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CD138-Negative Extra-oral Plasmablastic Lymphoma in an Immuno-competent Patient—Diagnostic Challenge: A Case Report and Review of Literature

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Abstract

Plasmablastic lymphoma (PBL) is an aggressive lymphoid neoplasm, classified as a distinct entity in 2017 World Health Organization classification. These are generally associated with immunodeficiency states especially in human immunodeficiency virus (HIV)-infected individuals with oral cavity as the most common site. PBL cases have morphologic and immunophenotypic features lying within the spectrum of large B-cell lymphoma and multiple myeloma with tumor cells displaying plasmacytic immunohistochemical markers; CD38, CD138, and IRF4/MUM1. Diagnosis poses a challenge when CD138 immunohistochemistry (IHC) is negative and the tumor presents at extra-oral sites in an immunocompetent patient.

We report an unusual case of CD138-negative PBL in an immunocompetent patient involving the gastrointestinal tract with extensive review of literature. The present case was a 51-year-old man who presented with abdominal fullness and pain. Imaging and endoscopy showed an extensive ulcero-proliferative lesion in the intestines involving the ascending colon to rectum and appendix. Small biopsy from the ascending colon was mistaken for an undifferentiated high-grade malignant neoplasm of uncertain lineage on limited IHC panel (negative CD45, Pan cytokeratin, Synaptophysin, CD20, CD3, but high Ki67).

After an extensive workup on resected hemicolectomy specimen combined with various hematological parameters, the final diagnosis of CD138-negative PBL was made, with three notable features; CD138 negativity, extraoral site, and HIV negativity, leading to delay in diagnosis. Lesson learnt from this case was that PBLs may be CD138-negative that can be missed if not included in the differential diagnosis of tumors with uncertain line of differentiation.

Keywords
- plasmablastic
- lymphoma
- CD138
- HIV
- EBV
- case report

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Introduction

Plasmablastic lymphoma (PBL) is an aggressive lymphoid neoplasm with plasmablastic or immunoblastic morphology and a terminal B cell differentiation phenotype predominantly presenting at extra-nodal sites.[1]

Oral cavity is the most common site of involvement, mostly in human immunodeficiency virus (HIV)-positive patients. However, these sometimes also develop in HIV-negative immunocompetent persons at extra-oral sites.[2,3] Cases of plasmacytoma, follicular lymphoma, and Richter's transformation of chronic lymphocytic leukemia can also develop into PBL.[4]

Diagnosis is comparatively easier when it is in the oral cavity and is Epstein–Barr virus (EBV)- and/or HIV-positive or there is history of immunodeficiency states like post-organ transplantation and elderly patients on long-term immunosuppressive agents.[2,3] However, PBL poses a diagnostic challenge when these arise in immunocompetent, HIV-negative individuals and at extra-oral sites.[4–6]

We report here a diagnostically challenging case of CD138-negative extra-oral PBL of gastrointestinal (GI) tract in an immunocompetent patient.

Case Report

A 51-year-old man was admitted with complaints of abdominal fullness and pain. Computed tomography (CT) enterography showed nodular, enhancing eccentric wall thickening involving terminal-most ileum, cecum, proximal ascending colon and appendix with associated luminal narrowing, pericolic fat stranding, and lymphadenopathy. Colonoscopy revealed a large ulcero-proliferative growth in ascending colon involving cecum with partial narrowing and multiple rectal ulcers suggesting possibility of a malignancy.

Endoscopy-guided biopsy from ascending colon showed small mucosal cores diffusely infiltrated by small- to medium-sized atypical cells with high nuclear cytoplasmic ratio, scant to moderate cytoplasm with cells arranged in vague acinar formation, suggestive of a poorly differentiated malignant neoplasm. Limited immunohistochemistry (IHC) panel on small biopsy was negative for epithelial, neuroendocrine, and preliminary lymphoma markers with high Ki67 proliferative index. Hence a provisional diagnosis of high-grade malignant neoplasm of uncertain lineage was informed to the clinician. Biopsy from rectal ulcers did not show any significant pathology.

Patient underwent laparoscopy-assisted right hemicolectomy with ileo-transverse colostomy.

Grossly a growth was identified in cecum measuring 14×12.5 cm situated 38 cm from proximal resection margin and 18 cm from distal resection margin; growth was reaching up to the mesenteric fat. Cut surface of the growth was solid gray-white, fleshy with intestinal wall thickening, and the tumor was also infiltrating the appendiceal wall (►**Fig. 1**).

Histopathological examination showed colonic wall infiltrated by a malignant tumor composed of sheets and singly dispersed medium- to large-sized cells. Individual tumor cells had scant cytoplasm with nuclei having irregular nuclear membrane, coarse chromatin, and prominent nucleoli (blastoid morphology). Many multinucleated cells and bizarre nuclear forms were also seen. Background showed frequent apoptosis, mitoses, and patchy areas of necrosis. The tumor was infiltrating the pericolic fat, attached appendix, and lymph nodes (►**Fig. 2**).

IHC showed tumor cells were negative for Pan cytokeratin, Synaptophysin, CD45, CD20, CD19, CD3, CD30, CD138, CD10, CD117, CD15, CD1a, CD34, CD5, CD56, CD68, CD99, CD21, CD23, ALK protein, melanoma markers (HMB 45, S100), and EBV (LMP1) and positive for Vimentin, BCL2, CD4, MUM1, Kappa, Lambda, CD79a, cMYC, and EBER-ISH. Ki67 proliferative index was more than 90% (►**Fig. 3** and ►**Table 1**).

Serum protein electrophoresis showed polyclonal expansion of Gamma globulins, no M spikes noted, and immunofixation did not show monoclonal bands.

Bone marrow examination was unremarkable. The smears did not show any plasmablasts.

Fig. 1 Gross images showing intestinal wall thickening with solid gray white fleshy growth. Growth is reaching up to the mesenteric fat.

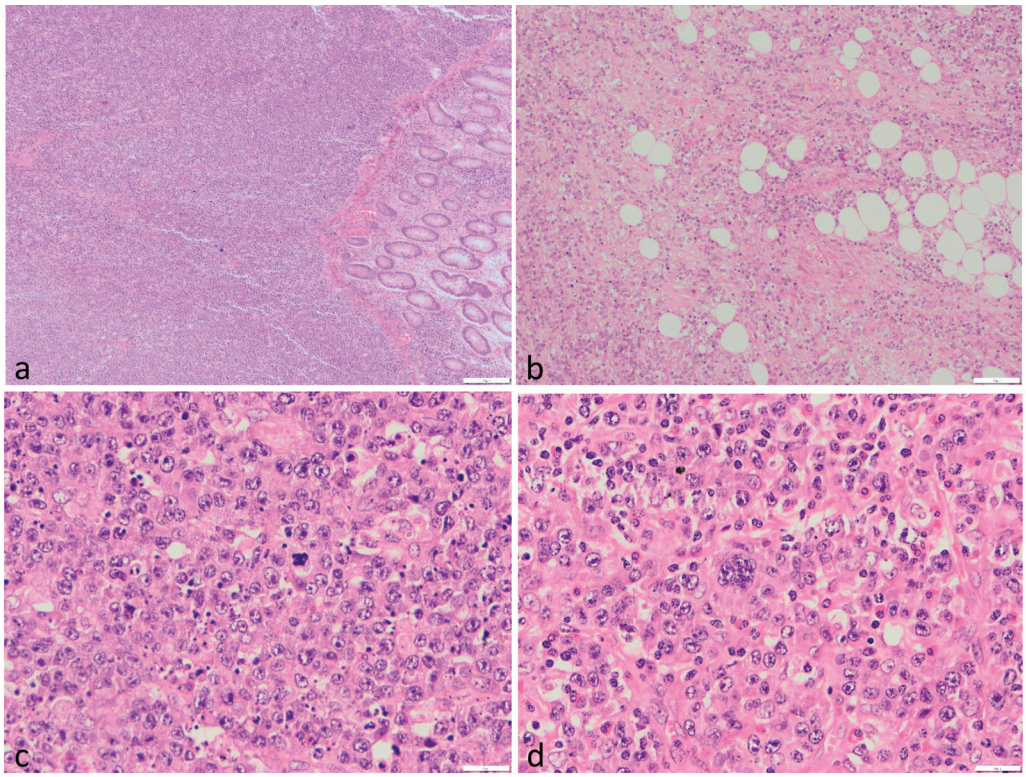

Fig. 2 (**a**) Colonic wall infiltrated by sheets of tumor cells (H&E, 40 ×). (**b**) Tumor is infiltrating the pericolic fat (H&E, 40 ×). (**c** and **d**) Singly dispersed medium to large-sized cells having irregular nuclear membrane, coarse chromatin, prominent nucleoli, and scant cytoplasm. Multinucleated cells and mitotic figures are noted (H&E, 400 ×).

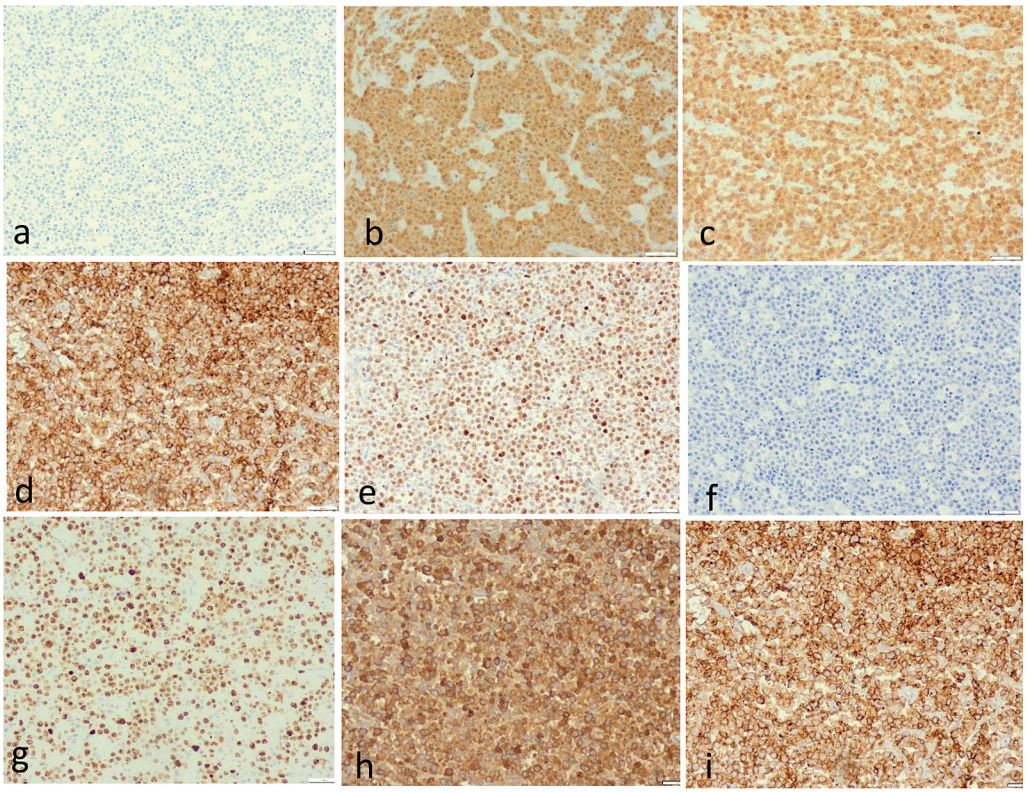

Fig. 3 Immunohistochemistry for CD20 is negative (**a**). CD79a, MUM-1, CD4, and cMYC are positive (**b–e**). CD138 is negative (**f**). Ki67 is >90% (**g**). Kappa and lambda are positive with equal intensity (**h, i**).

Table 1 Summarized details of immunohistochemistry markers

Epithelial/melanoma markers	Lymphoma/plasmacytoma markers	
Negative expression	**Negative expression**	**Positive expression**
Pan cytokeratin	LCA	**Vimentin**
Synaptophysin	CD3, CD5, CD56	**CD4**
S100	CD20, CD19, Pax 5	**Bcl2**
Melan A	CD30	**MUM1**
HMB 45	CD21, CD23	**CD79a**
	CD99	**EMA**
	CD68	**KAPPA = LAMBDA**
	EBV (LMP1)	**EBER-ISH**
	CD138	**cMYC**
	CD117, CD34	**K_i-67 >90%**

After correlation with all clinical, hematological, biochemical, radiological, and histomorphological features, extensive IHC, and exclusion of all probable differentials, a final diagnosis of "CD138-negative plasmablastic lymphoma with aberrant CD4 expression" was rendered.

Patient received three cycles of chemotherapy with Bendamustine + Polatuzumab. Fluorodeoxyglucose positron emission tomography (FDG-PET) done prior to initiating chemotherapy showed primarily extra-nodal disease in the colon. After three cycles, FDG-PET showed no substantial FDG avidity. Patient reported again with new findings in FDG-PET with omental involvement at 6 months review with FDG-PET (►**Fig. 4**).

Biopsy from the omental lesions showed tumor of similar morphology and immunophenotype to that in pre-chemotherapy specimen except the loss of CD79a expression this time.

Discussion

Most of the information about PBL comes from published case reports and series during past 10 years, with largely unknown etio-pathogenesis and prognosis.[6] PBL mostly affects males with a median age of 46 years in HIV-positive patients and 57 years in HIV-negative patients.[7] Our patient was 51-year-old HIV-negative and Epstein-BarrVirus-encoded small RNA (EBER-ISH)-positive.

Extensive literature search on CD138-negative plasmacytic neoplasms led us to a clue to the diagnosis of our current case of "CD138-negative plasmablastic lymphoma" from an excellent review by Choudhuri et al in their published case series of 42 cases of "CD138-negative PBLs," which included 21 cases of their own and 21 cases from multiple other institutions. The authors showed that CD138-negative PBL patients tend to have extraoral lesions, with much lower EBV infection rates. Amongst the extra-oral lesions, GI tract involvement was the second most common

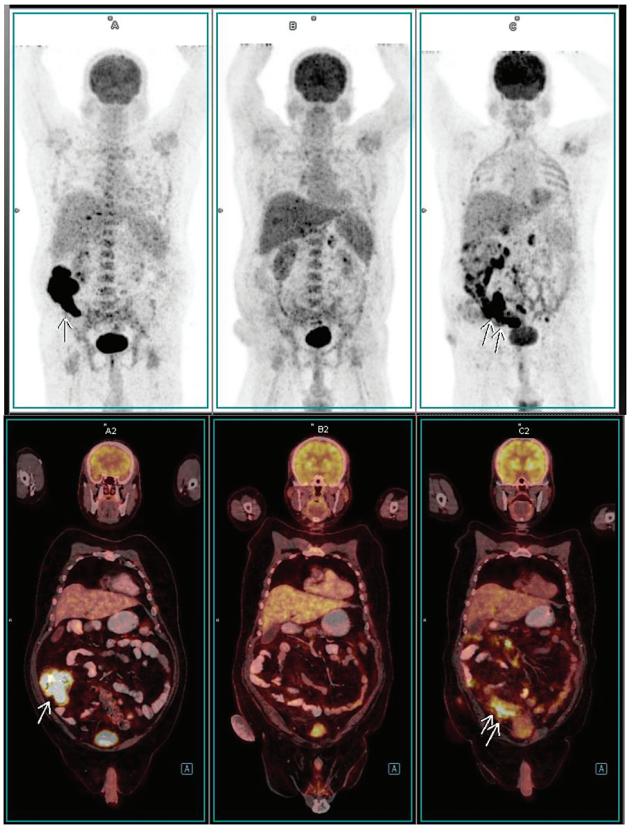

Fig. 4 PET CT scan. (**A**) Maximum intensity projection image—baseline, single arrow indicating disease in the lower abdomen (single arrow). (**B**) Maximum intensity projection image—3 months, no evidence of metabolically active disease. (**C**) Maximum intensity projection image—6 months, disease recurrence, predominantly in the lower abdomen (double arrow). Baseline, A2 (coronal): metabolically active disease in the terminal ileum, cecum, ascending colon, and ileocolic lymph nodes (single arrow). 3 Months: B2 (coronal): no evidence of metabolically active disease in the body, incisional site hernia. 6 Months: C2 (coronal): disease recurrence in the form of omental nodules, peritoneal thickening (double arrow).

extraoral site including stomach, cecum, rectum (13.3%; 4 of 30), and anal lesions (6.7%; 2 of 30) after lymph nodes (36.7%; 11 of 30) in their published series of 42 cases of CD138-negative PBLs.[5] Our case showed extensive involvement of GI tract, the second most common site of extraoral PBLs. However, only two out of six GI tract cases were HIV-negative and one had immunocompromised state due to chemotherapy.

Before 2017, the entity was described under various names. It was first described by Delecluse et al in 1997, with 16 cases of primary oral DLBCL (diffuse large B-cell lymphoma) displaying special immunophenotype, of which 15 cases were positive for HIV.[2] Subsequently, PBL was reclassified as HIV infection–associated lymphoma in 2001,[8] and further classified as acquired immunodeficiency syndrome-associated lymphoma after separating PBL from DLBCL.[9] In 2016 World Health Organization (WHO) classification, PBL was revised as an independent subtype of large B-cell lymphoma associated with HIV and EBV infections or other immunodeficiency states such as organ transplantation, long-term immunosuppressant use, or age-related immune decline.[10] PBL was classified as a distinct entity in 2017 WHO classification,[1] where the phrase "diffuse large B-cell lymphoma" (DLBCL) was modified to "large B-cell lymphoma" and has been retained in 5th edition also.

Morscio et al in their study of 277 cases, 50% of cases were HIV positive and another 14% had transplant related immunosuppression. Good number of cases in their series were HIV negative, immunocompetent. Further, the EBV-negative PBLs have been reported to have poorer prognosis as compared with EBV-positive PBLs.[3,11]

PBLs are believed to originate from plasmablast or immunoblast, an activated B lymphocyte that has undergone the process of somatic hypermutation and class switching recombination.[12] The plasmablastic morphology of tumor cells and aggressiveness of PBL have been reported to be associated with MYC gene rearrangements; the first cytogenetic abnormality identified in patients with PBL[8] playing a significant role in tumorigenesis in EBV-positive cases.[10]

PBL per se has been a diagnostic challenge with morphologic and immunophenotypic features lying within the spectrum of large B-cell lymphoma (LBCL) and multiple myeloma. Morphologically, they usually have large diffuse sheets of atypical cells with vesicular chromatin, prominent nucleoli, and moderate amount of basophilic cytoplasm.[12] The nuclei might be slightly eccentric, giving a clue for plasmacytic differentiation. The tumor cells display immunophenotypic markers of plasma cells, such as CD38, CD138, and IRF4/MUM1. Markers of mature B cells (CD19, CD20, and PAX5), common leukocyte antigen, and markers of mature T cells (CD2, CD3, CD5, and CD7) are not expressed or weakly expressed. CD79a is often expressed. Few cases show staining for CD4, CD10, CD30, and/or CD56.[12] EBER is positive in more than half of the cases.[3] Up to 10% cases are CD138-negative and diagnostically challenging, as was observed in our case.[3] Our case expressed CD79a and CD4.

Multiple myeloma with plasmablastic features, ALK-positive LBCL, and primary effusion lymphoma (extracavitary) are important differentials.[12] PBL has a high rate of recurrence and refractoriness to standard chemotherapy with an overall survival of 14 to 15 months in HIV-positive patients and 9 months in HIV-negative patients.[7] Our case recurred after 6 months of primary diagnosis, HIV-negative and EBER ISH-positive.

Usually, when we come across a poorly cohesive malignant tumor on morphology, we first choose a preliminary panel for lineage differentiation whether epithelial, mesenchymal, or hematopoietic. In the present case, the initial panel of markers, viz., CK, LCA, CD3, CD20, CD19, S100, Synaptophysin, and Melan A were all negative except Vimentin positivity and high Ki-67 proliferative index. These findings excluded carcinoma, melanoma, sarcoma, and neuroendocrine carcinoma. An extended panel as shown in the table showed MUM1, EMA, and CD79a positivity, indicating toward a B cell neoplasm lineage likely a plasmacytic neoplasm. However, IHC was extended to CD138 and to our surprise it showed negative expression adding to further diagnostic difficulty. CD138 was repeated thrice in different sections with controls but turned out negative. However, Kappa and Lambda showed almost equal intensity of staining pointing toward polyclonality, confirmed later on serum electrophoresis and immunofixation that showed polyclonal expansion of gamma globulins, no M spikes, and immunofixation did not show monoclonal bands.

Extensive diagnostic workup of our present case shows that sometimes limited-panel IHC and hurried decision by a surgical pathologist may lead to misdiagnosis. CD138-negative PBL can often be misdiagnosed if PBL is not in the initial differential diagnoses by morphology and/or if no further workup is done.[10] When it is CD45-positive, it can be misdiagnosed as undifferentiated hematopoietic malignant neoplasm because of negative expression of initial marker panel of CD3, CD20 (B & T cell markers), and CD138 (plasma cell marker). When it is CD45-negative, it can be misdiagnosed as an undifferentiated malignant neoplasm by surgical pathologists without further workup. Rarely can it be diagnosed as poorly differentiated carcinoma because of its positivity for EMA, as was observed in our case in initial small biopsy.

Our patient was given three cycles of Bendamustine + Polatuzumab. The decision to administer Polatuzumab–Bendamustine instead of intensive therapy by CHOP/DA-EPOCH regime in this patient was taken in view of the baseline strong CD79 expression on IHC and the associated comorbidities like age, poorly managed type 2 diabetes mellitus, hypertension, and postoperative poor performance status with impending risk of progression in to sub-acute intestinal obstruction. Therefore, these combinations were avoided that could have been unsafe for the patient. FDG-PET CT done prior to initiating chemotherapy showed primarily extra-nodal disease in the colon. After three cycles, FDG-PET showed no significant FDG avidity. However, the disease reappeared at 6 months of follow-up. Biopsy this time from

the omental lesions showed tumor of similar morphology and immune phenotype to that in pre-chemotherapy specimen except the loss of CD79a expression this time.

CD38 is another plasmacytic marker that was not available at the time of initial diagnosis.

At the time of omental biopsy from recurrence at 6 months, we could get the CD38 IHC outsourced and done on both the sections; first one prior to therapy and the second section from recurrence. Interestingly, both the sections showed CD38 positivity, further supporting our primary diagnosis of CD138-negative PBL. Biopsy from recurrence showed similar phenotype except loss of CD79a, which could possibly be therapy-related. The patient was again started the same chemotherapy regime as was done earlier.

Trial of Polatuzumab-Vedotin (Pola), a monoclonal antibody–drug combination, has recently been reported in two patients. The monoclonal antibody has been identified to target B cell receptor CD79b. It has been proposed as a possible targeted therapy in cases of relapse or refractory PBL cases that are CD79a/b IHC-positive, irrespective of their HIV or immunosuppression status.[13,14]

Our case however succumbed during the treatment after recurrence. Substantial number of cases needs to be included in the trial before arriving at a conclusive evidence of drug efficacy.

Conclusion

Presentation of PBL in extra-oral locations and CD138 negativity can cause diagnostic challenge. CD138-negative cases may be misdiagnosed if PBL is not in the initial differential diagnosis by morphology and CD38 IHC is not done.

Our only limitation in this case was the nonavailability of C38 antibody, though we could arrive at a correct diagnosis after exclusion of all possible mimickers after discussion in the tumor board with a strong multidisciplinary team and learning from the reported literature.

Take home message is that before starting any therapy or future follow-up therapy, correct histological diagnosis is essential in the era of targeted and personalized therapy. Surgical pathologist plays a pivotal role, who may have to walk an extra mile to get any additional IHC or molecular testing outsourced where required.

Authors' Contributions

S.K.: literature search, manuscript preparation, manuscript editing and review.
T.V.: concept, literature search.
A.D.: literature search, data acquisition.
N.S.: concept, manuscript review.
A.G.: concept, clinical review with follow-up, manuscript review.
K.R.: data acquisition.
S.K.V.: data acquisition, clinical content.
M.M.G.: concept, design, literature search, manuscript editing, and manuscript review.

Patient's Consent

Consent waiver form uploaded with reason for requesting consent waiver.

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None.

Conflict of Interest

None declared.

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