Case Report

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Pathology Section

Waldenstrom Macroglobulinaemia with Signet Ring Cells: A Case Report

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ABSTRACT

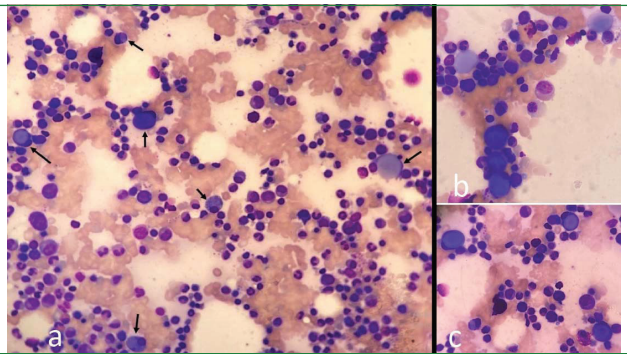
Waldenstrom Macroglobulinemia (WM) is an indolent lymphoproliferative disorder characterised by Immunoglobulin M (IgM) production and neoplastic lymphoid infiltrate. The morphology of the neoplastic cells show spectrum of maturation characterised by small lymphocytes, lymphoplasmacytoid cells and plasma cells. The infiltrate is predominantly lymphoid with relatively small population of plasma cells. The plasma cell morphology is commonly of mature type with basophilic cytoplasm, eccentric nucleus with clumped chromatin and perinuclear halo (hof). But incidence of signet ring cells in WM is very rare and only one case has been reported till date. Here, authors report an interesting case of a 61-year-old man who presented with on and off chest pain and later diagnosed as WM with signet ring cells. On examination, the patient was found to have anaemia and lymphadenopathy. Bone marrow aspirate cytology showed hypercellular particles and scattered signet ring like plasma cells with large globular cytoplasmic inclusions. Flow Cytometry (FCM) established the diagnosis by demonstrating the clonal nature of plasma cells and B-lymphoid cells. Immunofixation confirmed the presence of monoclonal protein of IgM lambda type. The cytoplasmic content in these signet ring plasma cells is probably the accumulated IgM due to the defect in releasing. Clustering of these signet ring cells in marrow may raise a suspicion of metastatic adenocarcinoma and should not be misinterpreted.

Keywords: Bone marrow examination, Flow cytometry, Lymphoplasmacytic lymphoma, Plasma cells

CASE REPORT

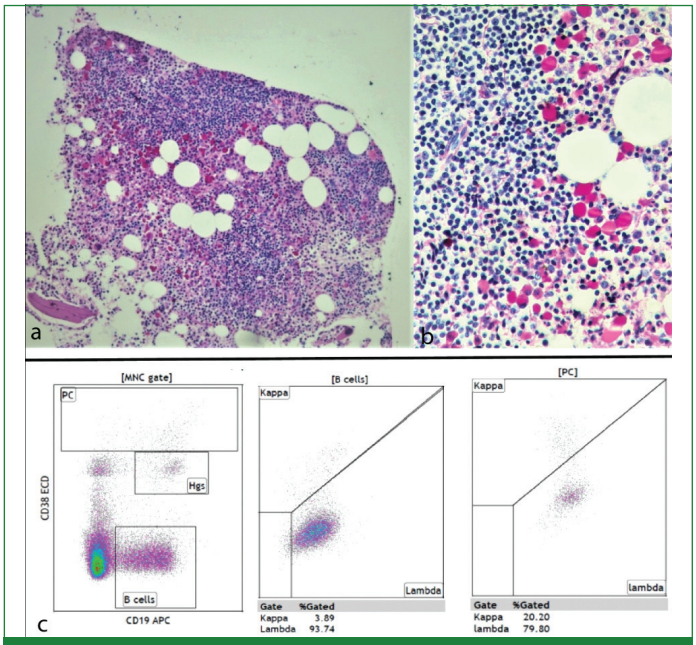
A 61-year-old gentleman presented to the Cardiology Department with history of chest pain on and off for three months. General examination showed mild pallor and an enlarged right axillary lymph node of approximately 1×0.5 cm^2. Examination of heart, lungs and abdomen was unremarkable. His routine blood and urine investigations were all normal, except Haemoglobin (Hb) of 8.4 g/dL and Erythrocyte Sedimentation Rate (ESR) of 63 mm/hr. Ultrasonogram showed mild hepatosplenomegaly. Coronary angiogram revealed triple vessel disease with 80% stenosis. Microcytic hypochromic anaemia with rouleaux formation and occasional atypical lymphocytes were found in the peripheral blood smear. Serum ferritin, vitamin B12, folate and Lactate Dehydrogenase (LDH) levels were within normal limits. The Hb electrophroresis and coomb's test were also unremarkable.

Bone marrow aspiration cytology showed hypercellular particles and scattered signet ring like plasma cells with large cytoplasmic inclusions [Table/Fig-1a-c]. Mild lymphocytosis was also noted. Trephine biopsy also showed neoplastic lymphoid nodules and increased plasma cells with signet ring like morphology [Table/Fig-2a,b]. Immunophenotyping (IPT) was performed with Beckman Coulter Navios flow cytometer, which is a three laser, ten colour instrument.



[Table/Fig-1]: a) Bone marrow aspirate cytology arrows showing signet ring cells (100X, Wright stain); b) Bone marrow aspirate cytology arrows showing signet ring cells (400X, Wright stain); c) Bone marrow aspirate cytology arrows showing signet ring cells (1000X, Wright stain).

The bone marrow aspirate sample was processed according to bulk lyse-stain-wash protocol using Beckman Coulter reagents. The IPT showed cytoplasmic lambda light chain restricted clonal plasma cells expressing bright CD38 and CD19 along with a clonal B-lymphoid population expressing moderate CD19, CD20, Bright IgM, CD43 and dim CD200 and negative for CD38 and FMC7 [Table/Fig-2c].



[Table/Fig-2]: a) Bone marrow trephine biopsy section showing neoplastic lymphoid aggregate and signet ring cells (100X, Periodic Acid-Schiff (PAS) stain); b) Bone marrow trephine biopsy section showing neoplastic lymphoid aggregate and signet ring cells (400X, PAS stain); c) Flow cytometry plots showing neoplastic clonal B-cells and plasma cells.

A diagnosis of Lymphoplasmacytic Lymphoma (LPL) was made. Electrophoresis showed presence of M protein in Beta 2 globulin region and immunoglobulin profile showed a serum IgM of more than 530 mg/dL. Hence, a final diagnosis of Waldenstrom Macroglobulinaemia (WM) was made. The Positron Emission

Tomography-Computed Tomography (PET-CT) showed no other hypermetabolic areas expect the marrow. The patient was started on Dexamethasone, Rituximab and Methotrexate (DRC) regimen. Coronary Artery Bypass Graft (CABG) surgery was planned after hyperviscosity subsides.

DISCUSSION

The Waldenstrom Macroglobulinemia (WM) is a neoplasm arising from the post germinal center B-cells, constituting less than 5% of non Hodgkin's Lymphoma and 1-2% of haematolymphoid malignancies. The neoplastic cells of WM show variable morphology with predominantly small lymphocytes and lymphoplasmacytoid B-Cells (WM-BC) and a small population of Plasma Cells (WM-PC). The WM presenting with signet ring like plasma cells is rare. This is the second WM case reported with signet ring cells only after Molero T et al., who described the first case [1]. Signet ring morphology is reported commonly in myelomas and follicular lymphomas, but also very rarely in T-cell, immunoblastic, Burkitt like, Mucosa Associated Lymphoid Tissue (MALT) and large cell lymphomas [2,3]. Many of these cases have been reported in biopsy specimens. Gore CR et al., reported signet ring cells in follicular lymphoma in lymph node cytology and confirmed it with biopsy [4]. Though it's clear that the cytoplasmic content in this scenario is IgM, the nature of cytoplasmic inclusions in signet ring cells of other lymphoma is not clear. The cause for these large inclusions may be due to the defect in releasing the immunoglobulin generated, resulting in accumulation.

Sometimes the distinction of LPL from other small B-cell lymphoma may be challenging and IPT along with MYD88L265P mutation analysis will be complimentary for establishing the diagnosis. On the other end it may also mimic myeloma, when the plasma cells predominates at diagnosis. These cases have poorer prognosis compared to those with less than 10% plasma cells. The IPT is very helpful in the diagnosis of LPL and also in differentiating it from myeloma. The PCs of LPL are CD19 positive, CD56 negative and show a continuum in expression of CD138 with neoplastic B-cells. They also show a similar light chain restriction as in the neoplastic B-cells. The presenting complaints are due to: (i) marrow infiltration by neoplastic B-cells leading to cytopenias specially anaemia; and (ii) hypersecretion of IgM protein leading to hyperviscosity causing coagulopathy, visual problems and peripheral neuropathy. Though symptoms due to marrow infiltration correlates with the burden of lymphoplasmacytic population at diagnosis, studies have shown that hyperviscosity correlates better with the plasma cell component [5].

The significance of signet ring cells in LPL is still to be unravelled. Clustering of these signet ring cells in marrow may raise a suspicion of metastatic adenocarcinoma [6,7]. The burden of plasma cell population correlates better with the IgM levels than the lymphoplasmacytic population. Current WM treatment protocol targets the WM-BC clone and is inefficient in eradicating the neoplastic WM-PC clone. It focuses more on clone specific therapy like rituximab and atumumab (anti CD52) targeting the neoplastic WM-BC cell population. The WM-PC clone is more resistant to the above targeted regimens [8,9]. This results in poor remission and persistence of neoplastic plasma cells. This WM-PC may expand and present later with predominant plasma cell population mimicking myeloma [10,11]. The IgM paraproteinemia presents without evidence of WM-BC population during post treatment follow-up of these cases. A better effective therapy targeting the Plasma Cells (PC) component simultaneously may give better outcome.

CONCLUSION(S)

Pathologist should be aware that plasma cells may present with signet ring morphology and should not be mistaken for metastatic adenocarcinoma. These cases should be properly investigated with ancillary techniques like flow cytometry and immunohistochemistry for establishing the correct diagnosis.

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