CASE REPORT

Plasmablastic Lymphoma of Small Intestine: A Rare Case Report with Review of Literature

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Abstract Plasmablastic lymphoma (PBL) is a rare aggressive neoplasm characterized by diffuse proliferation of large neoplastic cells with plasma cell immunophenotype. Cell of origin of PBL is believed to be a postgerminal center B-lymphocyte or plasmablast. The malignant cells in PBL usually do not express CD20 (B cell marker) but do express markers of plasmacytic differentiation, such as CD38, CD138, or MUM1/IRF4, akin to plasma cell myeloma (PCM). PBL though originally described in the oral cavity, has now been found to occur in extraoral locations as well. Small intestine as a site of PBL has been described very rarely. PBL remains a diagnostic challenge given its overlapping morphologic and immunophenotypic features with other high grade lymphomas and PCM. We report a rare case of PBL of small intestine in a 48 years old HIV infected male patient. To the best of our knowledge this represents sixth case in the literature described in this location. An unusual rare pattern of CD138 positivity by IHC is also reported along with extensive review of literature of PBL in extraoral locations.

Case Report

A 48 year old male presented with generalized abdominal pain, vomiting and abdominal distension since 1 week. Pain was distributed in suprapubic and umbilical region. Patient

was diagnosed to have acute intestinal obstruction with possibilities of intussusception or small intestinal tumor. His chest radiograph showed upper lobe collapse. Routine haematological evaluation revealed Haemoglobin (Hb) 122 g/L, Total leukocyte count (TLC) $8.1 \times 10^9/L$, Platelet count (PC) $190 \times 10^9/L$. CECT scan of abdomen revealed circumferential diffuse wall thickening of jejunal loop and enlarged mesenteric lymph nodes (Fig. 1). After preoperative evaluation he underwent explorative laparotomy, resection of small bowel with end to end anastomosis and omentectomy.

Screening tests for HIV I & II done by enhanced chemiluminescence method were reactive with test values being 85.1 (≥ 1.0 reactive, gray zone 0.9–0.99, <0.9 non reactive). Absolute CD3, CD4 and CD8 counts and percentages were assessed by flow cytometry (FCM) technique as showed in Table 1. Serum LDH and Uric acid levels were 702U/L (normal range 208–320U/L) and 4.7 mg/dl (normal range 3.5–7.2 mg/dL). Human immunodeficiency virus (HIV)-viral load as estimated by RT-PCR was 1,536,000 copies/ml (lowest limit of detection 40 copies/mL). Patient underwent explorative laparotomy, resection of small bowel, end to end anastomosis and omentectomy.

We received a segment of small intestine measuring 55 cm in length. On cutting open, an ulceroproliferative lesion measuring $7.5 \times 3 \times 1.5$ cm was identified. The lesion was involving the intestine circumferentially. Corresponding serosal surface was irregular. The fat along mesenteric border appears involved. Omentum measured $35 \times 5 \times 2$ cm and showed firm grey white areas.

Microscopic examination showed a tumor composed of large to intermediate sized lymphoid cells in sheets infiltrating the full thickness of bowel wall extending into adjacent fat with serosal involvement. The cells were large with round nuclei with small to prominent nucleoli and scanty cytoplasm (Fig. 2A). Some cells showed plasmacytoid morphology.

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Fig. 1 CECT scan of abdomen revealing circumferential diffuse wall thickening of jejunal loop and enlarged mesenteric lymph nodes

Table 1 Absolute CD3, CD4 and CD8 counts and percentages were assessed by flow cytometry (FCM) technique

Parameter	Value	Normal range
% CD3 + CD45 + Tcells	77	59–84 %
Absolute CD3 + Lymph count	1133	897–2341 cell/ μ l
% CD3 + CD4 + (T helper cells)	2	27–50 %
Absolute CD4 + lymph count	37	354–1110
% CD3 + CD8 + (T suppressor cells)	73	18–40 %
Absolute CD8 + lymph count	1067	296–1077/ μ l
CD4/CD8 ratio	0.03	0.72–2.10

Frequent mitotic figures including atypical ones, focal area of necrosis and tingible body macrophages giving starry sky appearance were also noted. Four out of twenty-six lymph nodes examined showed involvement (4/26). Mesenteric fat and omentum also showed lymphoma deposits. On immunohistochemistry, tumor cells were positive for leukocyte common antigen (LCA), MUM1, and CD138 (Fig. 2B–D). With CD138, tumor cells demonstrated cytoplasmic and perinuclear dot positivity. Ki-67 index was >90 % (Fig. 2E). Epstein–Barr virus (EBV) infection was detected positive by in situ hybridization for EBV-encoded RNA (EBER ISH) (Fig. 2F). Neoplastic cells were found to be negative for CD10, CD20, CD79a, Bcl2, Bcl6, PAX5, kappa & lambda light chains, CD3 and ALK1 (Fig. 3A–F). C-myc repeated twice elsewhere was negative. Serology for HHV-8 was not done. Bone marrow aspiration and biopsy were performed and revealed normal marrow with mild eosinophilia.

Discussion

Plasmablastic lymphoma (PBL) was first described as a specific clinicopathologic entity by Delecluse et al. [1] as an aggressive B cell lymphoma occurring in the oral cavity

arising in the context of HIV infection. However, in recent years, several cases of PBL have been reported at extra-oral sites, including the skin, [2] subcutaneous tissue, [3] stomach, [4] anal mucosa or perianal area [5], lung [6] lymph node [7], and other regions. Small intestine has rarely been reported as a site for PBL with only five cases [8–12] reported in the literature before, present case being the sixth case. Table 2 summarizes all the cases reported at this location so far including the present case.

Genetic and molecular mechanisms that may be involved in the pathogenesis of PBL are not very well understood. Infection of the neoplastic cells by EBV which is present in most of the cases, seems to have very important role in the tumorigenesis of HIV-associated PBL. HIV infection creates a conducive environment for chronic EBV infection, with a subsequent latency period which predisposes the B-cells transformed by EBV to become malignant [7].

The morphological differential diagnosis of PBL include Plasmablastic variant of multiple myeloma, Plasmablastic variant of Burkitt's lymphoma (BL), blastoid variant of mantle cell lymphoma (MCL), anaplastic large cell lymphoma kinase (ALK) positive diffuse large B-cell lymphoma (DLBCL), extracavitary primary effusion lymphoma (PEL), large B-cell lymphoma associated with human herpesvirus 8 (HHV-8) infection, Extramedullary myeloid tumor, poorly differentiated carcinoma and malignant melanoma.

Immunophenotypically, the neoplastic cells express a plasma cell phenotype including positivity for CD138, CD38, Vs38c and IRF4/MUM1 and are negative or only weakly positive for CD45, CD20 and PAX5. CD79a is positive in approximately 50–85 % of the cases. EMA and CD30 are frequently expressed. Ki67 index is usually very high (>90 %). EBV EBER in situ hybridization is positive in 60–75 % of the cases [13].

In our case, plasma cell phenotype of neoplastic cells was evident by positivity for CD138 and MUM1. Immunostain for CD138 demonstrated cytoplasmic and perinuclear dot positivity in neoplastic cells unlike usual membranous pattern of staining in cases of PBL. Granular and golgi region positivity with CD138 similar to that seen in our case has been described previously in plasma cells in cases of multiple myeloma [14]. In addition, negativity for CD20, CD79a and PAX5, CD10, Bcl2, Bcl6, ALK1 helped in ruling out B cell lymphomas like BL and blastoid variant of MCL and ALK + DLBCL. Our diagnosis was further supported by positivity for (EBV) infection detected by EBER ISH.

Rare HHV8-positive lymphomas indistinguishable from PEL present as solid tumour masses, and have been termed extracavitary PEL. These tumours with morphologic and phenotypic characteristics similar to PEL and occur in extranodal sites including the gastrointestinal tract, skin, lung. Morphologically, neoplastic cells show varied appearances

Fig. 2 **A** H&E stained section showing sheets of large to intermediate cells with round nuclei and small to prominent nucleoli and scanty cytoplasm ($\times 400$) **B–D** $\times 400$: neoplastic cells showing membranous positivity for LCA (**B**); nuclear positively for MUM1

(**C**); cytoplasmic and perinuclear dot positively for CD138 (**D**); **E** neoplastic cells showing very high Ki67 index (90 %) ($\times 400$) **F** tumor cells showing positivity by EBER ISH indicating EBV infection ($\times 400$)

Fig. 3 **A–F** Neoplastic cells showed negative staining with CD20, CD79A, PAX5, CD10, Bcl-2, Alk1 and Bcl-6 (not shown)

ranging from large immunoblastic or plasmablastic to anaplastic. A perinuclear hof consistent with plasmacytic differentiation may be seen. Lymphoma cells in PEL usually express CD45, but lack pan-B cell markers such as CD19, CD20 and CD79a. HLA-DR, CD30, CD38, Vs38c, CD138 and EMA are often demonstrable. Solid tumours

representing the extracavitary variant of PEL have a phenotype similar to PEL but express B-cell associated antigens and immunoglobulins (IG) slightly more often than cases of PEL [15] unlike in our case.

Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease (HHV8 MCD) is composed

Table 2 Summarizes cases of PBL reported in small intestine

S. no.	Year		HIV status	EBV	Presentation	IHC markers
1	Dong et al. [8]	38/F	Positive	Positive	Small bowel, perigastric and mesenteric LNs	CD45, CD138, IgG, κ light chain
2	Cha et al. [11]	60/M	Negative	Negative	Ulcerofungating mass over 10 cm segment in the proximal jejunum	Diffuse positivity for MUM1, EMA and λ light chains and focal positivity for CD79a; negative for CD3, CD20, CD30, CD34, CD45RO, CD56, CD99, CD117, and CD138
3	Olivas et al. [12]	36/M	Positive	Positive	Small bowel tumor causing chronic bleeding	NA
4	Wang et al. [9]	55/M	Negative	Negative	Small intestine with multi organ involvement	Diffuse positive for CD79a, CD138, CD10, CD38 and EMA, negative for CD45, CD20, CD3, CD30, ALK-1, Bcl-2, Bcl-6, Mum-1, CD56, HMB45, S-100, CD34, CD117 and cytokeratin.
5	Bahari et al. [10]	17/F	Not known	Not done	Small intestinal polyposis	LCA, EMA, CD138 positive and negative for CD3, CD20, CD30, ALK 1 and melan A
6	Present case		Positive	Positive	Small bowel, mesentric LNs, omentum	LCA,CD138,MUM1 and negative for CD10, CD20, CD79a, Bcl2, Bcl6, PAX5, Kappa, Lambda, CD3 and Alk1

of a monoclonal proliferation of HHV8-infected lymphoid cells resembling plasmablasts expressing IgM and arising in the setting of MCD and is usually associated with HIV infection. Neoplastic cells resemble plasmablasts arranged in confluent sheets and completely efface the lymph node or splenic architecture and might as well involve liver, lung, GIT as sometimes peripheral blood. This lymphoma must be distinguished from PBLs. The neoplastic cells are positive for HHV8 latent nuclear antigen 1 (LANA-1), negative for CD79a, CD138, and may or may not express CD20 and CD38. Epstein–Barr encoded RNA in situ hybridization (EBER ISH) is negative in contrast to our case where EBV infection was detected positive by EBER ISH; However IHC for HHV-8 LANA was not done.

Tumours with features of PBL may occur in patients with prior plasma cell neoplasm, including plasma cell myeloma (PCM). Such cases should be considered plasmablastic transformation of myeloma and must be distinguished from primary PBL. In many cases, the clinical features of the disease, such as osteolytic lesions, diffuse bone marrow involvement, and the presence of an M protein in the case of PCM or the frequent association with HIV infection, common manifestation in the oral cavity, and EBV positivity in PBL aid in arriving at the correct diagnosis. However, cases of PCM or PBL with atypical clinical features can pose significant diagnostic challenges [16].

Bone marrow involvement in PBL may be seen, but the clinical disease distribution is that of a lymphoma rather than a PCM. In our case BM examination revealed a normal marrow with mild eosinophilia.

Poorly differentiated carcinoma and malignant melanoma might be considered in the differential diagnosis of PBL at this location. Poorly differentiated carcinoma may

be differentiated from PBL according to its consistent immunological staining for cytokeratin. Malignant melanoma can be ruled out by using S-100 protein and HMB45.

PBL can also occur in HIV sero-negative patients. Cases of HIV-negative PBL have been mostly described after solid organ transplantation, in association with steroid therapy for autoimmune disease and some other types of immunosuppression. Castillo et al. [17] studied PBL arising in HIV-positive and HIV-negative individuals and concluded that these two groups have distinct clinical and pathological differences. Amongst the most notable clinical differences were that HIV positive PBL patients are younger, include a higher proportion of male cases, have more common oral involvement, and have a better response to chemotherapy than their HIV-negative counterparts.

MYC rearrangements are the most common recurrent structural chromosomal alteration identified in PBL, occurring in almost 50 % of the cases and the *IG* genes being the *MYC* partners in most tumors [18]. *MYC* rearrangement studies done in our case were found to be negative.

Conclusion

PBL is a distinct type of NHL, that most frequently affects the oral tissue of HIV-positive patients and that usually behaves very aggressively. Meticulous integration of clinical, morphological, phenotypic and molecular features is important for rendering the correct diagnosis which is quite difficult in the absence of an exhaustive workup. The diagnosis of such neoplasm might be even more challenging in the setting of

extra-oral localizations and in immunocompetent patients. The presence of a high proliferation index, extra nodal location, history of immune deficiency and the presence of EBV by in situ hybridization helps in reaching to a diagnosis in most cases. Authors suggest that larger studies be carried out on such cases in order to establish criteria's to differentiate PBL from plasmablastic myeloma and high grade lymphoma.

Conflict of interest The authors declare that they have no conflicts of interest.

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