. In situ hybridization was positive for kappa light chain and Epstein-Barr virus (EBV), and negative for lambda light chain. No Helicobacter organisms were observed with Giemsa special stain.

Serologic testing was negative for HIV, but did show evidence of past EBV infection, with viral capsid antigen (VCA) IgG interpreted as positive and VCA IgM interpreted as negative (EBNA-1 IgG 2.25 U/mL, VCA IgG 9.08 U/mL, VCA IgM 0.37 U/mL). The patient sought oncologic care at an outside hospital, where the lymphoma was determined to be Ann Arbor stage 1AE. He was treated with three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with partial response, followed by radiation. He had multiple readmissions due to comorbid conditions, including hospital-acquired pneumonia, and ultimately entered home hospice. He died eleven months after his gastric lymphoma diagnosis.

Discussion

The first clear report of a lymphoma with plasmablastic differentiation was made in 1978, in a 71-year-old woman who presented with a rapidly growing submandibular mass [14]. The first suggestion of a similar tumor occurring in the stomach came eleven years later, when a high grade lymphoma with plasmablastic morphology was reported in the stomach of a 59-year woman [15]. Immunohistochemical analysis showed the tumor cells were positive for several B-cell markers, kappa light chain, IgA, EMA, and several keratins, but negative for CD45 (leukocyte common antigen, LCA).

Gastric PBL was first reported by Pruneri *et al.* in a 53-year-old woman who had low stage disease and survived at least 19 months following chemotherapy [6]. From 2009 to 2015 an additional seven cases were described, with no clear sex predilection and ages ranging from 21-82 (Table 1) [7–13]. The seemingly disproportionate number of cases reported since 2012 suggest this entity may have been previously under recognized, possibly being mischaracterized as a plasmablastic plasmacytoma, extranodal lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), or other malignancy.

Table 2 summarizes selected immunophenotypic features of published cases of gastric PBL. Most express some combination of plasmacytic antigens (CD38, CD138, MUM1) with less frequent expression of mature B-cell antigens (CD20, CD79a), CD45, and CD56. Expression of EMA and cytokeratin has been

Table 1: Clinical features and tumor EBV status of published gastric PBL cases in HIV-negative patients

Case	Age	Sex	EBV	Evidence of spread	Treatment	Outcome
Pruneri *et al.* (1998)	53	F	NR	None (Stage IE)	Chemotherapy (ProMACE-cytaBOM)	Alive at 19 months
Kim *et al.* (2009)	61	M	EBER-negative	LN, pancreas, adrenal	Surgery	Dead of disease at 3 months
Hashimoto *et al.* (2012)	70	F	EBER-negative	LN, esophagus, duodenum	Chemotherapy (CHOP then DeVIC)	Died during second cycle of DeVIC
Mihaljevic *et al.* (2012)	60	M	EBER-negative	None	Chemotherapy (CHOP)	Died before second cycle
Riaz *et al.* (2012)	41	M	NR	Adrenal	Chemotherapy (hyper-CVAD)	Alive
Marques *et al.* (2013)	82	F	NR	None	Chemotherapy (CHOP)	Died before second cycle
Cao *et al.* (2014)	50	F	EBER-negative	Marrow, tumor cells in ascitic fluid (Stage IVA)	Chemotherapy (BAD then TD-CHOP)	Dead of disease at 9 months
Huang *et al.* (2015)	21	M	EBER-negative	Tumor cells in ascitic fluid	None	Died prior to initiation of therapy
Current report	82	M	EBER-positive	None (Stage IAE)	Chemotherapy (CHOP) then radiation therapy	Dead at 11 months

Abbreviations: EBER, EBV-encoded small RNAs; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; LN, lymph node; NR, not reported

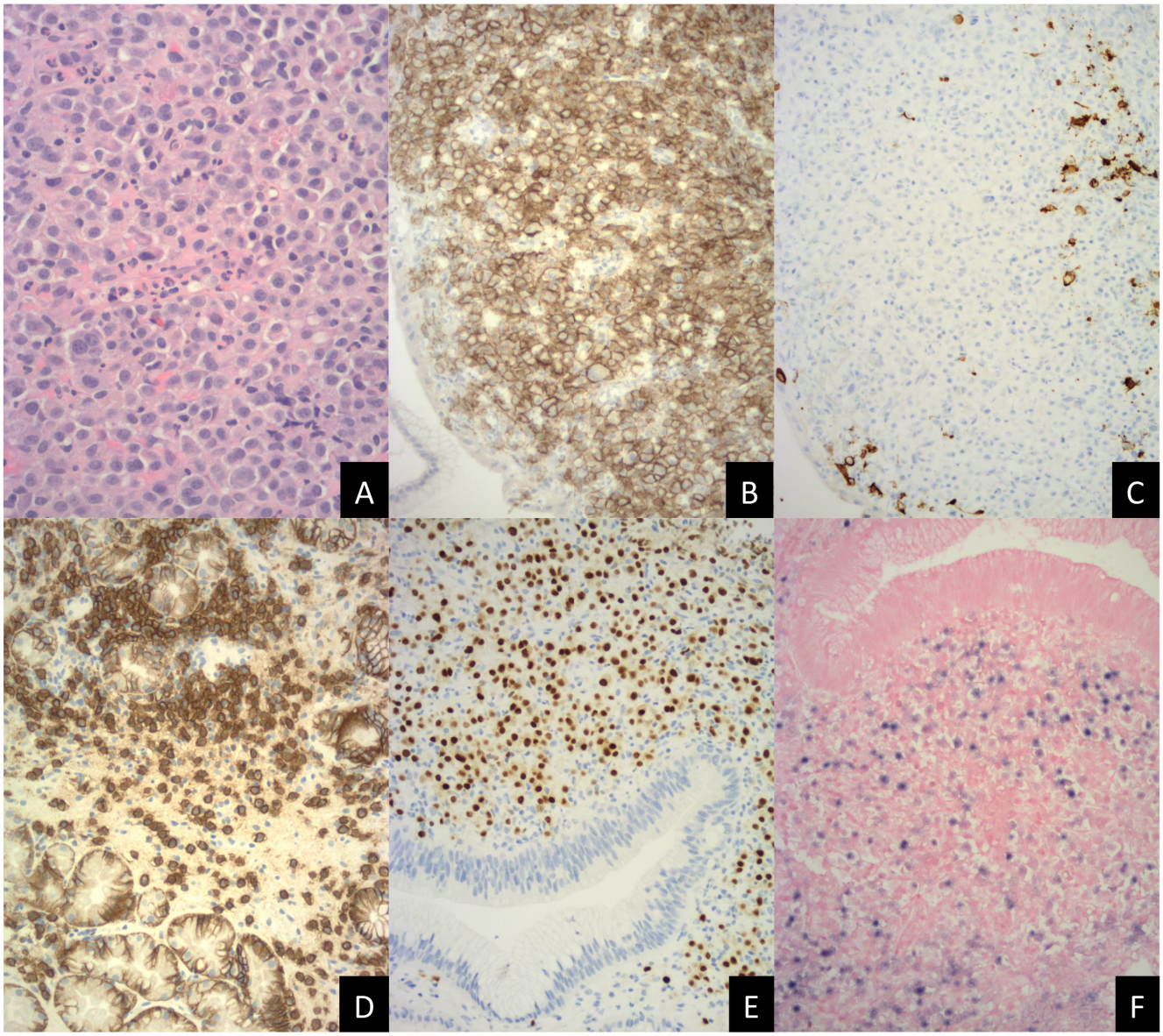

Figure 1: Gastric biopsy from the 82-year-old man with gastric lymphoma.
A, High-power view showing infiltrative proliferation of large cells with conspicuous nucleoli and pink cytoplasm (H&E). Immunoperoxidase stains for CD19 (B), CD20 (C), CD138 (D), and MUM1 (E). F. In situ hybridization for EBV-encoded small RNAs (EBER).

noted sporadically. The Ki-67 proliferation index for these neoplasms is relatively high, ranging from 70-100% in almost all cases. Distinguishing this entity from blastic plasmacytomas can be challenging, and relies on properly integrating clinical, serologic, imaging, and pathologic data.

In this case we report the first known incidence of an EBV-positive gastric PBL in an HIV-negative patient. The identification of EBV-encoded small RNAs (EBER) in the tissue biopsy, combined with a paucity of serologic evidence of acute EBV infection, suggest focal reactivation of a latent viral infection within

Table 2: Selected immunophenotypic features of published gastric PBL cases in HIV-negative patients

Case	CD19	CD20	CD38	CD45	CD56	CD79a	CD138	MUM1	LC	Ig Type	Ki-67
Pruneri *et al.* (1998)	-	-	+	-	-	-	NR	NR	NR	IgM	50%
Kim *et al.* (2009)	NR	-	NR	+	-	+/-	+/-	-	λ	NR	70%
Hashimoto *et al.* (2012)	NR	-	NR	-	-/+	-	+	+	-	IgM	100%
Mihaljevic *et al.* (2012)	NR	-	-	NR	-	NR	-	+	λ	NR	70%
Riaz *et al.* (2012)	+	-	+	NR	-	NR	+	NR	κ	IgG	NR
Marques *et al.* (2013)	NR	NR	NR	-	NR	NR	+	+	κ	NR	90%
Cao *et al.* (2014)	NR	-	NR	-	-	-	+	+	λ	IgA	>80%
Huang *et al.* (2015)	NR	-	+	+	NR	-	NR	+	-	NR	>95%
Current report	+	-	NR	+	-	+	+/-	+	κ	Eq	80%

Abbreviations: Eq, equivocal result; Ig, immunoglobulin; LC, light chain; NR, not reported

the gastric mucosa. While EBV has been hypothesized to drive tumorigenesis in a wide variety of lymphoproliferative disorders, including a subset of DLBCLs that occurring in the elderly and immunosuppressed, its significance in this case is unknown [16].

Given the rarity of this disease, currently no established treatment strategy has emerged, although CHOP-based chemotherapy regimens have been the most frequently employed (Table 1). The outcome data underscore the aggressive nature of this neoplasm, with three of the nine patients dying during treatment, three dying 3-11 months after diagnosis, and one dying before therapy could be initiated. The latter case is remarkable for the presence of an unspecified rearrangement of *c-MYC*, a factor that has been implicated in poor survival [4, 5, 13].

In summary, PBL is a rare but increasingly recognized type of aggressive B-cell lymphoma, and should be considered in the differential diagnosis of any high-grade plasmacytic lymphoma involving the stomach. Gastric PBL occurs across a wide age range, and may be identified in immunocompetent patients. Further studies will be required to delineate the molecular pathogenesis of this malignancy and define optimal treatment strategies.

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