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Case Report

Oncology Section

Plasmablastic Myeloma- A Diagnostic Dilemma

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ABSTRACT

Plasmablastic neoplasms comprise various haematolymphoid tumours with plasmablastic morphology which includes Plasmablastic Myeloma (PBM) and Plasmablastic Lymphoma (PBL). Distinguishing between these two entities remains a major diagnostic challenge. In view of Epstein Barr Virus (EBV)-Encoded RNA (EBER) negativity, Human Immunodeficiency Virus (HIV) negativity, high Serum Free Light Chain (SFLC) assay and absence of hypermetabolic lymphadenopathy, a final diagnosis of PBM was made. This report is about a 55-year-old lady who presented with fatigue, significant loss of weight, and appetite. She had mild enlargement of the liver, spleen and no significant lymphadenopathy. There were atypical cells in peripheral blood. Bone marrow evaluation showed 51% atypical mononuclear cells. Flow cytometry was negative for acute leukaemia diagnostic markers. Immunohistochemistry (IHC) on the bone marrow biopsy revealed positivity for Cluster of Differentiation (CD) 138, Multiple Myeloma 1 (MUM1) with kappa light chain restriction and negative for EBER. The free light chain showed a kappa:lambda light chain ratio of 28,885 (0.26-1.65). The diagnosis of PBM was made and she was started on a daratumumab-based immunotherapy regimen. She achieved complete remission after induction with Measurable Residual Disease (MRD) <0.01%. She is presently doing well on follow-up with the disease in remission status.

Keywords: Multiple myeloma, Plasma cell disorders, Plasmablastic lymphoma

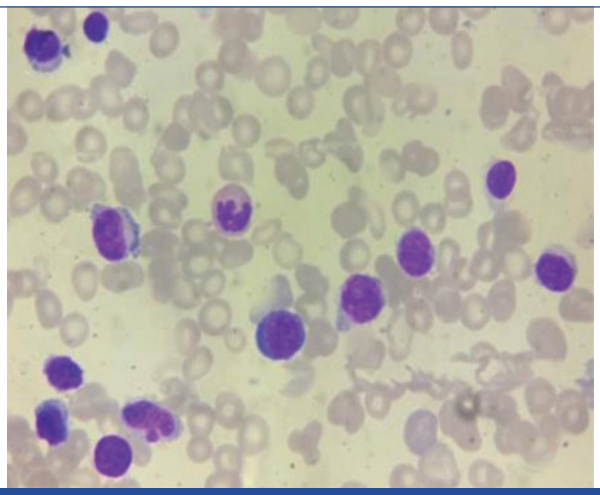
CASE REPORT

A 55-year-old female with no co-morbidities, presented with fatigue and leg pain for six months. She had a history of significant weight loss and loss of appetite. She did not have any significant medical complaints in the past. No significant family history was present. On clinical examination, there was pallor with right axillary lymphadenopathy and mild hepatosplenomegaly. Systemic examination of other systems was normal. On initial evaluation, the peripheral smear showed dimorphic anaemia and thrombocytopenia with 10% atypical cells (suspected blasts). Her metabolic parameters were within normal limits [Table/Fig-1]. She was initially suspected to have acute leukaemia. Bone marrow aspiration and biopsy revealed hypercellular marrow with 51% atypical mononuclear cells [Table/Fig-2,3].

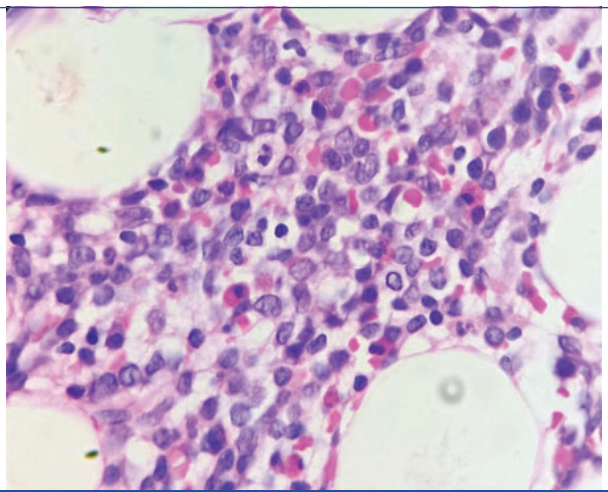
Laboratory parameter	Patients value	Reference value
Haemoglobin (gm/dL)	6.7	12-16
Total white cell count (cells/µL)	17,200	4000-11,000
Platelet count (cells/µL)	53,000	1,50,000-4,50,000
Serum creatinine (mg/dL)	0.8	0.6-1.1
Potassium (m.mol/L)	4.4	3.5-5.0
Calcium (mg/dL)	8.6	8.5-10.1
Uric acid (mg/dL)	1.9	2.6-6
Albumin (gm/L)	4.1	3.4-5.0
Globulin (gm/L)	2.0	2.0-3.5
Beta 2 microglobulin (mg/dL)	3.03	0.81-2.19
Free light chain (mg/L) Kappa	1580	3.30-19.4
Free light chain (mg/L) Lambda	0.054	5.71-26.3
Kappa/Lambda ratio	28884.8	0.26-1.65

[Table/Fig-1]: Baseline haematological and biochemical parameters.

Flow cytometry for atypical cells was negative for CD markers CD 34, CD 10, CD 19, CD 20, cytoplasmic CD 3, CD 4, CD 5, CD 7, CD 33, CD 117, Human Leukocyte Antigen-DR (HLA-DR) isotype, cytoplasmic Myeloperoxidase (cMPO) and TdT. CD 38 was dim positive and CD 200 was bright positive. Hence, acute leukaemia

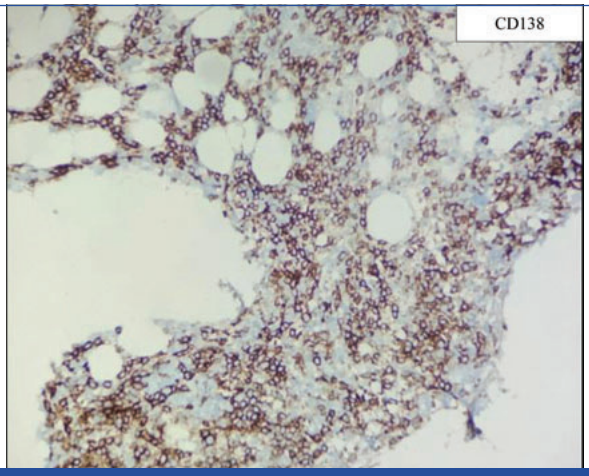


[Table/Fig-2]: Bone marrow aspiration revealed atypical mononuclear cells characterised by a high N:C ratio, scanty agranular blue cytoplasm, variable fine nuclear chromatin with inconspicuous to conspicuous nucleoli. Occasional plasmacytoid cells were seen (100X, Wright-Giemsa stain).

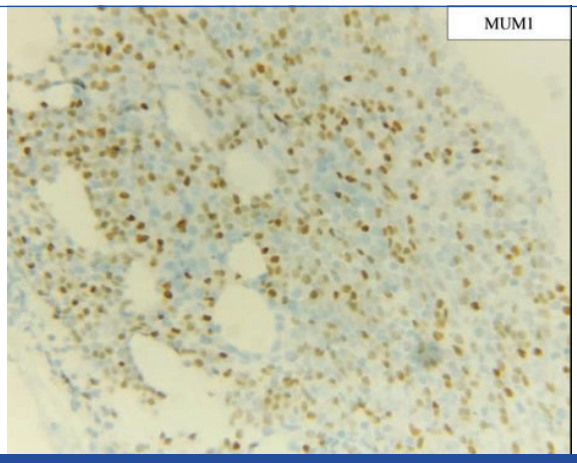


[Table/Fig-3]: Bone marrow biopsy show sheets of atypical mononuclear cells with irregular nuclear contour (100X, Haematoxylin and Eosin).

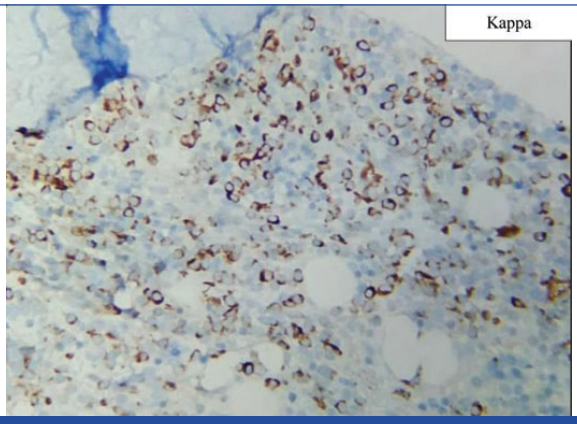
was ruled out. Immunohistochemistry (IHC) on bone marrow biopsy revealed sheets of tumour cells, positive for CD 138 [Table/Fig-4] and MUM1 [Table/Fig-5] with kappa light chain restriction [Table/Fig-6] and lambda negative [Table/Fig-7]. Tumour cells were negative for CD 20, CD 56, CD 117, E-cadherin, cyclin D1, ALK, and EMA with a Ki-67 index of 60 to 70%. Atypical cells were negative for EBER. Differential diagnosis of PBM and PBL was considered and evaluated further. Her serum immunofixation electrophoresis showed free kappa paraproteinemia and the free light chain assay showed a free kappa chain of 1580 mg/L and free lambda chain of 0.054 mg/L with a kappa: lambda light chain ratio of 28885 (0.26-1.65). Beta-2 microglobulin level was high at 3.03 mg/dL (0.8-2.19). Chromosomal analysis showed a normal karyotype (46 XX). The Fluorescence In-Situ Hybridisation (FISH) Panel revealed 1p32.3 deletion, 14q32.33 deletion, and 1q21 amplification. Positron Emission Tomography (PET) did not show any fluorodeoxyglucose (FDG) avid lesions or lytic bony lesions and her HIV test was negative. Hence, the final diagnosis of PBM was made considering the overall clinical and laboratory results.



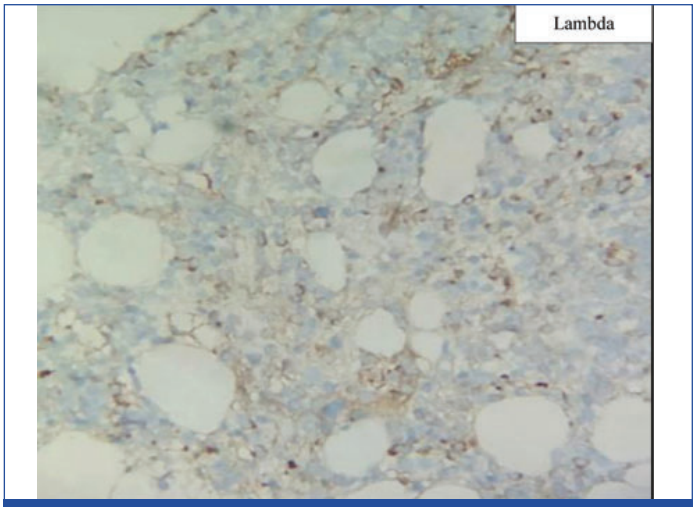
[Table/Fig-4]: IHC showing diffuse CD138 membrane positivity (20X).



[Table/Fig-5]: IHC showing MUM1 nuclear positivity (20X).



[Table/Fig-6]: IHC showing Kappa restriction (40X).



[Table/Fig-7]: IHC showing Lambda negativity (40X).

She was started on daratumumab, bortezomib, and dexamethasone therapy in view of high risk as per mSMART (Mayo Stratification for Myeloma and Risk adapted Therapy) classification [1]. After induction therapy (eight weekly injections), MRD by flow cytometry was negative (<0.01%). Following induction, she received consolidation with the same regimen once in two weeks for four more doses. Her free light chain ratio was normal (1.212). She received two further doses of maintenance of daratumumab therapy with intervals of one month between. Due to the COVID-19 pandemic, autologous cells were collected and cryopreserved with a plan to perform autologous transplantation at a later date.

She is on follow-up presently two years post-therapy with the latest free light chain assay showing a mild increase in kappa: lambda ratio of 27.194 with other blood parameters in the normal range. She did not want to undergo autologous transplantation presently, hence, she has been advised to follow-up every three months to monitor for any further progression of the disease.

DISCUSSION

Multiple Myeloma (MM) accounts for 1% of all malignancies and 10% of haematological malignancies [2]. Plasmablastic morphology is seen in approximately 10% of newly diagnosed myeloma patients [3]. It is a very rare and aggressive MM subtype, associated with an overall poor prognosis and survival [4,5]. The initial presentation can also be confused with acute leukaemia if there are circulating atypical blastoid cells in the peripheral blood [6]. Another frequent problem faced by clinician and pathologist is distinguishing it from PBL which is defined as a variant of Diffuse Large B-Cell Lymphoma (DLBCL). PBL is frequently associated with extramedullary disease, HIV and EBV positivity [7].

In the present case, the patient presented with isolated medullary disease and was negative for both HIV and EBV viruses. The distinction between PBM and PBL is often difficult, especially in EBV-negative tumours in immunocompetent adults. A combination of morphological, phenotypical and selected clinical findings can help in differentiating PBM from PBL. PBM and PBL are terminally differentiated plasma cells (B-cells) and are positive for CD138 and MUM-1, while negative for CD20 and PAX-5 [8,9].

A study by Vega F et al., found that the only significant difference between PBL and plasma cell myeloma was the presence of EBER, which was positive in all PBL cases tested and negative in all plasma cell myelomas [10]. In yet another study by Ahn JS et al., again the most useful histopathological parameter was a positive EBV in situ hybridisation [11]. Other factors such as associated lymphadenopathy and/or oral mass in the absence of complete myeloma-defining signs were used to favour a diagnosis of lymphoma [11]. Ki-67 may not help in distinguishing PBM from PML as both entities usually demonstrate high rates of proliferation [10].

In the present case, because of EBER negativity, high SFLC assay and absence of hypermetabolic lymphadenopathy a final diagnosis of PBM was made. In a post-transplant lymphoproliferative disorder case reported by Ramadas P et al., the authors highlight the diagnostic dilemma to differentiate between PBM and PBL [12]. Presence of a paraprotein with lambda restriction, lytic lesion and negativity for EBER supported PBM. Such case reports highlight the importance of multimodality diagnostic methods including clinical, radiological, morphological and immunophenotypic features to distinguish between these two conditions.

PBM is treated with various combinations of steroids, proteasome inhibitors, immunomodulatory agents, and alkylators while PBLs have been treated with lymphoma-based regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (hyper CVAD), infusional etoposide, vincristine and doxorubicin with bolus cyclophosphamide and prednisone (EPOCH) [13].

The index patient here was treated with a triple-drug regimen of daratumumab (anti-CD38 antibody), bortezomib, and dexamethasone combination therapy considering the high-risk nature of the disease. She achieved stringent Complete Response (sCR) and was counselled for autologous transplantation. High-dose therapy followed by autologous rescue is routinely considered in all eligible patients with PBM though the plasmablastic variant has been associated with poor prognosis even after autologous transplantation [14]. In a case report by Suarez-Londono JA et al., aggressive PBM with spinal cord involvement was treated with radiation and systemic treatment with a combination of daratumumab along with cyclophosphamide, doxorubicin, vincristine, and prednisone every three weeks, which resulted in partial response after three cycles [15]. Unfortunately, he decompensated due to severe sepsis secondary to pneumonia, leading to respiratory failure and death.

The outcomes of PBM have been traditionally very poor with a median survival of 1.9 years [5]. The newer drugs in the pipeline have the potential to increase the event free-and median survival rates. Daratumumab is a newer IgG1κ human monoclonal antibody against CD38 and inhibits the growth of tumour cells by inducing apoptosis. Daratumumab has been well studied in MM and is being used in newly diagnosed high-risk myeloma and relapsed/refractory myeloma [1]. As PBM and PBL express the CD38 marker there is interest in using this drug in these diseases though the experience has been limited to case reports. There are multiple case reports of daratumumab-based regimens in PBL and PBM with good results [16-19].

CONCLUSION(S)

The PBM is a diagnostic dilemma with overlapping clinical, morphological, and immunophenotypic features with that of PBL. It is often difficult to distinguish between these two entities but some clues such as EBV negativity, HIV negativity, high serum-free light chains, and lack of lymphadenopathy may swing the pendulum towards PBM diagnosis.

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