CASE REPORT

Manifestations of gastrointestinal plasmablastic lymphoma: A case series with literature review

Lynette Luria, Johnny Nguyen, Jun Zhou, Michael Jaglal, Lubomir Sokol, Jane L Messina, Domenico Coppola, Ling Zhang

Plasmablastic lymphoma (PBL) rarely occurs in the gastrointestinal (GI) tract with limited studies reported. We reviewed the clinical histories and pathology of four patients with GI PBL at our institute and similar case reports published in peer-reviewed journals. In our first case, a 40-year-old male presented with a hemorrhoid-like sensation, and was diagnosed with PBL via biopsy of a rectal mass. The second case involves a 65-year-old healthy male with bloody diarrhea who was found to have PBL in a resected sigmoid mass. The third patient was a 41-year-old male with a history of Crohn’s disease who presented with abdominal pain, diarrhea, and weight loss. A small intestinal mass (PBL) was removed. The fourth patient was a 65-year-old male who was found to have PBL after surgical resection of bowel for his florid Crohn’s disease. He later developed secondary acute myeloid leukemia. Clinical outcome was very poor in 3 out of 4 patients as reported in the literature. One patient survived chemotherapy followed by autologous transplant. The prototypical clinical presentation and variations of PBL can help create a more comprehensive differential diagnosis for GI tumors and establish an appropriate therapeutic guideline.

Luria L, Nguyen J, Zhou J, Jaglal M, Sokol L, Messina JL, Coppola D, Zhang L. Manifestations of gastrointestinal plasmablastic lymphoma: A case series with literature review. World J Gastroenterol 2014; 20(33): 11894-11903  Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i33/11894.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i33.11894

Abstract

Plasmablastic lymphoma (PBL) rarely occurs in the gastrointestinal (GI) tract with limited studies reported. We reviewed the clinical histories and pathology of four patients with GI PBL at our institute and similar case reports published in peer-reviewed journals. In our first case, a 40-year-old male presented with a hemorrhoid-like sensation, and was diagnosed with PBL via biopsy of a rectal mass. The second case involves a 65-year-old healthy male with bloody diarrhea who was found to have PBL in a resected sigmoid mass. The third patient was a 41-year-old male with a history of Crohn’s disease who presented with abdominal pain, diarrhea, and weight loss. A small intestinal mass (PBL) was removed. The fourth patient was a 65-year-old male who was found to have PBL after surgical resection of bowel for his florid Crohn’s disease. He later developed secondary acute myeloid leukemia. Clinical outcome was very poor in 3 out of 4 patients as reported in the literature. One patient survived chemotherapy followed by autologous transplant. The prototypical clinical presentation and variations of PBL can help create a more comprehensive differential diagnosis for GI tumors and establish an appropriate therapeutic guideline.

Key words: Plasmablastic lymphoma; Undifferentiated carcinoma; Non-Hodgkin lymphoma; Diverse clinical manifestation and treatment

Core tip: Plasmablastic lymphoma rarely occurs as a primary lesion within the gastrointestinal tract. It frequently occurs in human immunodeficiency virus-positive patients, usually within the oral cavity. Its unique immunohistochemical profile may mislead unaware pathologists, and may potentially delay an accurate diagnosis and proper clinical treatment.
INTRODUCTION

Plasmablastic lymphoma (PBL) is classified by the World Health Organization as a type of mature B-cell lymphoma that expresses plasma cell antigens (CD38, CD138, MUM1) but not common B-cell antigens (CD20, CD19, PAX5)

While its pathogenesis is not yet fully understood it has been shown that the Epstein-Barr Virus (EBV) is present in a majority of cases and a small percentage of cases are associated with MYC gene rearrangement[2]. PBL was initially identified in the oral cavity of human immunodeficiency virus (HIV) positive individuals and this continues to be the prototypical presentation of approximately 80% of PBL cases within this population[3]. Since first described in 1997, there have been numerous cases in immunocompromised non-HIV individuals. PBL has also been found in areas outside the oral cavity, favoring sites such as the gastrointestinal (GI) tract, lymph nodes, and skin[1].

The gastrointestinal (GI) tract is one of the most common extranodal sites, especially in HIV negative patients. Given its unique phenotypic presentation by loss of common leukocyte antigen (CD45) expression, it might not directly lead to a diagnosis of conventional non-Hodgkin lymphoma, which is CD45 positive. Instead, initial differential diagnoses might include likely all CD45 negative neoplasms that could potentially involve the GI tract including poorly or undifferentiated carcinomas, including colorectal carcinoma, neuroendocrine cell neoplasms/carcinoid tumors, medullary carcinoma, signet ring cell carcinoma, metastatic tumors, angiosarcoma, de novo diffuse large B-cell lymphoma (DLBCL) and anaplastic plasmacytoma and rarely plasmablastic myeloma.

Misinterpretation of GI PBL would have a great impact on treatment strategy and clinical outcome. PBL is considered an aggressive lymphoma with a median overall survival of 14 mo[4,5]. There is no consensus on treatment protocol in place, and while more aggressive regimens are suggested, they have not provided statistically significant improved outcome[6]. As of date, there are only a handful of case reports[7,8], but not a large case series emphasizing its clinical and pathologic variations as well as appropriate treatment implications.

CASE REPORT

Here we describe 4 cases of PBL found in the GI tract of patients who presented to Moffitt Cancer Center for evaluation and treatment. We have also conducted a review of the literature of other reported cases of GI plasmablastic lymphoma (GI-PBL).

Case 1

At an outside facility, a 40-year-old Caucasian male presented with complaints of recent onset weight loss, nausea, and a “hemorrhoidal type” sensation in his anal area. The patient was diagnosed with HIV in 2004 and attributed his initial weight loss to recent changes in his antiretroviral therapy (ART) therapy (lamivudine, tenofovir and efavirenz). He also had a history of hepatitis B virus infection. A mass was identified under endoscopy and was subsequently resected. A diagnosis of GI plasmablastic lymphoma (GI-PBL) was suspected by a surgical pathologist at the outside facility but the other neoplastic or non-neoplastic process involving GI tracts could not be completely excluded. The patient presented at our institution for evaluation one month after the resection for second opinion. The initial laboratory data showed a white blood cell count of $4.4 \times 10^9/L$, hemoglobin 133 g/L, and platelets of $145 \times 10^9/L$. His lactate dehydrogenase (LDH) level was slightly elevated at 952 U/L (normal range 313–618 U/L). Pathologic review of the resected mass showed squamous mucosa covered tissue with a diffuse lymphoid infiltrate composed of intermediate-to-large cells with dispersed chromatin and prominent nucleoli, which showed round-to-slightly irregular nuclear borders (Figure 1A and B). Numerous single apoptotic bodies and tingible body macrophages were noted. Immunohistochemistry showed the atypical cells to be strongly positive for CD138 (Figure 1C), CD79a, BCL2, and BCL6. The tumor cells were also weakly positive for CD56 and CD45. In-situ hybridization was strongly positive for EBV-encoded RNA (EBER) (Figure 1D). The proliferation index was high (80%), as measured by a Ki-67 immunostain (Figure 1F). The specimen was negative for CD3, CD5, CD10, CD20 (Figure 1E), CD30, EMA, ALK, and human herpesvirus 8 (HHV-8). A fluorodeoxyglucose positron emission tomography (FDG-PET) scan showed hypermetabolic areas in the anal area, mediastinum, right hilum, retroperitoneum, and right common iliac chain. His bone marrow biopsy was unremarkable. Based on these clinical and pathologic findings, the final diagnosis was PBL. The patient was treated with dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone) therapy, including intrathecal prophylaxis with methotrexate, which he tolerated very well. A follow-up computer axial tomography (CT) scan showed a decrease in his lymphadenopathy after 3 cycles. He was on ART and prophylactic antibiotics (Azithromycin, trimethoprim-sulfamethoxazole, and acyclovir). However, at his 12 mo follow-up, the patient had developed PBL of the bladder that was confirmed by biopsy. Per CT, massive nodal soft tissue involvements were noted within the left and right retroperitoneal regions of the pelvis anterior to the mid sacrum measuring (7.0 cm), periaortic region (2.0 cm) and adjacent to kidneys (6.0 cm). Additional chemotherapy was continued. However, the patient was lost of follow up after the visit.

Case 2

A 64-year-old male presented with bloody diarrhea. A pelvic CT with contrast was performed, which disclosed a large mass arising from the mid to distal sigmoid colon with prominent thickening of the sigmoid colon and exophytic extension (measuring 6.5 cm $\times$ 7.4 cm) into the soft tissues posterolateral to the sigmoid colon on the left side. An outside facility performed a colonoscopy and subsequent resection of the sigmoid mass. A diag-
nosis of “favoring a hematopoietic tumor” was issued by the outside pathology facility. Differential diagnoses included, but was not limited to, anaplastic plasmacytoma, DLBCL and cytokeratin negative, poorly differentiated carcinoma. The patient was transferred to our hospital for consultation. Laboratory tests performed at our institution revealed a white blood cell count of $9.5 \times 10^9$/L, hemoglobin of 150 g/L, platelets of $309 \times 10^9$/L. His chemistry profile and liver function tests were normal. An HIV test was negative. The slides of bowel resection were reviewed and further ancillary studies were ordered. Microscopic examination of the resected specimen showed atypical plasmacytoid cells with intermediate to large nuclei with peripheral chromatin and many prominent nucleoli. The atypical cells were positive for CD45 (dim), CD10, CD38 (bright), and VS38. There was focal positivity for EMA, BCL6, CD30, and cyclin-D1. CD117 staining showed weak positivity. They were negative for CD19, CD20, CD5, CD79a, CD138, CD34, and HLA-DR. According to the outside pathology report, the neoplastic cells were negative for cytokeratin AE1/AE3, CK7, CK20, CAM5.2, CDX2, melan A, S100, ALK, BCL2, CD34, CD4, CD7, CD56, CD68, and TdT. Light chain studies were non-contributory due to heavy background staining. The proliferation fraction by Ki-67 was estimated to be greater than 90%. Additional studies performed at our institution confirmed that the tumor was negative for CD20 and strongly positive for EBER. While EBV associated DLBCL of the elderly can be CD20 negative and present with immunoblastic fea-

Figure 1 Microscopic examination. A: Microscopic examination of rectal biopsy showed intact squamous mucosa with submucosal dense lymphoid infiltrate associated with increased angiogenesis (HE, magnification × 40); B: High power view demonstrated sheets of large atypical lymphoid cells with plasmablastic differentiation (big round to oval nuclei, dense or disperse chromatin, prominent nucleoli and abundant amphophilic cytoplasm with increased apoptosis and mitosis and scattered inflammatory cells (HE, magnification × 600); C: CD138 immunostain highlighting the neoplastic cells (Immunoperoxidase, magnification × 600); D: In situ hybridization by using epstein barr virus-encoded RNA probe showed diffuse and strong signals (ISH, magnification × 600); E: Plasmablastic lymphoma cells being purely negative for CD20 (Immunoperoxidase, magnification × 100); F: High proliferation index was highlighted by Ki67 immunostain (approximately 80%) (Immunoperoxidase, Magnification × 100).
tures resembling PBL, it is usually non-germinal center type, and this patient also showed negativity for CD19, CD79a, and BCL2 and positivity for CD10 and BCL6. These findings made this a less likely diagnosis, and the final diagnosis was PBL. A FDG-PET scan showed hypermetabolic areas in the pelvis. A bone marrow biopsy showed normocellular bone marrow with no evidence of involvement by malignant lymphoma. He was initially treated with R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone-rituximab) therapy because the immunohistochemistry (IHC) panel received from the referring entity did not contain a CD20 stain. The clinician thought it would be prudent to add rituximab to the patient’s therapy until our institution ran an additional IHC study to confirm that the lymphoma cells completely lacked CD20 expression. The patient went into complete remission after six cycles of chemotherapy and received an autologous hematopoietic stem cell transplant (auto-HSCT). Follow-up 44 mo after the initial diagnosis and 35 mo post transplant showed complete remission.

Case 3
A 41-year-old male with a longstanding history of Crohn’s disease diagnosed in 1999 had undergone a right colectomy almost 10 years prior to presentation. He was on 6-mercaptopurine (6-MP) and budesonide (Entocort) since 2001, and was clinically stable under his primary care physician besides a chronic fistula-in-ano for the last two years. He presented with a 35 pound weight loss, abdominal pain, and diarrhea at a local hospital, where a CT of the abdomen showed diffuse bowel wall thickening of small bowel loop and associated with a mass showing irregular central area of non-enhancement (phlegmon) measuring 7.0 cm × 4.0 cm around the small intestine. The patient was initially treated with steroids and antibiotics without improvement. The involved section of bowel was removed after a CT-guided needle biopsy failed to drain any fluid from the mass. The patient came to our institution for further evaluation and treatment. A microscopic review of the mass showed muco-adherent tissue associated with focal dense infiltrates of sheets of large atypical lymphoid cells throughout the whole thickness of the small bowel wall, which was superimposed with inflammatory process. The atypical cells had eccentrically round to oval nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. The tumor cells stained positive for CD30, CD79a, MUM-1 and weakly positive for PAX5 and CD68. There was variable staining for CD45, CD20, CD138, CD3, CD5, CD25, ALK1, cytokeratin, CAM5.2, and CD56 were negative. EBER was positive. Ki-67 showed a proliferation index of 75%. This confirmed the diagnosis of a primary GI PBL. The uninvolved segments of small bowel display characteristic histology for Crohn’s disease. Bone marrow staging was negative for involvement by lymphoma. A FDG-PET/CT scan demonstrated increased metabolic activity within loops of proximal large intestine and no evidence of metabolically active lymphadenopathy within the neck, chest, abdomen or pelvis. The patient was started on HyperCVAD chemotherapy (cyclophosphamide, vincristine, doxorubicin and dexamethasone). Before starting cycle 3 of the chemotherapy regimen, he was found to have a mass on his bladder wall. After 3 cycles of chemotherapy, a CT scan showed growth of the bladder mass with biopsy confirming PBL. He was started on radiation therapy but unable to continue due to declining health. The patient was discharged to hospice care and subsequently died of disease.

Case 4
A 65-year-old white male presented to our clinic in 2011 with a history of Hashimoto’s thyroiditis diagnosed in 1988, status post right thyroidectomy in 1999, and a history of Crohn’s disease (CD) diagnosed in 2000, which was treated with oral steroids, infliximab and budesonide. He also underwent left thyroidectomy for a thyroid nodule in January 2006, which revealed a limited-stage of low-grade extranodal marginal zone lymphoma (MZL) requiring no additional treatment. In June 2011, he developed acute small bowel obstruction, which was initially considered to be associated with exacerbation of Crohn’s disease. He underwent resection of the ileum and cecum. Unexpectedly, the histology and immunohistochemistry studies reported a multifocal involvement of ileum and cecum with PBL. (CD138 (+), partial CD79a (+), focally CD20 (+), kappa light chain (+), lambda light chain (-) and high proliferation index, 100%, highlighted by Ki67) in addition to Crohn’s disease. All 14 biopsied lymph nodes were free of lymphoma. Staging bone marrow biopsy showed no involvement with lymphoma. ELISA testing for HIV-1 and 2 was negative. A CT scan of the abdomen revealed a new soft tissue mass along the right kidney. He was treated with two cycles (4 arms) of hyperCVAD and rituximab between August and October 2011 and achieved complete remission, per restaging reports. He was consolidated with conditioning regimen BEAM+R (BCNU, etoposide, ara-C and melphalan and rituximab), followed by auto-HSCT in November 2011. His post-transplant course was complicated with protracted moderate to severe thrombocytopenia ranging from 3.0-53.0 × 10^9/L that required platelet transfusions. He had mild normocytic anemia and normal absolute neutrophil count. The patient was treated with steroids, danazol and thrombopoietin receptor agonist (El trombopag) for a possible immune-mediated peripheral destruction of platelets given sustained thrombocytopenia and normal bone marrow findings (2 biopsies within 6 mo) but did not achieve a durable response. Subsequent restaging FDG-PET/CT scan performed in February 2013 showed no evidence of recurrent PBL. However, a repeat bone marrow biopsy in May 2013 revealed hypercellularity (60%) with increased myeloblasts (40%) and cytogenetic abnormalities including del(7q) and isochromosome 9 in 2/30 cells. Fluorescent in situ hybridization (FISH) also demonstrated both del(7q31) and del(5q31). The overall findings supported a diag-
nosis of therapy-related acute myelogeneous leukemia (tAML). He underwent induction chemotherapy with CLAG (cladribine, ara-C and G-CSF), but his day 14 bone marrow biopsy revealed residual leukemia. His hospital course was complicated with bacterial and fungal infections along with significant physical deconditioning. Although the patient was offered reinduction therapy, he opted for comfortable measures with hospice. He succumbed to tAML two months later. A comparison of the clinical and pathological features in our four cases is summarized in Table 1.

**Discussion**

Plasmablastic lymphoma tends to present in the oral cavity of HIV-positive patients. In HIV-negative patients, extranodal, mucosal areas are the most common primary sites\(^7\). A diagnosis of PBL of GI tract could be difficult since morphologically PBL could mimic a poorly differentiated carcinoma, DLBCL, Burkitt lymphoma, plasmacytoma and EBV associated DLBCL of the elderly. The morphologic spectrum of PBL includes immunoblastic, Burkitt, and plasmacytic variants. Of note, there are morphologic variations among the current cases. In case 1, the tumor cells are Burkitt-like, intermediate to large in size with dispersed chromatin, brisk mitoses, and increased apoptosis. The lymphoma cells in cases 2, 3 and 4 are predominantly immunoblastic, centroblastic or focally mixed with the two components. Phenotypically, some PBL lacks or expresses weak CD45, which could be misinterpreted as carcinoma if extensive ancillary studies are not performed; a small subset of PBL retains CD20 expression also results in diagnostic difficulty to separate it from de novo DLBCL, not otherwise specified (NOS) when encountering a limited biopsy sample. Thus, comprehensive immunophenotyping is necessary to distinguish PBL from the other neoplasms\(^9,10,21\).

PBL could also be linked to immunocompromised status including the elderly. Both immunocompromised and immunocompetent patients tend to present with late stage disease\(^3\). B symptoms are symptoms associated with lymphoma and include weight loss, fever, and night sweats. These symptoms are more commonly reported in HIV-negative (50%) patients as compared to HIV-positive patients (33%)\(^4\). While not all patients with GI PBL presented with B symptoms, they all had gastrointestinal symptoms or signs (Table 1). Without imaging studies and biopsy, many could be missed at an earlier course in the disease. Moreover, of the 4 cases of primary GI PBL that presented to our institution and the 14 reported cases in the literature, 39.5% of the patients (5 of 13, 1 not available) had a known HIV-positive status. For the other case studies, it is unclear if any of the patients were immunosuppressed due to other reasons that could be attributed to disease development or progression. Three of the 14 patients were previously diagnosed with other neoplasms, including adenocarcinoma of the colon\(^13\), meningioma\(^14\), and squamous cell carcinoma of the maxillary sinus\(^8\). However, there were no details with regard to chemotherapy treatment, radiation or immunomodulation. Cases 3 and 4 from our institution had a history of Crohn’s disease that developed PBL. To our knowledge, this is the first report of PBL arising in the GI tract of 2 patients with inflammatory bowel disease. The incidence of non-Hodgkin lymphoma within the inflammatory bowel disease population is common in the literature. There is debate as to whether the increased risk of non-Hodgkin lymphoma in these patients is related to their disease, use of immunomodulators, or the use of anti-Tumor Necrosis Factor (anti-TNF) medications. Biancone et al\(^23\) found in their cohort study that immunomodulators and anti-TNFs did not increase overall cancer risk for patients with Crohn’s disease, but that a

**Table 2.** Only 8 of the cases were tested for the presence of EBV. Of these cases, 4 (50%) were positive. Three of the 14 patients were previously diagnosed with other neoplasms, including adenocarcinoma of the colon\(^13\), meningioma\(^14\), and squamous cell carcinoma of the maxillary sinus\(^8\). However, there were no details with regard to chemotherapy treatment, radiation or immunomodulation. Cases 3 and 4 from our institution had a history of Crohn’s disease that developed PBL. To our knowledge, this is the first report of PBL arising in the GI tract of 2 patients with inflammatory bowel disease. The incidence of non-Hodgkin lymphoma within the inflammatory bowel disease population is common in the literature. There is debate as to whether the increased risk of non-Hodgkin lymphoma in these patients is related to their disease, use of immunomodulators, or the use of anti-Tumor Necrosis Factor (anti-TNF) medications. Biancone et al\(^23\) found in their cohort study that immunomodulators and anti-TNFs did not increase overall cancer risk for patients with Crohn’s disease, but that a
Table 1 Literature review and case study summary of demographic, clinical presentation, treatment and outcomes of plasmablastic lymphoma of gastrointestinal tract

| No. | Study | Year | Age/sex | Tumor location | HIV status | GI S/Sx | B symptoms | Chemotherapeutic treatment | Response | Outcome |
|-----|-------|------|---------|---------------|------------|---------|------------|----------------------------|----------|---------|
| 1   | Mari et al | 2008 | 40/M   | Esophagus, stomach |  + | Progressive dysphagia | WL, F, NS | LACE | Remission | Alive at 6 mo |
| 2   | Cha et al | 2010 | 60/M   | Small intestine |  - | Dyspnea, melena | WL + | CHOP | PR | Relapse, alive at 24 mo |
| 3   | Brahmania et al | 2011 | 59/M   | Ano-rectal |  - | Painless rectal bleeding | NR | CHOP | Remission | Alive at 5 yr |
| 4   | Mihajlovic et al | 2012 | 60/M   | Stomach |  - | Melena | WL + | CHOP | UR | DOD after one cycle of CHOP |
| 5   | Hashimoto et al | 2012 | 70/F   | Stomach |  - | Melena | NR | CHOP, VP 16, ifosfamide, carboplatin | UR | Died during treatment |
| 6   | Chapman-Fredricks et al | 2012 | 46/F   | Stomach |  + | N/V, diarrhea, melena | NR | EPOCH | NL | NL |
| 7   | Bahari et al | 2012 | 17/F   | Small intestine |  ND | Diarrhea, distention | F + | NL | NL | DOD before diagnosis made |
| 8   | Pruneri et al | 1998 | 53/F   | Stomach |  - | Postprandial fullness, stomach ache | F + | ProMACB-OM | Remission | Alive at 19 mo |
| 9   | Rajagopal et al | 2006 | 35/M   | Ano-rectal |  + | Rectal bleeding, tenesmus, constipation | WL + | CHOP | Remission | Alive at 5 mo |
| 10  | Wang et al | 2012 | 55/M   | Small intestine |  - | Distention, vomiting, anorexia | WL + | CHOP | UR | DOD at 1.5 mo |
| 11  | Hatanaka et al | 2010 | 75/M   | Cecum |  - | NL | F + | NL | NL | NL |
| 12  | Lim et al | 2009 | 47/F   | Ano-rectal |  + | Anal bleeding, pain, fistula for 1 yr | NR | CHOP | Received 3 cycles of chemotherapy, status unknown | NL |
| 13  | Marques et al | 2013 | 82/F   | Stomach |  - | Melena, epigastric pain, abdominal fullness | WL + | CHOP | UR | DOD after 1 cycle of chemotherapy |
| 14  | Mansoor et al | 2012 | 77/F   | Cecum, colon |  - | Recal bleeding, diarrhea, vomiting | WL + | CHOP | UR | DOD 3 wk after presentation |
| Case 1 | Luria et al | 2003 | 40/M  | Rectal |  + | Hemorrhoids like sensations | WL + | EPOCH | PR | Relapsed PBL in pelvic, abdomen, bladder 1 yr after PBL diagnosis - loss of follow after it |
| Case 2 | Luria et al | 2004 | 64/M  | Sigmoid colon |  NR | Bloody diarrhea | NR | CHOP-R, Auto-HSCT | CR | Alive at 44/35 mo |
| Case 3 | Luria et al | 2004 | 41/M  | Terminal ileum |  NR | Abdominal pain, diarrhea, 35-pound weight loss | WL + | Hyper-CVAD + Velcade | UR | Progressive, bladder mass, hepatic metastases, DOD, 17 mo after PBL diagnosed |
| Case 4 | Luria et al | 2004 | 65/M  | Terminal ileum and cecum |  - | Acute bowel obstruction | NA | Hyper-CVAD + rituximab, auto-HSCT | UR | CR for PBL, but developed tAML and DOD 2 mo after tAML diagnosed and 25 mo after PBL diagnosed |

1 Accompany abdominal pain; 44/35: 44 mo after diagnosis and 35 mo post transplant; +: Positive; -: Negative; ND: Not done; GI S/Sx: GI tract symptoms and signs; WL: Weight loss; F: Fever; NS: Night sweats; NR: None reported; NL: None listed; CHOP: Cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; CHOP-R: Cyclophosphamide, doxorubicin, vincristine, prednisone-ruxitimab; LACE: Lomustine, cytarabine, cyclophosphamide, etoposide; EPOCH: Etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone; proMACB-OM: Cyclophosphamide, doxorubicin, etoposide cytozor, bleomycin, vincristine, methotrexate and prednisone; Hyper-CVAD: Fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone; PR: Partial remission; UR: Unresponsive to therapy; NA: Not Applicable; DOD: Died of disease.
fistulizing pattern of disease did. A recent case report also addressed a concern about whether using infliximab (anti-TNF) for inflammatory bowel disease (ulcerative colitis) was associated with a significantly increased risk of developing lymphomas. However, a meta-analysis by Siegel et al. did not show a statistically increased risk of non-Hodgkin lymphoma in patients who were treated with anti-TNF and immunomodulator as compared to the general population. They were unable to establish a clear-cut link and expressed concern that age might be a confounding variable. Our patient had a long history of treatment with steroids (Budesonide) and/or 6-mercaptopurine. Both drugs are immunosuppressive. Immunosuppressed status, in conjunction with reactivation of EBV, could be inciting factors for PBL with adverse clinical outcomes.

The presence of EBV in PBL has been cited repeatedly, and there is interest if this represents a route of pathogenesis. EBV has been shown to be involved in malignant transformation in a number of other lymphoproliferative disorders including Burkitt lymphoma and Hodgkin lymphoma. It appears the viral-encoded product LMP1 has been linked to growth and proliferation. This membrane bound protein is functionally similar to CD40 and is constitutively active. Moreover, since DNA methylation occurs ubiquitously in human cancer from the earliest measurable stages, a novel study of Hansen KD group revealed that extensive blockage of hypomethylation occurred in EBV-induced B-cells, which could be another reason for their immortalization. EBV RNA is present in the majority of HIV-positive PBL cases and about half of HIV-negative cases. Right now, the presence or absence of EBER is being used to help diagnose PBL. However, there have been recent reports of clinicians attempting to track their patient’s response to treatment and possible relapse by measuring EBV DNA viral load in blood samples at different intervals. They found that lower levels from diagnostic baseline corresponded with remission, while higher levels corresponded with relapse.

Researchers have also sought to understand the pathogenesis of PBL by understanding its common genetic anomalies. The proto-oncogene c-MYC is frequently observed in a variety of tumors. c-MYC is a well-studied phosphoprotein whose rearrangement has been associated with poor clinical outcome. It is most commonly associated with Burkitt lymphoma but is seen in other malignancies as well. In a study conducted by Valera et al., 49% of the 41 cases of PBL that were able to be investigated demonstrated rearrangement of c-MYC. Five of these patients had PBL of the GI tract, and of those, two showed rearrangements with immunoglobulin heavy chain (IgH) and one showed gains in IgY expression. The most common rearrangement encountered in the literature is between c-MYC and IgH. c-MYC status was not well investigated in PBL. In an article describing 3 cases of PBL with c-MYC/IgH rearrangement by Bogusz et al., they found that these patients had extremely low CD4 counts (21, 48, and 35 cells/mm³) as compared to 6 PBL patients without the rearrangement. In these 6 patients, the median CD4 count was 300 cells/mm³. One of the 3 c-MYC/IgH rearrangement cases PBL was found in the anus and bone marrow. The case was not included in our review set because it was part of a table, and a full patient history was not present. Of 14 listed cases (Table 2) and all 4 cases at our institution, only one study was analyzed by fluorescence in-situ hybridization (FISH) for c-MYC, which was positive. Since a dysregulated c-MYC gene could be a potential therapeutic target, further investigation of c-MYC in PBL may potentially have important therapeutic and prognostic implications.

One of the reasons patients with PBL may not present with B symptoms can be explained by a proposed mechanism for its pathogenesis. B lymphocyte-induced maturation protein-I (BLIMP1) and X-box-binding protein 1 (XBP1) are proteins that serve as reliable plasma cell markers because they are involved in terminal B-cell differentiation. They have come to be recognized as markers of PBL because the morphology and immunoprofile of this disease can overlap with other entities such as multiple myeloma, DLBCL, and primary effusion lymphoma. As BLIMP1 expression increases there has been shown to be a correlative decrease in expression of human leukocyte antigen DR (HLA-DR) and by association major histocompatibility complex class II (MHC II). MHC II is involved in recruiting and activating tumor-infiltrating T cells which could potentially help combat tumor growth and contribute to the manifestation of B symptoms. Loss of this protein has been linked with more aggressive forms of DLBCL and it has been theorized that this may contribute to PBL’s behavior.

Chemotherapy regimens that have been used with partial or complete response include CHOP, infusional EPOCH, hyperCVAD, and CODOX-M/IVAC. Anti-viral therapy and monitoring of HIV viral titers and CD4 count also play a critical role in the treatment of HIV positive patients. Aggressive chemotherapy regimens have not shown to produce a statistically significant improvement in outcome. Further study of the occurrence of MYC dysregulation in PBL may help us better understand the disease mechanism and guide future pharmacological research and chemotherapeutic regimens. Until a more focused treatment option can be provided to patients, there has been some success with adding bortezomib to the current regimens or having the patients undergo auto-HSCT should they achieve complete remission on therapy. Case 2 in our study was treated with auto-HSCT after his chemotherapy and showed the longest remission of the 3 (44 mo). Case 4 achieved complete response for his PBL but developed secondary AML two years after auto-HSCT. To date, no study has specifically analyzed the overall survival of auto-HSCT for the treatment of PBL. Liu et al. reported four patients who received auto-HSCT after chemotherapy at their institution and showed a median survival of 27.5 mo.
In summary, clinical manifestations and treatments are varied among cases. Understanding the rare disease entity would benefit patient care by rendering earlier correct diagnosis, predicting clinical outcome and taking appropriate therapeutic strategies. A large scale study with standard approaches is eventually needed.

### COMMENTS

#### Case characteristics

Plasmablastic lymphoma of gastrointestinal tract (GI-PBL) is a rare variant of B-cell non-Hodgkin lymphoma with an aggressive clinical course and shorter overall survival of 1-2 years, which is primarily associated with human immunodeficiency virus (HIV) infection but can also be seen in immunocompromised status including the elderly.

#### Clinical diagnosis

It often presents with gastrointestinal (GI) symptoms and signs such as bloody stool, diarrhea, abdominal pain accompanied with or without weight loss.

#### Differential diagnosis

Differential diagnoses should include, but not be limited to, poorly differentiated carcinomas, of GI tract, metastatic neoplasms, some sarcomas, de novo diffuse large B-cell lymphoma, and plasma cell neoplasms.

#### Laboratory diagnosis

Laboratory investigations should include routine CBC, serum lactate dehydrogenase level, and virology including HIV and Epstein-Barr Virus.

#### Imaging diagnosis

Imaging study using positron emission tomography scan/computer axial tomography scan revealed a mass with or without bowel obstruction.

#### Pathological diagnosis

PBL poses a diagnostic challenge given its unique immunophenotypic profile (negative for CD45, B-cell markers, CD20, PAIX, and positive for plasma cell markers such as CD138, CD38, MUM1 and partially CD79a) and a high proliferation index. Thus, a comprehensive study including careful morphologic examination, extensive immunoperoxidase (immunohistochemistry or flow cytometry) and cytogenetic/ FISH study should be completed before the diagnosis is rendered.

### Treatment

Although both CHOP and EPOCH are considered the common therapeutic choices, standard therapy or treatment guidelines have not been established yet. Autologous transplant is considered optional and tends to have a good outcome but still limited in experience.

#### REFERENCES

1. Hsi ED, Lorsbach RB, Fend F, Dogan A. Plasmablastic lymphoma and related disorders. Am J Clin Pathol 2011; 136: 183-194 [PMID: 21757592 DOI: 10.1093/ajcp/l12wqizkzknj]
2. Stein H, Campo E. Plasmablastic Lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, editors. WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues. 4th ed. Sterling, VA: International Agency for Research on Cancer (IARC), 2008
3. Hansra D, Montague N, Stefanovic A, Akunyili I, Harzand A, Natkunam Y, de la Ossa M, Byrne GE, Lossos IS. Oral and extraoral plasmablastic lymphoma: similarities and differences in clinicopathologic characteristics. Am J Clin Pathol 2010; 134: 710-719 [PMID: 20959653 DOI: 10.1093/ajcp/hj6ekeseqclu]
4. Castillo JJ, Reagan JL. Plasmablastic lymphoma: a systematic review. ScientificWorldJournal 2011; 11: 687-696 [PMID: 21442146 DOI: 10.1100/tsw.2011.59]
5. Castillo JJ. Plasmablastic lymphoma: are more intensive regimens needed? Leuk Res 2011; 35: 1547-1548 [PMID: 21788074 DOI: 10.1016/j.leukres.2011.06.036]
6. Mani D, Guinee DG, Aboulafia DM. AIDS-associated plas-
Clinical manifestations of gastrointestinal plasmablastic lymphoma

Plasmablastic lymphoma presenting as a poorly differentiated esophageal tumor: a diagnostic dilemma. World J Gastroenterol 2008; 14: 4395-4399 [PMID: 18666332

Cha JM, Lee JI, Joo KR, Jung SW, Shin HP, Lee JI, Kim GH. A case report with plasmablastic lymphoma of the jejunum. Korean J Med Sci 2010; 25: 496-500 [PMID: 20191056 DOI: 10.3344/jkms.2010.25.3.496

Wang HW, Yang W, Sun ZJ, Lu JY, Li M, Sun L. Plasmablastic lymphoma of the small intestine: case report and literature review. World J Gastroenterol 2012; 18: 6677-6681 [PMID: 23263245 DOI: 10.3748/wjg.v18.i45.6677

Rajagopal AS, Copson E, Addis B, Shinkend M, Mead G. Plasmablastic lymphoma: a case of rectal disease with spinal cord compression. Leuk Lymphoma 2006; 47: 2670-2673 [PMID: 17169819 DOI: 10.1080/10428190600990727

Pruner G, Graziaedi G, Erlemanno L, Baldini L, Neri A, Bufo R. Plasmablastic lymphoma of the stomach. A case report. Haematologica 1998; 83: 87-89 [PMID: 9542256

Babari A, Jahantighi M, Mishalhadi A, Bari Z, Bari A. Plasmablastic Lymphoma presenting as small intestinal polyposis: A case-report. Iran Red Crescent Med J 2009; 2009: 10-13 [PMID: 19981129 DOI: 10.4143/1111/pin.12005

Mansoor M, Alani FS, Aslam MB, Kumar SN, Sahasrabudhe N, Khan D. A case report of cecal plasmablastic lymphoma in a HIV-negative patient. Eur J Gastroenterol Hepatol 2012; 24: 332-335 [PMID: 22228369 DOI: 10.1097/MEG.0b013e32834e6d10

Marques I, Lagos A, Costa-Neves B. Gastric plasmablastic lymphoma in HIV-negative patient. Rev Esp Enferm Dig 2013; 105: 166-167 [PMID: 23735024

Chapman-Fredricks J, Montague N, Akuyilli I, Ilkpat O. Extraropal plasmablastic lymphoma with intravascular component and MYC translocation. Ann Diagn Pathol 2012; 16: 48-53 [PMID: 21239197 DOI: 10.1016/j.anndiagpath.2010.11.002

Hashimoto M, Hatanaka K, Nakamura N, Kishimoto K, Sugino K, Uekusa T. Plasmablastic lymphoma of the stomach: a case with T-cell lymphoma in the ano-rectal junction presenting in an immunosuppressed HIV-negative patient. Pathol Int 2012; 119: 121-124 [PMID: 22597581 DOI: 10.1111/pin.12005

Hansen KD, Sabuncianli S, Langmead B, Salamon D, Feinberg AP. Large-scale hypomethylated blocks associated with Epstein-Barr virus-induced B-cell immortalization. Genome Res 2014; 24: 177-184 [PMID: 24068705 DOI: 10.1101/gr.157743.113

Friedman AS, Akerlund B, Christensson B, Gyllensten K, Aleman A, Zou JZ, Ernberg I. Epstein-Barr virus DNA analysis in blood predicts disease progression in a rare case of plasmablastic lymphoma with effusion. Infect Agent Cancer 2013; 8: 28 [PMID: 23880011 DOI: 10.1186/1750-9378-8-28

Law MF, Poon WL, Ng KS, Chan HN, Lai HK, Ha CY, Ng C, Yeung YM, Yip SF. Quantification of plasma Epstein-Barr virus DNA for assessing treatment response in a patient with plasmablastic lymphoma. Ann Hematol 2012; 91: 789-791 [PMID: 21881823 DOI: 10.1007/s12032-011-1313-3

Slack GW, Gascoyne RD. MYC and aggressive B-cell lymphomas. Adv Anat Pathol 2011; 18: 219-228 [PMID: 21940439 DOI: 10.1097/PAP.0b013e3182169948

Bogus AM, Seegmiller AC, Garcia R, Shang P, Ashfaq R, Chen W. Plasmablastic lymphomas with MYC/IgH rearrangement: report of three cases and review of the literature. Am J Clin Pathol 2009; 132: 597-605 [PMID: 19762538 DOI: 10.1309/apjcp11b8kudo6

Valera A, Barlag O, Colomo L, Martínez A, Delabie J, Tadesse-Heath J, Jafe ES, Campo E. IgH/MYC rearrangements are the main cytogenetic alteration in plasmablastic lymphomas. Am J Surg Pathol 2010; 34: 1686-1694 [PMID: 20962620 DOI: 10.1097/PAS.0b013e3181fe29

Helm F, Kammertoons T, Lehmann FM, Wilke A, Bruns H, Mautner J, Bornkamm GW, Gerbitz A. Targeting c-MYC with T-cells. PLoS One 2013; 8: e77375 [PMID: 24130880 DOI: 10.1371/journal.pone.0077375

Wyce A, Ganji G, Smitheman KN, Chung CW, Korenchuk S, Bai Y, Barbash O, Le B, Crapps PD, McCabe MT, Kennedy-Wilson KM, Sanchez LV, Gosmith RL, Parr N, McHugh CF, Dhanak D, Prinjha RK, Auger KR, Tummino PJ. BET inhibition suppresses osteosarcoma cell proliferation and MYC expression. Mol Cell Biol 2013; 33: 91

Wilkinson ST, Vanpatten KA, Fernandez DR, Brunhoeber P, Garsha KE, Glinsmann-Gibson BJ, Grogan TM, Teruya-Feldstein J. Rimuzma LM. Partial plasma cell differentiation as a mechanism of lost histocompatibility complex class II expression in diffuse large B-cell lymphoma. Blood 2012; 119: 1459-1467 [PMID: 22167754 DOI: 10.1182/blood-2011-07-363820

Schmelz M, Montes-Moreno S, Piris M, Wilkinson ST, Rimsza LM. Lack and/or aberrant localization of major histo-
compatibility class II (MHCII) protein in plasmablastic lymphoma. *Haematologica* 2012; 97: 1614-1616 [PMID: 22689685 DOI: 10.3324/haematol.2011.060186]

Liu JJ, Zhang L, Ayala E, Field T, Ochoa-Bayona JL, Perez L, Bello CM, Chervenick PA, Bruno S, Cultreria JL, Baz RC, Kharfan-Dabaja MA, Raychaudhuri J, Sotomayor EM, Sokol L. Human immunodeficiency virus (HIV)-negative plasmablastic lymphoma: a single institutional experience and literature review. *Leuk Res* 2011; 35: 1571-1577 [PMID: 21752466 DOI: 10.1016/j.leukres.2011.06.023]

P- Reviewer: Arihiro S, Kojima M, Lagoo AS, Miranda RN, Pellicelli AM, Sugimoto KJ S- Editor: Ma YJ L- Editor: AE- Editor: Wang CH

Luria L *et al.* Clinical manifestations of gastrointestinal plasmablastic lymphoma
