

[CASE REPORT]

Plasmablastic Lymphoma of the Small Intestine in an HIV- and EBV-negative Patient

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Abstract:

Plasmablastic lymphoma (PBL) is a rare aggressive B-cell lymphoproliferative disorder that is strongly associated with immunodeficiency, most often with human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV) infection, and that mainly occurs in the oral cavity. Although some clinical features can lead to a diagnosis, PBL in an extraoral site is difficult to suspect clinically in a patient who is HIV negative. The small intestine as a site of PBL has also been described very rarely. We herein present a rare case of PBL of the small intestine in an 85-year-old HIV- and EBV-negative male.

Key words: plasmablastic lymphoma, small intestine, HIV, Epstein-Barr virus

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Introduction

Plasmablastic lymphoma (PBL) is an aggressive lymphoid neoplasm usually seen in the oral cavity (1). The malignancy is strongly associated with immunodeficiency, and most particularly, human immunodeficiency virus (HIV) infection and Epstein-Barr virus (EBV) infection. Plasmablastic lymphoma of the small intestine is extremely rare. We herein describe an HIV-negative and EBV-negative male with PBL of the small intestine with ileoileal intussusception and provide a comprehensive review of relevant literature on this malignancy (2).

Case Report

An 85-year-old man underwent partial resection of the left upper lobe for left lung cancer. Even though the pathological tissue was large cell carcinoma G4, pT1b1, ly0, v0, pl0, which indicated additional resection, because of age and other factors the patient was merely followed up. Six months after the surgery, PET-CT showed a high degree of

accumulation in the small intestine, and contrast-enhanced CT showed thickening of the intestinal wall at the same site (Fig. 1A-C). Multiple lymph nodes were seen in the intraperitoneal cavity.

Due to self-interruption of hospital visits, capsule endoscopy was performed three months after the contrast-enhanced CT. Capsule endoscopy revealed an ulcerative lesion with bleeding (Fig. 2A). Double-balloon endoscopy (DBE) was performed following the results of the capsule endoscopy and revealed an ulcerative and fungating tumor near the ligament of Treitz (Fig. 2B). Examination of the small intestine by gastrografin contrast was performed during DBE. As a result, stenosis was observed due to the presence of the tumor which remained about 20 cm from the ligament of Treitz (Fig. 1D).

Pathologically, a few atypical cells that were suspicious of lymphoma or undifferentiated carcinoma were found in the biopsy specimen of the tumor. The amount of the tumor specimen was so small in the biopsy tissue when DBE was performed that a definite diagnosis could not be made by immunostaining.

Approximately 2 weeks after DBE of the small intestine,

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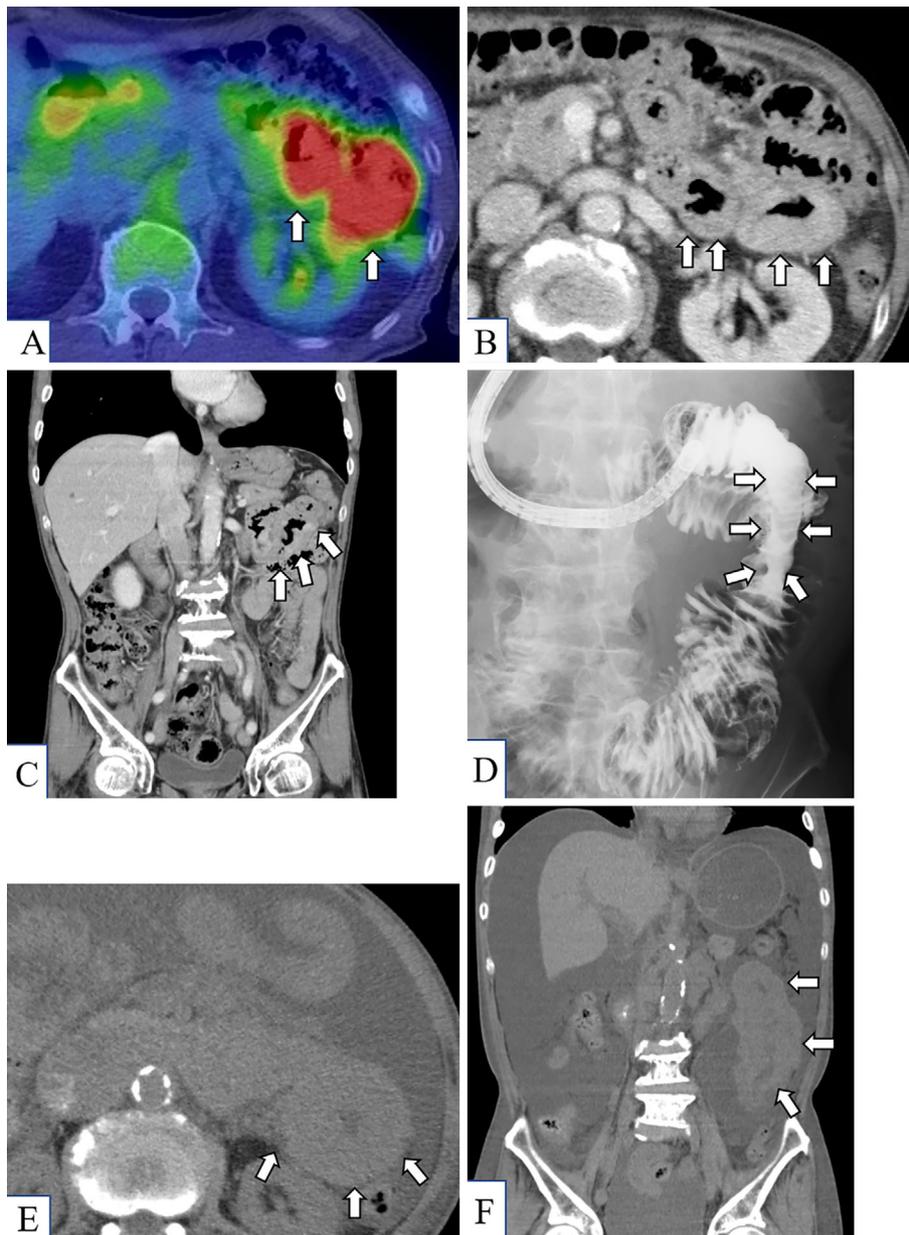


Figure 1. Radiologic images. A: PET-CT, B: Contrast-enhanced CT (axial view), C: Contrast-enhanced CT (coronal view), D: CT (axial view), E: CT (coronal view). (A) PET-CT showed a high degree of accumulation in the small intestine (arrow). (B) Contrast-enhanced CT showed thickening of the intestinal wall at the same site (arrow). (C) Contrast-enhanced CT revealed enhancement of thickening of the intestinal wall (arrow). (D) Examination of the small intestine by gastrografin contrast showed an area of stenosis due to the presence of a tumor which remained about 20 cm from the ligament of Treitz (arrow). (E, F) A CT scan showed that the small intestinal tumor had grown (arrow) with the swelling of multiple lymph nodes and abundant ascites.

the patient was admitted for lower leg edema and ascites. Laboratory data revealed the following: white blood cell count of 13,500/ μ L, hemoglobin 9.3 g/dL, albumin 1.2 g/dL, blood urea nitrogen 78 mg/dL, creatinine 2.86 mg/dL, C-reactive protein 7.34 mg/dL, and sIL-2R 4,560 U/mL. HIV-Ab and HIV-Ag were negative. A CT scan showed that the tumor in the small intestine. A CT scan showed that the tumor in the small intestine had grown from 79.6 mm \times 39.3 mm to 133.6 mm \times 56 mm with large amounts of ascites and swelling of multiple lymph nodes (Fig. 1E, F). An ascites

puncture revealed the proliferation of only naked nuclear atypical cells with a high N/C ratio accompanied by nuclear atypia, suggesting malignant lymphoma. On the second day of hospitalization, the patient developed aspiration pneumonia and died after a sudden change in status. An autopsy was performed by family consensus.

At autopsy, multiple tumor nodules were found in the wall and mesentery of the small intestine. According to the results of autopsy, the walls of the small intestine were thick and many mesenteric lymph nodes were markedly swollen.

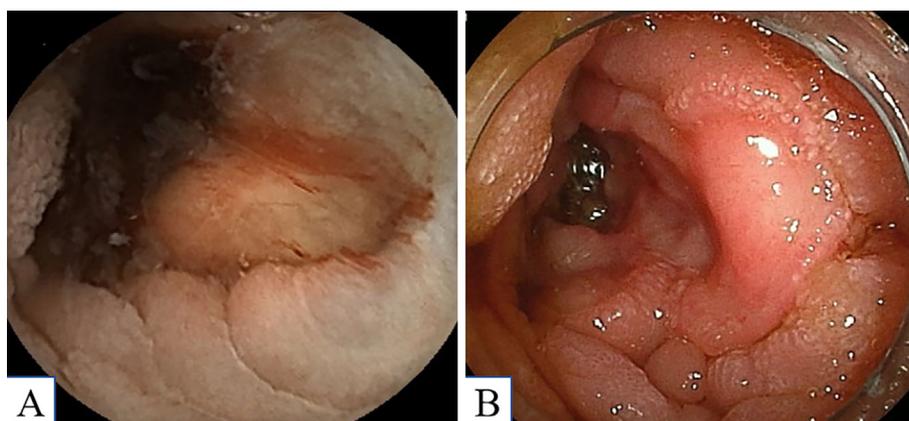


Figure 2. (A) Capsule endoscopy, (B) Double-balloon endoscopy. (A) Capsule endoscopy showed a rough mucosa and ulceration with oozing from the ligament of Treitz. The rounded tumor in the vicinity of the ligament of Treitz caused stenosis of the intestine and it was considered to be a major lesion. (B) Double balloon endoscopy showed a friable mass measuring over 10 cm in size.

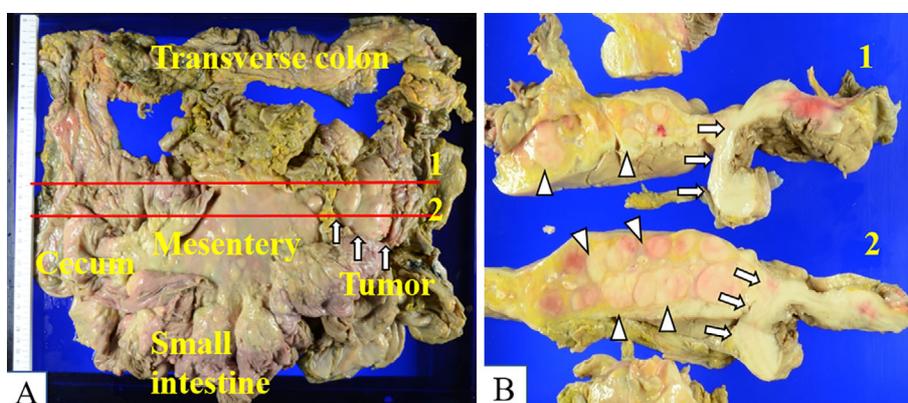


Figure 3. Macroscopic findings. (A) Pathology showed that the lesion was mainly located in the small intestine. (B) The walls of small intestine were thickened (arrows) and numerous mesenteric lymph nodes were markedly swollen (arrowheads).

Abdominal organs such as the omentum, inferior vena cava, abdominal aorta, and entire intestine adhered to each other (Fig. 3).

Microscopically, the lymph nodes were occupied diffusely by tumor cells. Tumor cells were medium to large with marked apoptosis. The tumor cells had diffusely infiltrated the abdominal organs, especially the intestinal walls as mentioned above. On immunohistochemistry, the tumor cells were positive for leukocyte common antigen (LCA), CD30, CD138, and CD79a. The tumor cells were found to be negative for CD20 and BCL2 (Fig. 4). Ki-67 staining was positive in approximately 90% of the tumor cells. EBV infection was negative by in situ hybridization for EBV-encoded RNA (EBER ISH). These findings were compatible with the diagnosis of PBL.

Discussion

PBL of the oral cavity was first described in 1997 (1). It was described as a rare variant of diffuse large B-cell lymphoma, which was most frequently present in the oral cavity

with rapid dissemination and a poor prognosis. Extra-oral PBL is considered to be very rare (3), with only 19 cases of PBL in the intestinal tract having been previously reported.

The forms of intestinal lymphoma tend to vary and can be classified into 5 types (4, 5). In one type, endoscopically the lymphoma appears to be a fungating, ulcerative, infiltrative, multiple lymphomatous polyposis (MLP) and an ulcerofungating lesion. Follicular lymphoma often presents as MLP and is relatively easy to detect while MALT lymphoma often is fungating and infiltrative. Diffuse large B cell lymphoma (DLBCL) is often ulcerative and fungating and mantle cell lymphoma is in many cases a mixture of MLP and the fungating type. T-cell lymphoma often presents as infiltrative and does not form a mass or ulcer. This case also forms fungating and ulcerative. It is difficult to distinguish PBL from DLBCL from endoscopic images. Tissue examinations from biopsies are important for identification, and immunostaining is essential for making a diagnosis.

The clinical and pathological characteristics of the published cases are summarized in Table. Of the 19 cases, 15

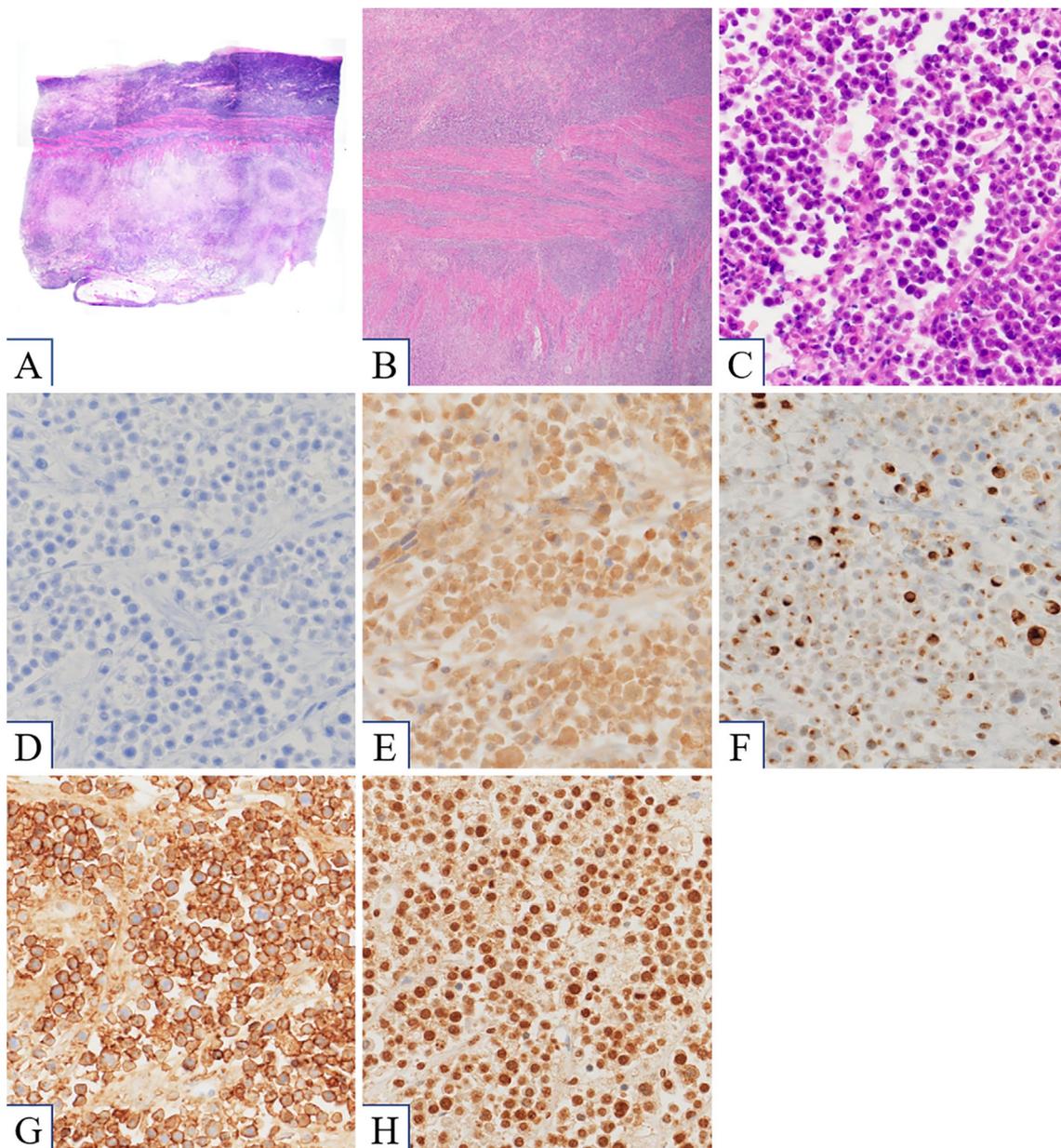


Figure 4. Microscopic findings. A: An HE picture with lower magnification (loupe) for an overview of the main small intestinal lesion. B: Tumor cells had diffusely infiltrated into the intestinal wall ($\times 20$). C: Tumor cells were medium to large in size, had rounded nuclei and scanty cytoplasm that resembled plasmacytoid morphology with marked apoptosis ($\times 400$). D: Tumor cells showed negative staining for CD20 ($\times 400$). E: Tumor cells showed weakly positive staining for CD79a ($\times 400$). F: Cytoplasmic and perinuclear positivity for CD138 ($\times 400$). G: Tumor cells showing membranous positivity for LCA ($\times 400$). H: Tumor cells showed positive staining for EMA ($\times 400$).

were males, 4 were females, and the median age was 50 years (range 17-85 years). Three males and two females ranging in age from 38 to 48 years (median 40 years) were positive for both HIV and EBV (3, 6-9). Among these 5 cases, the underlying diseases were HIV and EBV infection in 4 cases and unknown in 1 case. The symptoms included bleeding, anemia, abdominal pain, and weight loss. Seven of the 19 cases, 6 men and one woman, were negative for both HIV and EBV (age range 50-85 years, median age 60 years) (10-15). Co-existent diseases included Crohn's disease in one (15), malignancies in two (13), diabetes in

one (14), and unknown disease in one patient (10). The other 2 cases had no co-existent diseases that were recognized (11, 12). The symptoms included bloody stools, abdominal pain, and ileus symptoms. Of the remaining 7 of the 19 patients, whether they had either EBV or HIV infection was not clear (2, 3, 16-18). Six of the 19 cases survived for more than a year (3, 12, 15); 1 was HIV positive (3), 4 were HIV negative (3, 12, 15), and the HIV status was unknown in 1 case (3). Of those 6 patients, 2 had chemotherapy and surgery (3, 15) and 4 had only chemotherapy (3, 12).

Table. A Summary of the Reported Cases of PBL in the Intestine.

Reference number	Year	Age/ Sex	Main lesion	HIV	EBV	Symptom	Co-existent disease/ History of treatment	Treatment	OS
6	2005	38/F	Small intestine mesenteric	+	+	NR	NR	CHOP	7 mo
11	2008	60/M	Jejunum	-	-	Dyspnea dizziness	None	CHOP	8 mo
7	2009	47/F	Ano-rectal	+	+	Rectal bleeding	HIV	CHOP	NL
12	2011	59/M	Ano-rectal	-	-	Rectal bleeding	None	CHOP	Alive at 5 yr
10	2011	75/M	Cecum	-	-	Abdominal pain, fever	NR	NR	NR
8	2011	36/M	Small intestine	+	+	Melanotic stool, anemia	HIV	Operation R-CHOP	NR
16	2012	17/F	Small intestine	ND	ND	Abdominal pain, diarrhea	None	None	DOD before diagnosis
17	2012	77/F	Cecum	-	ND	Rectal bleeding, diarrhea, vomiting	NR		DOD 3 wk after diagnosis
18	2012	33/M	Sigmoid	-	+	None (Screening CS)	CD/ADA	EP-OCH	Remission
13	2012	55/M	Small intestine	-	-	Abdominal pain, vomiting	HBV maxillary sinus carcinoma/ Radiotherapy	Operation CHOP	DOD at 1.5 mo
14	2014	65/F	Jejunum	-	-	Anemia	Diabetes mellitus	Operation	DOD
3	2014	40/M	Rectal	+	+	Weight loss, nausea, hemorr-hoids		EP-OCH	Relapsed PBL 1yr after diagnosis
3	2014	64/M	Sigmoid	-	+	Bloody diarrhea	None	Operation R-CHOP	Alive at 44 mo
3	2014	41/M	Terminal ileum	ND	+	Abdominal pain	CD/6MP, PSL	Hyper-CVAD+ Velcade	DOD 17 mo after diagnosis
3	2014	65/M	Terminal ileum Cecum	-	ND	Small bowel obstruction	Hashimoto's thyroiditis CD/IFX, PSL	Hyper-CVAD+ Rituximab HSCT	DOD 25 mo after diagnosis
15	2015	50/M	Small intestine	-	-	Abdominal pain, vomiting, diarrhea	CD/IFX,6MP,PSL	Operation EP-OCH	Alive at 3 yr
9	2015	48/M	Small intestine	+	+	Abdominal pain, vomiting	NR	NR	NR
2	2016	42/M	Small intestine	-	+	Weight loss, anorexia	None	Operation CHOP	DOD 9 mo after diagnosis
Our case		85/M	Small intestine	-	-	None (Screening PET-CT)	Lung cancer	None	DOD before diagnosis

CD: Crohn's disease, +: positive, -: negative, OS: over survival, yr: year, mo: month, wk: week, NR: not recorded, NL: none listed, ND: not done, DOD: died of disease, CHOP: cyclophosphamide, hydroxydaunorubicin, oncovin, predonisonone, R-CHOP: cyclophosphamide, hydroxydaunorubicin, oncovin, predonisonone, rituximab, EP-OCH: etoposode, vincristine, doxorubicin, cyclophosphamide, predonisonone, Hyper-CVAD: fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, HCV: hepatitis C Virus, IFX: infliximab, ADA: adalimumab, AZA: azathioprine, PSL: prednisolone, HSCT: hematopoietic stem cell transplantation, CS: colonoscopy

PBL that occurs in the intestinal tract is often accompanied by symptoms such as ileus symptoms, diarrhea, and bloody stools, which may enable an early diagnosis. Such an early diagnosis might lead to a favorable long-term prognosis. Of the 19 cases described 7 died within one year (2, 6, 11, 13, 16, 17). The general prognosis of PBL with or without HIV and EBV infection is very poor with a rapidly progressive clinical course.

It has been reported that HIV-positive PBL patients have a better response to chemotherapy than their HIV-negative counterparts (19). It is well known that EBV is closely related to PBL. Indeed, of 107 cases of HIV-associated PBL, 79 (74%) were also positive for EBV (20). Thus, there is support that EBV may play an important role in the tumorigenesis of HIV-associated PBL. Castillo et al. noted that

HIV infection created a conducive environment for chronic EBV infection, accompanied by a subsequent latency period allowing the B-cells transformed by EBV to become malignant (21). However, EBV-negative cases have been reported and a recent investigation of Koreans revealed that EBV infection was detected in only 17% of HIV-negative PBL cases (20).

In our case, EBV was not detected by in situ hybridization, suggesting that in this case EBV may not have been a unique participant in the pathogenesis of PBL. PBL can occur in HIV sero-negative patients, and most often has been described after solid organ transplantation in association with steroid therapy for autoimmune disease and other means of immunosuppression (10). In the present case, a history of lung cancer probably led to an immunocom-

promised state. This suggests that the immunocompromised state related to factors such as age, coexistent diseases, cancer, and use of immunosuppressants and anticancer agents might be related to the pathogenesis of PBL.

Conclusion

In conclusion, PBL can occur without HIV and EBV infections. The clinical features of PBL, including its association with HIV, prevalence among males and manifestations in the oral cavity, may help when making a differential diagnosis. However, a lesion in the extra-oral regions in a HIV-seronegative patient impedes the suspicion of PBL. PBL that occurs in the digestive tract is often accompanied by abdominal pain, bloody stools, and ileus symptoms and occurs in individuals without HIV or EBV, in the elderly, and in patients with underlying diseases like cancer.

The authors state that they have no Conflict of Interest (COI).

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