Case Report

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Pathology Section

Persistent Monotypic Plasma Cells with Absence of Neoplastic B Cell Component in a Treated Case of Waldenström Macroglobulinemia: A Sign of Residual Disease?

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ABSTRACT

Waldenström macroglobulinemia (WM) is a rare indolent variant of non- Hodgkin's lymphoma characterised by lymphoplasmacytic infiltration of bone marrow (BM) associated with a serum IgM paraprotein. The WHO classification states that the neoplastic cells of WM usually are positive for monotypic surface immunoglobulin light chain, IgM, CD19, and CD20 and are negative for CD5, CD10, and CD23. Serum monoclonal protein detection by serum protein electrophoresis and bone marrow aspirate and biopsy are required for WM diagnosis, monitoring and response assessment. Pathologist must dissuade themselves from making a hasty decision on calling a complete response in WM when neoplastic B cell component is absent. Evaluation of clonality of any residual plasma cells must be done in all cases of WM to evaluate the presence and extent of residual or persistent disease. Role of additional therapy targeted at these residual plasma cells in WM can be evaluated as tools for achieving complete remission. Herein, we present a case of WM with residual monotypic plasmacytosis in BM, without B lymphocytes after therapy.

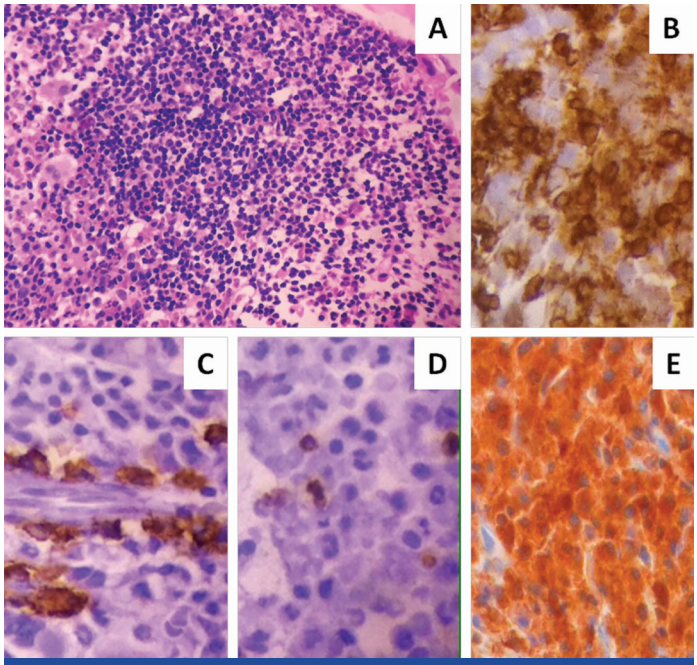
Keywords: Monotypic plasma cells, Residual disease, Waldenström macroglobulinemia

CASE REPORT

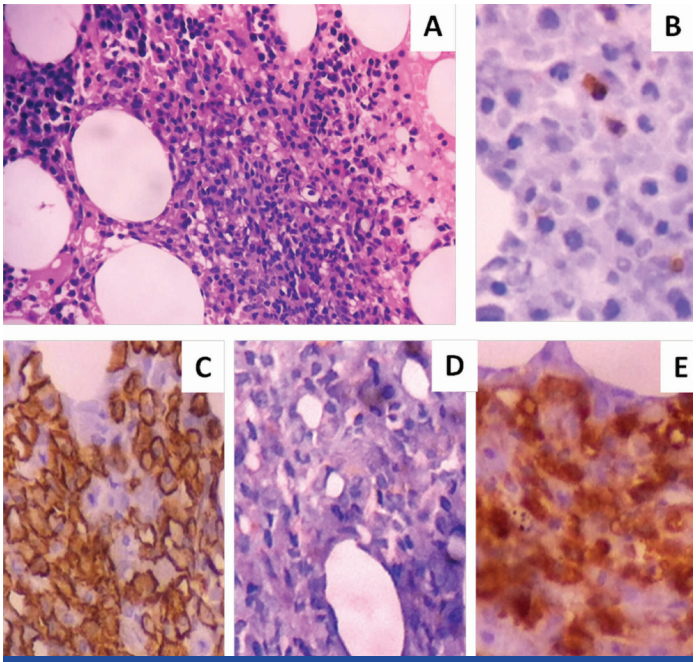
A 57-year-old male, known case of chronic inflammatory demyelinating polyneuropathy with POEMS Syndrome (Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) presented with generalized weakness. Peripheral blood smear findings were within normal limits. Bone marrow smears showed mild increase in lymphoid cells including many lymphoplasmacytoid cells and increased in plasma cells. Bone marrow biopsy revealed hypercellular marrow spaces with small and large lymphoid aggregates interstitially and in paratrabecular location along with few plasma cell clusters. On immunohistochemistry, these lymphoid aggregates were CD20 positive with lambda restriction, and CD 56, CD5 and CD10 negative [Table/Fig-1a-e]. Serum protein electrophoresis and immunofixation showed monoclonal M band of Ig M lambda type constituting 1.4 g/dl. Overall features were consistent with WM. The patient was started on Bendamustine and Rituximab chemotherapy. Disease status was evaluated after 4 cycles of chemotherapy. Peripheral blood smear was within normal limit with bone marrow smear showing normal marrow components with approximately 25% lymphoid cells and 3% plasma cells. Bone marrow biopsy revealed small interstitial aggregates of CD3 positive lymphoid cells along with many plasma cell clusters. CD20 and PAX 5 were negative. CD138 showed multiple aggregates of plasma cells with lambda light chain restriction, suggesting residual monotypic plasma cells [Table/Fig-2a-e].The patient is on regular follow up since 14 mnth. Clinically, besides persistence of neurological symptoms, he does not show any signs of disease progression.

DISCUSSION

Waldenstrom's macroglobulinemia is characterized by a monoclonal expansion of predominantly small B-lymphocytes with variable plasmacytoid differentiation [1]. Serum monoclonal protein detection by serum protein electrophoresis and bone marrow aspirate and biopsy are the required for WM diagnosis, monitoring and response assessment. Differential diagnosis of WM includes other Ig M secreting B-cell lymphoproliferative disorders (mantle cell lymphoma, B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma and marginal zone lymphoma) and plasma cell neoplasms (MGUS and multiple myeloma). Histopathological examination



[Table/Fig-1a-e]: Waldenström macroglobulinemia before therapy. The bone marrow biopsy (A, H&E, ×400) showed hypercellular bone marrow with lymphoid aggregates and increased interstitial plasma cells. CD20 was positive by immunohistochemical analysis (B, ×400) in these lymphoid aggregates, while staining for CD138 (C, ×400) showed few scattered clusters of plasma cells. Most of the plasma cells and lymphocytes were negative for immunoglobulin κ light chain (D ×400) and positive for immunoglobulin λ (E, ×400)



[Table/Fig-2a-e]: Residual monotypic plasma cells after therapy. Bone marrow biopsy showed rare lymphoid aggregates with increased in plasma cells (A, H&E, ×400). CD 20 immunostain showed very rare B lymphocytes (B, ×400). Plasma cell clusters are positive for CD138 (C, ×400). The plasma cells immunoglobulin κ light chain (D, ×400) and were negative for positive for immunoglobulin λ (E, ×400)

along with Immunohistochemistry and Immunophenotyping are important for differentiating the above entities. The pattern of bone marrow infiltration may be diffuse, interstitial, or nodular and is composed of small lymphocytes, plasmacytoid lymphocytes, and plasma cells in variable percentages. This should be supported by immunophenotypic studies (flow cytometry and/or immunohistochemistry). By flow cytometric immunophenotyping two distinct subsets of cells can be identified in WM: monotypic B lymphocytes that are surface IgM+, CD19+,CD20+,CD22+,CD79+ and CD138– and monotypic plasma cells that are cytoplasmic IgM+, CD38+,CD138+, and mostly negative for B cell antigens. Other antigens which are expressed in WM cells include CD25, CD27, FMC7, BCL-2, CD52 and PAX-5. Expression of CD5, CD10, CD11c, CD23 and CD103 is very uncommon [2,3]. Rituximab is an anti-CD20 monoclonal antibody that has emerged as a useful chemotherapeutic agent in treating B cell lymphoma. CD20 is expressed consistently in WM, thereby providing rationale for its use [4]. At the end of therapy, responses in serum M protein were typically delayed, but bone marrow responses occurred promptly as no detectable clonal B cells in the bone marrow. Persistent monoclonal plasma cells were, however, identified by CD138 and immunoglobulin light chain immunohistochemistry, explaining the persistence of serum M protein, as found in our case. Barakat et al., also described 10 cases of WM with persistent monotypic plasma cells in bone marrow after therapy with absence of clonal B cells [5]. Varghese et al., reported the persistence of low level plasma cell clones in 5 patients with WM after chemotherapy using fludarabine alone or in combination with cyclophosphamide [6]. Goteri et al., described 2 patients with LPL who had clusters of monotypic plasma cells in BM after rituximab therapy [7]. Rituximab and/or other chemotherapeutic agents successfully eliminated the clonal B lymphocytes of WM but were unable to eliminate clonal plasma cells, which are more resistant to chemotherapy. In response evaluation of WM, both clonal B cells and plasma cells should be assessed by combining serum electrophoresis and bone marrow examination with immunohistochemistry. Bone marrow must be evaluated for residual monotypic plasma cells in absence of monoclonal B lymphoid cells. This persistence of monotypic plasma cells explain the delayed response of Ig M component by protein electrophoresis and may suggest a combination of plasma cell targeted therapy in WM to eliminate these cells and achieve complete remission.

CONCLUSION

To conclude, pathologist must dissuade themselves from making a hasty decision on calling a complete response when neoplastic B cell component is absent. Evaluation of clonality of any residual plasma cells must be done in all cases to evaluate the presence and extent of residual or persistent disease. Role of additional therapy targeted at these residual plasma cells can be evaluated as tools for achieving complete remission.

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