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The Odd One Out: CD138-Negative Plasma Cell Neoplasm

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Abstract

We report a case of a 36-year male patient with no previous comorbidity presenting with a history of fever, generalized weakness and body pains for the last six months. His bone marrow biopsy was done. Bone marrow was infiltrated with atypical looking plasma cells that were negative for CD138. Serum Protein electrophoresis and serum immunofixation were performed along with extensive panel of immunohistochemistry to exclude all the possible differential diagnosis. The results were suggestive of CD138 negative, lambda restricted plasma cell neoplasm.

Key words: Bone marrow biopsy, Immunohistochemistry, Plasma cell neoplasm.

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Introduction

Patients with plasma cell neoplasm can present with variable clinical manifestations. Diagnosis and classification of plasma cell neoplasm depend primarily on morphological features, immunophenotypic findings and the clinical manifestations(1). There are three groups of plasma cell disorders that can be based on their clinical presentation. First is multiple myeloma the most common disease, characterized by diffuse bone marrow infiltration and diverse manifestations of organ damage; second is localized plasma cell tumors, namely solitary plasmacytoma of bone and primary extraosseous/extramedullary plasmacytoma; and the third are the disorders primarily characterized by the consequences of abnormal immunoglobulin deposition, namely immunoglobulin light chain amyloidosis and non-amyloid light and/or heavy chain immunoglobulin deposition diseases(2).

CD138, also known as syndecan-1, is a heparin sulphate proteoglycan that is responsible for growth factor binding, cell–cell adhesion, apoptosis and control of myeloma cells. In normal PCs, CD138 is absent on plasmablasts but increases in expression in conjunction with PC maturation(3).

Loss or absence of CD138 expression is uncommon and can pose a diagnostic challenge, particularly when the morphologic features are atypical or when other lineage-specific markers are negative. In such cases, a broad immunohistochemical panel and correlation with serum protein studies become essential to avoid misclassification with entities such as plasmablastic lymphoma, diffuse large B-cell lymphoma with plasmacytic differentiation, or metastatic malignancy.

Here, we report a case of a young male patient with prolonged constitutional symptoms whose bone marrow biopsy revealed infiltration by atypical plasmacytoid cells that were CD138-negative but demonstrated lambda light chain restriction and CD38 positivity. This case highlights the diagnostic complexity of plasma cell neoplasms with aberrant immunophenotypic profiles and underscores the importance of a comprehensive, methodical approach in evaluating unusual presentations.

Case Report

A 36 years old male patient, resident of Quetta presented to Chughtai Lab with the history of fever and generalized weakness for past six months. There was a vague history of lethargy and generalized body aches. He also complained of undocumented weight loss in span of last 6 months. His drug history comprised use of analgesics for pain relief. There was no history of intake of any Hakeem medications. There was no history of blood transfusion. Patient was negative for viral markers (Hep B, Hep C, and HIV).

On examination, the patient was pale with no visceromegaly. His complete blood counts (CBC) showed: hemoglobin (Hb) of 11.2 g/dL, total leucocyte count (TLC) of 22×10^3 /µl, and platelets of 145×10^3 /µL. The red blood cell (RBC) indices were MCV: 110fL, MCH: 30.3pg and MCHC: 27.2g/dl The peripheral smear showed neutrophilic leukocytosis with occasional reactive lymphocytes and immature granulocytes. RBC morphology showed macrocytosis with anisocytosis and

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occasional nucleated red blood cells. Platelets were reduced on the smears and few platelet clumps were also seen.

Based on the findings of the peripheral smear, the decision was made to perform a bone marrow biopsy with the patient's consent. Bone marrow aspiration and bone marrow trephine biopsy were done under aseptic conditions.

The bone marrow aspirate showed prominence of atypical looking cells. These cells had abundant basophilic cytoplasm with perinuclear Hoff, high N:C ratio and prominent nucleoli. Some pleomorphic forms including multinucleated and multilobulated forms were also seen. Occasional mature plasma cells, erythroid and myeloid precursors were also seen. Morphologically these atypical cells appeared to belong to the plasmacytic lineage.

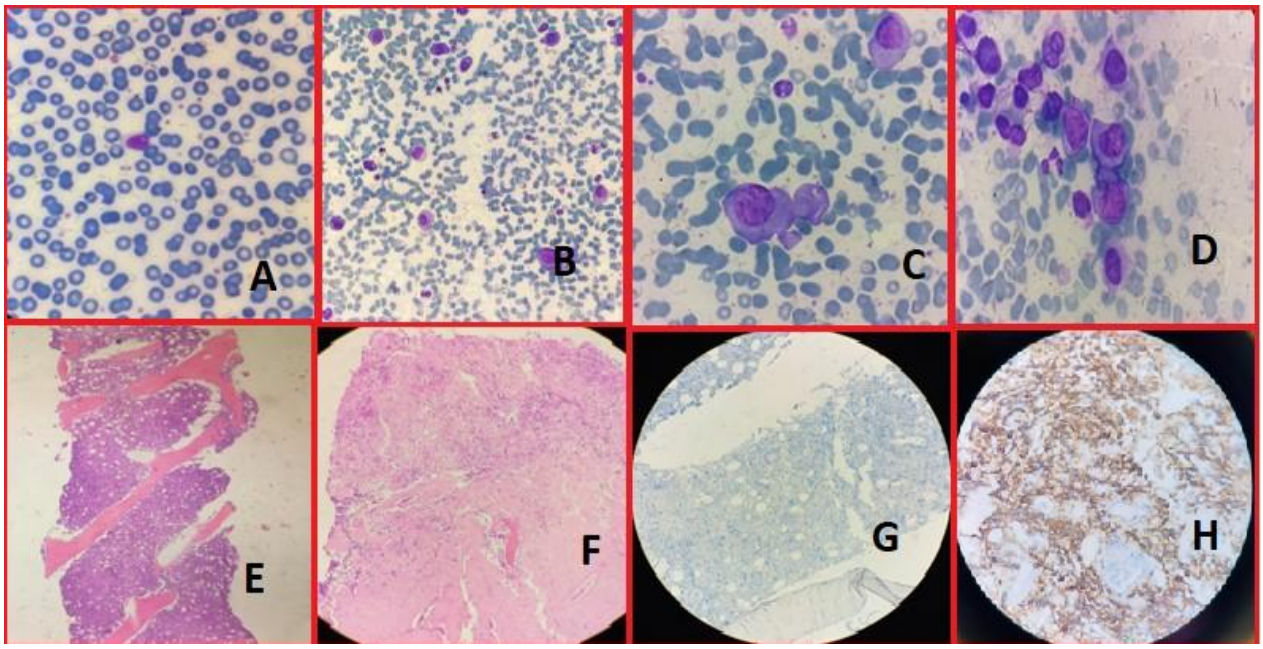

Figure 1: (A) Peripheral smear showing reactive lymphocyte (20X), (B) Hemodiluted bone marrow aspirate, (C) Plasmacytoid cells (40X), (D) Bone marrow aspirate (40X), (E) Hypercellular trephine (10X), (F) Trephine showing pale pink hyaline deposits, (G) CD138: Negative, (H) CD38: Positive.

Histological examination of trephine showed adequate length trephine biopsy with normal bony trabeculae and hypercellular bone marrow with focal areas of pale pink hyaline deposits. Trilineage haematopoiesis is seen at places. Bone marrow was infiltrated predominantly with atypical/ plasma cells which were present interstitially throughout the section examined. Focal areas showed scattered histiocytes.

To establish the lineage of these atypical cells, immunohistochemistry was performed on the trephine which showed negativity for CD20, CD3, CD138, CD19, CD56, PAX-5 and CD45. MUM1 results were inconclusive. To demonstrate pale pink focal hyaline change in marrow tissue, Congo red stain was used which showed apple green birefringence under polarized light.

As CD138 was negative, extended panel of immunohistochemistry was done to rule out other disorders like plasmablastic lymphoma and diffuse large b-cell lymphoma. C-MYC, BCL2, BCL6 were negative. Ki-67 showed 30-40% proliferation index thus ruling out our differential diagnosis.

Other differential diagnosis included plasmablastic myeloma, plasma cell myeloma and metastatic bone marrow. To rule out these CK, Synaptophysin, Chromogranin and CD34 were performed which all turned out to be negative.

Due to the strong suspicion of plasma cell neoplasm, CD38 was performed which was positive in infiltrating cells. The serum protein electrophoresis and immunofixation were performed which showed only lambda restriction.

Based on the findings of bone marrow biopsy, immunohistochemistry and serum electrophoresis and immunofixation we diagnosed the patient as ''CD138 negative, lambda restricted plasma cell neoplasm.''

Further work-up was suggested to the patient which included serum free light chain ratio, Diffusion weighted MRI/ Low dose whole body CT-Scan, renal function tests, serum calcium levels and cytogenetic analysis.

Unfortunately, the patient was lost to follow-up and his prognosis and treatment details could not be obtained.

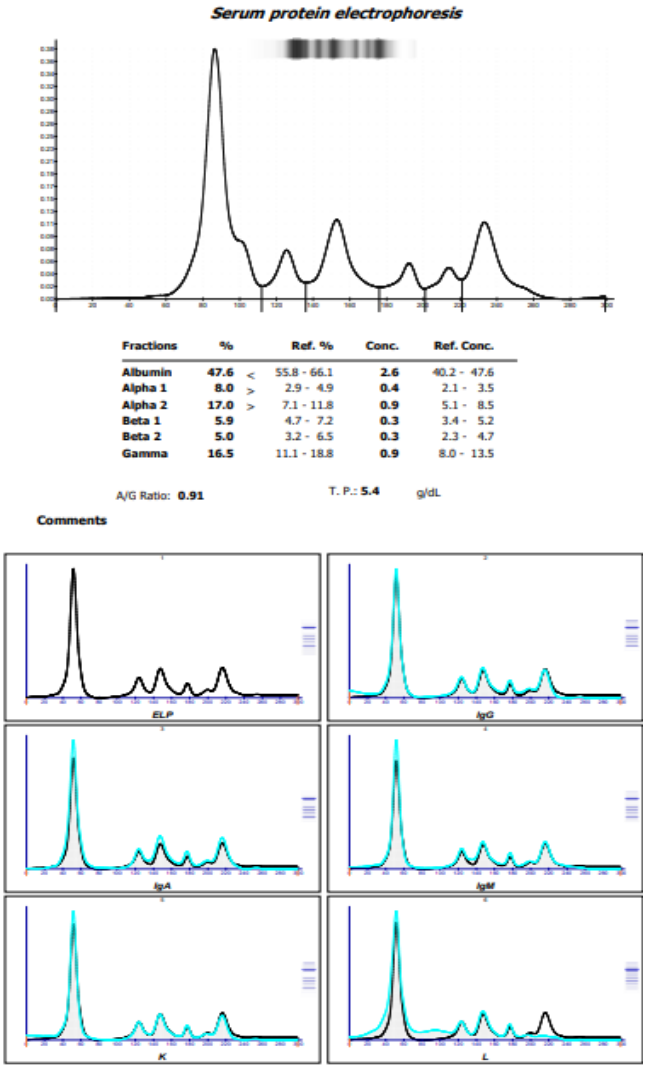

Figure 2. Serum protein electrophoresis and immunofixation showing lambda restriction

Discussion

Plasma cell neoplasms represent a heterogeneous group of clonal B-cell disorders characterized by abnormal proliferation of plasma cells and production of monoclonal immunoglobulins.

Normal PCs are nondividing cells and mostly undergo cell death after immunoglobulin (Ig) secretion. However, the malignant myeloma cells secrete Ig in an unregulated fashion, lose control of cell cycle and apoptosis and secrete antibody without activation. The plasmablast is the most immature form of PC and is characterized by CD138-, CD45++, while early PCs are characterized by CD138+ CD45+ and mature PCs are by CD138++ CD45- or weak positive. CD38 positivity and clonal Ig light chain expression is present at all stages(4).

The diagnostic evaluation of suspected plasma cell neoplasm typically integrates morphological assessment, immunophenotyping, and clinical features to classify these neoplasms accurately. Most plasma cell neoplasms, including multiple myeloma (MM) and related disorders, demonstrate strong expression of plasma cell-associated antigens such as CD38 and CD138 on immunohistochemistry and flow cytometry, along with light chain restriction on Immunohistochemstry, serum and/or urine studies (e.g., immunofixation) consistent with clonality(5,6).

In this report, we describe a 36-year-old male whose bone marrow shows infiltration by atypical plasmacytoid cells that were CD138-negative, lambda light chain restricted, and CD38 positive. The absence of CD138 expression, a membrane heparan sulfate proteoglycan considered a canonical plasma cell marker, complicated the initial diagnostic interpretation. CD138 (syndecan-1) is highly expressed in mature plasma cells and is conventionally used in bone marrow biopsies to quantify plasma cell burden and aid in the diagnosis of plasma cell neoplasms(3).

However, CD138 negativity in plasma cell neoplasms is increasingly recognized as a rare immunophenotypic variant that can pose significant diagnostic challenges. Several case reports have documented plasma cell myeloma and anaplastic plasma cell neoplasms with absent CD138 expression, requiring extended panels of markers such as CD38, MUM1, light chain assessment, and exclusion of B-cell or non-hematopoietic neoplasms to avoid misclassification(7,8). For instance, Setiadi et al. reported a CD138-negative plasma cell myeloma mimicking a mature B-cell lymphoproliferative disorder

and highlighted the importance of ancillary testing for accurate diagnosis(5).

CD138-negative plasma cells may represent a more immature or clonogenic subpopulation with higher proliferative potential and “stem-like” properties, which might influence disease behavior and response to therapy. In vitro studies have identified CD138-negative plasma cells with greater proliferative activity compared to their CD138-positive counterparts, suggesting potential implications for disease progression and therapeutic resistance(4,9).

Immunophenotypically, neoplastic plasma cells in classic myeloma typically exhibit bright CD38 and CD138 expression, cytoplasmic kappa or lambda light chain restriction, and often lose B-cell markers such as CD19 and CD20(10). The lack of CD138 expression in our patient’s marrow biopsy required careful exclusion of other entities that can present with plasmacytoid morphology, including lymphomas with plasmacytic differentiation, plasmablastic lymphoma, and non-hematopoietic tumors. Extensive immunohistochemical panels (negative CD20, CD3, PAX5, CD45, CD56, BCL2, BCL6, and CK/Synaptophysin/Chromogranin) ruled out alternate diagnoses, and strong CD38 expression with lambda restriction supported a clonal plasma cell population.

Chaudari et al presented a rare case of anaplastic myeloma with cardiovascular involvement. This patient did not have any typical clinical features of myeloma, except lytic lesion in the femur. His cardiac biopsy showed sheets of anaplastic cells with multinucleation. The initial immunohistochemical panel was negative for CD3, CD20, CD138, AE1/3, and kappa. However, it was positive for lambda. This led to an extended panel which showed positivity for CD79a and MUM1 and negative for LMP-1, HHV-8, CD43, CD117, CD56, and CD30. The flow cytometry on the bone marrow showed a small population of atypical cells positive for CD38 and negative for CD138 with lambda restriction. This case highlighted the importance of need to test for plasma cell markers when myeloma is suspected as to avoid missing atypical plasma cells which maybe CD38+/CD138-(7).

This case underscores several important clinical and diagnostic principles. First, it highlights that CD138 negativity does not exclude a plasma cell neoplasm, and reliance on a single marker can lead to misdiagnosis if not interpreted in the context of morphology and additional markers. Comprehensive panels including CD38, CD79a, MUM1, and light chain restriction are critical when the immunophenotype is atypical(1).

Additionally, the inability to obtain complete staging and follow-up data, including serum free light chain assays, imaging for lytic lesions, and cytogenetic analysis, limits full risk stratification and therapeutic planning in this patient. Future studies are needed to better delineate the frequency, clinical relevance, and optimal management strategies for plasma cell neoplasms with expression of aberrant marker expression, particularly in younger patients with atypical presentations.

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