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Severe Thrombocytopenia in a Splenectomized Patient with Waldenstrom Macroglobulinemia

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Abstract *Introduction*. Patients with Waldenström macroglobulinemia (WM) can present with a diverse array of findings. One such manifestation is autoimmune thrombocytopenia which may occur as a consequence of autoantibody activity against platelets. *Case Presentation*. We report a case of a 57-year- old African American male who presented with a two-week history of fatigue, recurrent epistaxes and gingival hemorrhage. His past medical history was significant for liver cirrhosis secondary to Hepatitis C and a splenectomy 2 years prior for traumatic rupture of the spleen. Complete blood count demonstrated platelets 3 $x10^9$/l. Serum protein electrophoresis and immunofixation demonstrated an IgM Lambda monoclonal paraprotein of 7.6 g/dl. Serum viscosity was elevated at 10.8 cP. He was diagnosed with a hyperviscosity syndrome secondary to suspected Waldenstrom's Macroglobulinemia (WM) and plasmapheresis was emergently initiated due to bilateral retinal vein thrombosis. A bone marrow aspirate and biopsy revealed an interstitial plasmacytoid proliferation which was CD138 positive and lambda restricted. With plasmapheresis, his serum IgM was lowered to less than 4 g/dl and his serum viscosity decreased to 4.4 cP. A weekly regimen of bortezomib, dexamethasone and rituximab (BDR) was used for treatment. On follow-up three months later he continued on the weekly BDR regimen and his platelet count had normalized to 219 $x10^9$/l. *Conclusion.* Severe thrombocytopenia is an uncommon presentation of WM that may be secondary to complement mediated thrombocytopenia associated with monoclonal IgM antiplatelet antibody. In such cases, therapies for ITP such as corticosteroids and high-dose immunoglobulins may not be as effective as anti-tumor chemotherapy.

Keywords: *Waldenström macroglobulinemia, Thrombocytopenia, immune thrombocytopenic purpura (ITP), hyperviscosity syndrome, splenectomy, hemorrhage, complement mediated thrombocytopenia*

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1. Introduction

Waldenström macroglobulinemia (WM) is a distinct hematologic malignancy characterized by a lymphoplasmacytic bone marrow infiltration and the presence of immunoglobulin (IgM) monoclonal protein [1]. WM patients can present with a diverse array of symptoms and findings. The clinical manifestations associated with WM can be classified according to those related to direct tumor infiltration, to the amount and specific properties of circulating IgM, and to the deposition of IgM in various tissues [2]. The paraprotein may include an autoantibody resulting in autoimmune complications in 5–16 % of patients with WM [3]. One such manifestation is autoimmune thrombocytopenia which has been rarely reported in the literature but may occur as a consequence of autoantibody activity against platelets [4]. We report the case of a 57-year-old man who presented with severe symptomatic thrombocytopenia and was subsequently diagnosed with WM.

2. Case Report

A 57-year- old African American male presented with a two-week history of fatigue, recurrent epistaxes and gingival hemorrhage. His past medical history was significant for liver cirrhosis secondary to Hepatitis C and a splenectomy 2 years prior for traumatic rupture of the spleen.

Complete blood count demonstrated platelets 3 $x10^9$/l. Immature platelet fractionation was elevated at 18.3%. Examination of the blood film revealed no abnormalities. His severe thrombocytopenia and attendant bleeding manifestations were attributed to an immune thrombocytopenia. He was given platelet transfusions and started on treatment with steroids and immune globulin (IVIG). This resulted in a prompt but transient improvement in his platelet count to 20 x 10^9/l. He unfortunately continued to have bouts of epistaxis and his thrombocytopenia worsened. It was decided to add Rituximab at a dose of 375 mg/m^2 for steroid refractory ITP. He then displayed an incremental and sustained

improvement in his thrombocytopenia with platelet count remaining in the 20-30 x10^9/l range.

During the course of his evaluation, laboratory testing demonstrated normal renal and hepatic function but an elevated total protein of 13.1 g/dl. Serum protein electrophoresis and immunofixation demonstrated an IgM Lambda monoclonal paraprotein of 7.6 g/dl. Serum viscosity was elevated at 10.8 cP.

He was therefore diagnosed with a hyperviscosity syndrome secondary to suspected Waldenstrom's Macroglobulinemia (WM) and plasmapheresis was emergently initiated due to bilateral retinal vein thrombosis. A bone marrow aspirate and biopsy revealed an interstitial plasmacytoid proliferation which was CD138 positive and lambda restricted (Figure 1 and Figure 2, A&B).

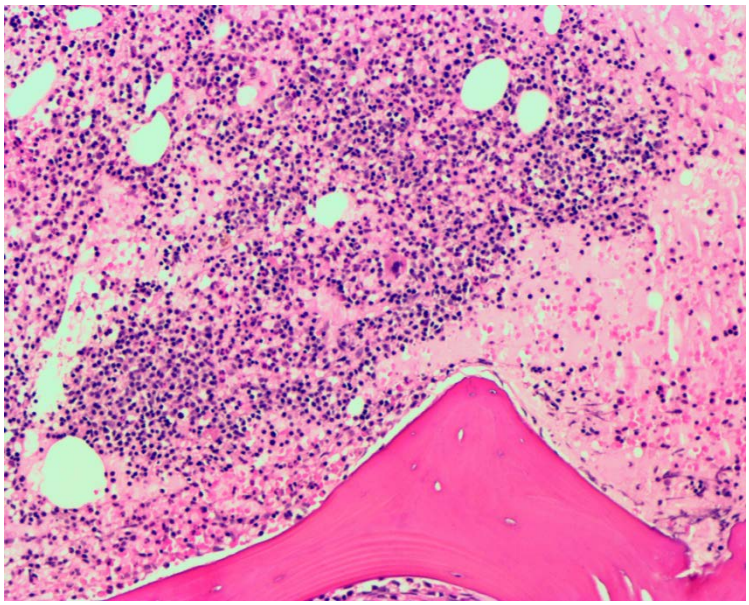

Figure 1. Bone marrow at 100x magnification (H&E) showing lymphoplasmacytic infiltration of the bone marrow with a background trilinear hematopoiesis

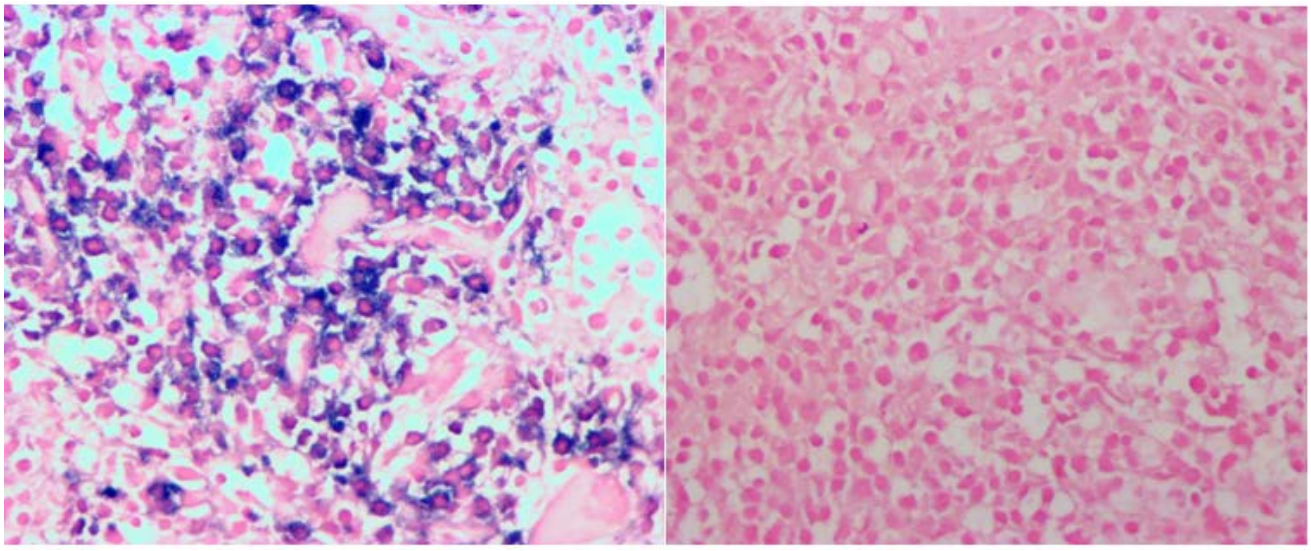

Figure 2. a and b: Bone marrow mRNA in situ hybridization at 400X magnification showing positive staining with lambda light chain and negative staining for kappa light chain supporting a clonal lambda light chain restricted population

The megakaryocytes appeared adequate in morphology and number. Flow cytometry revealed a small abnormal population of B cells (CD22 positive and lambda restricted).

With plasmapheresis, his serum IgM was lowered to less than 4 g/dl and his serum viscosity decreased to 4.4 cP. A weekly regimen of bortezomib, dexamethasone and rituximab (BDR) was used for treatment. Bortezomib was dosed at 1.6 mg/m^2 per week with dexamethasone (20 mg/week). Since the patient had already received Rituximab, it was re-introduced with the next cycle at a dose of 375 mg/m^2 per week every 4 weeks.

On a follow-up visit three months later he continued on the weekly BDR regimen and his platelet count had normalized to 219 x10^9/l.

3. Discussion

We report the case of a 57-year-old male who presented with severe thrombocytopenia and consequent bleeding manifestations with a working diagnosis of immune thrombocytopenic purpura (ITP). A diagnosis of WM was made on the basis of Ig M monoclonal gammopathy and

lymphoplasmacytic lymphoma infiltration of the bone marrow. The severity of thrombocytopenia in the setting of adequate platelets in the marrow, suggested a specific pathophysiologic mechanism directed against platelets. Furthermore, this patient's suboptimal response to platelet transfusions suggested a destructive thrombocytopenia. We believe therefore that his thrombocytopenia was not consistent with tumor cell infiltration of the bone marrow and instead suggested the presence of an autoimmune basis for this finding.

There is sufficient evidence in the literature to suggest that WM-related morbidity can be a manifestation of the physicochemical and immunologic properties of the monoclonal IgM protein produced by tumor cells [5]. In particular, autoimmune thrombocytopenia is a rarely reported manifestation of WM and the incidence therefore has not been systematically evaluated. Furthermore, there are no large studies of WM. In a single institution study done by Owen et al, review of the case records of 105 cases of WM identified 3 cases of autoimmune thrombocytopenia. On the basis of these findings the authors concluded that the overall incidence of autoimmune thrombocytopenia in WM is 3.8% [4].

In our case, the degree of thrombocytopenia at presentation was striking and was not typical of WM. When the laboratory findings for 356 newly diagnosed patients with WM were compared at the Dana Farber Cancer Institute by Treon, the median platelet count was 275 x 10^9/L [5]. By comparison, in all of the previously reviewed cases of immune thrombocytopenia secondary to WM the platelet count was less than 15 x 109/L [3,4,6,7]. The clinical presentation and severity of thrombocytopenia was consistent with other cases of autoimmune thrombocytopenia in WM.

Previous reports have referred to the mechanism of immune thrombocytopenia associated with WM, and both platelet-associated IgM (PA-IgM) and IgG (PA-IgG) have been implicated. In the case reported by Owen et al, platelets derived from their patient demonstrated normal levels of PA-IgG, but PA-IgM was clearly elevated compared to the normal controls [4]. In a report by Yamanouchi et al, flow cytometry assay done on a patient with WM showed that his IgM bound to normal platelets whereas his IgG did not. Further analysis revealed that the patient's monoclonal IgM derived from WM had antiplatelet activity against GPIb/IX [3]. It has been postulated that this antiplatelet activity leads to ITP and gives rise to hemorrhagic symptoms in some patients with WM. In another case study by Nakazaki et al, thrombocytopenia was accompanied by increased PA-IgG. The authors were able to show a reduction in PA-IgG levels and a concomitant reduction of tumor cells in the bone marrow in response to chemotherapy. Based on these findings, it has been hypothesized that aberrant IgG production may be responsible for platelet destruction in some cases of WM [7].

An interesting feature of our case was that the patient presented with autoimmune thrombocytopenia despite having a prior splenectomy. The mechanism of platelet destruction in idiopathic thrombocytopenic purpura is thought to be primarily mediated by splenic macrophages that capture opsonized platelets caused by IgG antiplatelet autoantibodies [8]. This suggests that the mechanism of immune thrombocytopenia in our case is different from that of idiopathic thrombocytopenic purpura. In a case reported by Lehman et al, a patient with a lymphoid neoplasm was found to have complement mediated thrombocytopenia associated with monoclonal IgM antiplatelet antibody [9]. Similar to our case, this patient had severe thrombocytopenia that was refractory to corticosteroids and splenectomy. Further investigation revealed that the patient had an antibody that was able to induce potent complement activation in vitro as well as lysis of target platelets. Since our patient had a splenectomy prior to presentation, we postulate that the mechanism of autoimmune thrombocytopenia in this case was complement mediated.

Given the difference in the pathophysiologic basis of autoimmune thrombocytopenia accompanying WM and idiopathic thrombocytopenic purpura, there is a difference in the treatment approach of both entities. As seen in our case, the use of steroids and high dose immunoglobulins yielded a transient and suboptimal response. We were only able to obtain a sustained response with the use of Rituximab which has been established as a frontline therapy for WM [1]. In a review of autoimmune thrombocytopenia in non-Hodgkin's lymphomas by Hauswirth et al, therapy directed against the lymphoma in the form of chemotherapy and tumor excision was far more effective than standard treatment with corticosteroids, immunosuppressants and high-dose immunoglobulins [10]. This was also true for our case, because the BDR regimen successfully induced normalization of the platelet count.

In conclusion, severe thrombocytopenia is an uncommon presentation of WM that may be secondary to complement mediated thrombocytopenia associated with monoclonal IgM antiplatelet antibody. In such cases, first-line therapies for ITP such as corticosteroids and high-dose immunoglobulins may not be as effective as anti-tumor chemotherapy.

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