

Ibrutinib effect in acquired von Willebrand syndrome secondary to Waldenström macroglobulinemia

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Abstract: The pathological increase of clonal IgM in Waldenström macroglobulinemia can be associated with acquired von Willebrand syndrome and can be a major risk of bleeding symptoms in this subgroup of patients with Waldenström macroglobulinemia. The Bruton tyrosine kinase inhibitor ibrutinib is one of the approved treatments for symptomatic Waldenström macroglobulinemia. However, some controversy exists regarding the use of ibrutinib in these patients with high risk of bleeding because of its antiaggregant effect that could increase the risk of bleeding. Here, we present the case of a patient with Waldenström macroglobulinemia with associated acquired von Willebrand syndrome and progressively significant bleeding symptoms, who experienced a rapid increase in von Willebrand factor with ibrutinib treatment, despite only reaching a partial response in IgM levels similar to those reached with other previous treatments. We suggest that the control over the monoclonal protein is not the only mechanism that explains the good response, improvement in the bleeding symptoms and von Willebrand factor levels. This fact could be explained by the reduced glycoprotein Ib receptor expression induced by ibrutinib and the consequent von Willebrand factor increase in peripheral blood.

Keywords: case report, ibrutinib, von Willebrand syndrome, Waldenström macroglobulinemia

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Introduction

Waldenström macroglobulinemia (WM) is a lymphoproliferative disorder characterized by the infiltration of IgM-secreting lymphoplasmacytic cells of the bone marrow and other tissues. The hyperproduction of clonal IgM causes blood hyperviscosity phenomena and is associated with acquired von Willebrand syndrome (AVWS),¹ which is defined by the decrease of von Willebrand factor (VWF) function in the absence of personal or family history of bleeding. Despite the fact that only 2–4% of patients with AVWS are diagnosed with WM, up to 13% of patients with WM are diagnosed with AVWS. This association is not related to a worse outcome, in contrast to the elevation of VWF >110 UI/dl that predicts lower overall survival.¹

Bleeding symptoms derived from AVWS establish starting treatment in patients with WM, because it is suggested that decreasing IgM levels reverses AVWS.¹ However, chemotherapy regimens with their particular characteristics and other therapeutics are not well established in this subgroup of patients.^{2,3} We report the use of ibrutinib in a 63-year-old woman who was diagnosed in our hospital with WM and associated AVWS.

We have de-identified all patient details and we have followed the CARE Case Report Guidelines.

Case description

A 63-year-old woman with a personal history of Sjögren's syndrome was attended in our hospital

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with mild bleeding symptoms (epistaxis and ecchymosis grade 1). The patient denied any personal or family history of bleeding. In the initial analysis, IgMk monoclonal protein (M-protein) of 4 g/dl (total IgM 5.6 g/dl) and elevated β 2 microglobulin (3.7 mg/l) were found. A bone marrow biopsy established the diagnosis of WM, and the L265 P MYD88 mutation was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). AVWS was also determined with the following laboratory findings: activated partial thromboplastin time (aPTT) 40", VWF antigen (VWF:Ag) 47%, VWF ristocetin cofactor activity (VWF:RCo) 46% and factor VIII activity (FVIII) 47%.

Six months later, due to increasing frequency and severity of epistaxis and ecchymosis with worsening laboratory markers (IgM 4.4 g/dl, aPTT 45", VWF:Ag 34%, VWF:RCo 32%, FVIII 37%), a first-line treatment was initiated with bortezomib sc, dexamethasone and rituximab (BDR). At that moment, the international prognostic index of WM was low risk.⁴

After initial doses of rituximab, a 'flare phenomenon' occurred (IgM rose to 7.66 g/dl), worsening AVWS (aPTT 48", VWF:Ag 27%, VWF:RCo 27%, FVIII 27%), bleeding symptoms and requiring several plasmaphereses. Rituximab was stopped and the patient continued treatment with bortezomib and dexamethasone (BD) for two more cycles achieving a serological partial response (M-protein 1.1 g/dl; IgM 2.6 g/dl), but not a clinical response. However, the therapy had to be discontinued because of grade 4 sensitive peripheral neuropathy, and during the following 21 months, a progressive rise in IgM (up to 5.5 g/dl) was observed, accompanied by worsening of bleeding symptoms (recurrent epistaxis and large spontaneous haematomas).

These facts triggered the start of second-line therapy with ibrutinib monotherapy (420 mg, orally QD) 1 year later. At that moment, AVWS markers were aPTT 40", VWF:Ag 38%, VWF:RCo 29% and FVIII 47%. The patient evolved favourably, showing a rapid and notable reduction of bleeding symptoms 2 weeks after starting ibrutinib. Within 2 months of treatment, a partial response was attained (M-protein 2.1 g/dl and IgM 2.7 g/dl) and haemostasis parameters were normalized. Over the last 2 years, ibrutinib has only been discontinued during 20 days due to

catarrhal symptoms and suspected SARS-CoV-2 infection, which was not confirmed. This interruption caused a disease flare (M-protein and IgM rebound to 3.3 and 3.7 g/dl, respectively) and elongated aPTT producing recurrent epistaxis. However, restarting ibrutinib led to a rapid clinical and analytical response. To date, after 26 months of ibrutinib, the patient maintains a partial response and has a good quality of life. No bleeding symptoms have been reported and the coagulation analysis remains unaltered. Figure 1 shows laboratory findings from diagnosis to the present.

Discussion

AVWS is a rare syndrome developed in the course of some haematological malignancies, autoimmune diseases and cardiovascular disorders such as congenital heart defects, aortic stenosis and mechanical circulatory support systems. Its treatment is that of the underlying cause.

AVWS has been correlated with elevated IgM concentrations and hyperviscosity, and a decrease of both conditions is associated with higher levels of VWF.^{1,2} This fact can be explained by AVWS physiopathology. It has been reported that exposure of VWF high-molecular-weight-multimers to shear stress induced by hyperviscosity on capillaries causes a higher susceptibility to proteolytic activity of ADAMTS13.¹⁻³ Also described is an increased clearance of VWF due to the complex interaction between serum IgM and VWF.^{3,5,6} Alternatively, AVWS can be seen due to autoimmune disorders in the presence of low tumour burden.

Bleeding symptoms secondary to AVWS caused by IgM monoclonal gammopathies seem to be a clear indication to start treatment.^{4,5,7} Unlike IgG gammopathies, in IgM-related AVWS plasmapheresis is associated with better outcomes than the administration of intravenous immunoglobulins; likewise, it is proved that treatment of the underlying disorder is necessary to stop bleeding symptoms and achieve long-term remissions.^{1,5,8,9} But the optimal treatment in this subgroup is not well stipulated.

In our case, therapy was initiated with a bortezomib-based regimen consisting of Bortezomib-Dexamethasone-Rituximab (BDR). However, two considerations must be taken into account.

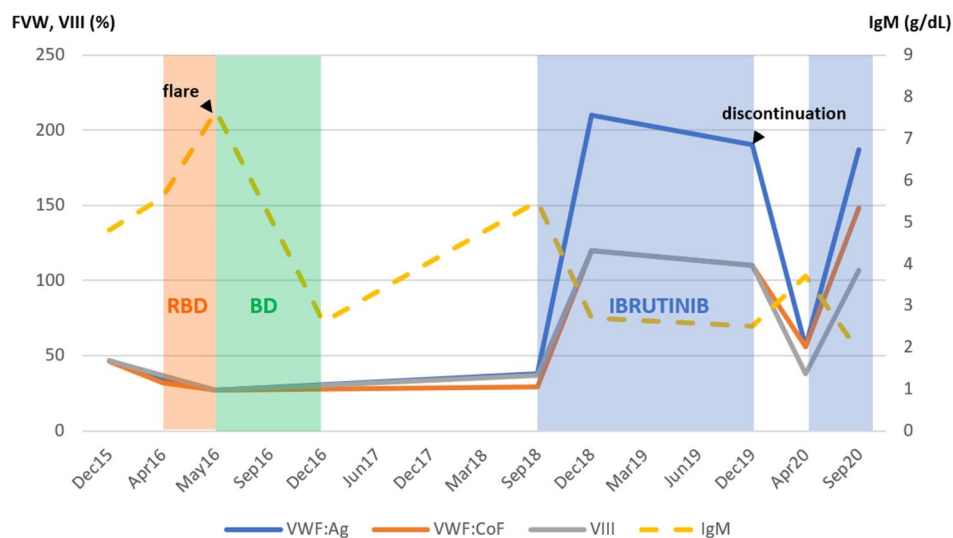


Figure 1. IgM protein values (mg/L), factor VIII activity (%) and von Willebrand factor antigen and ristocetin cofactor activity (%) during the disease course.

First, the initiation of rituximab in patients with high IgM concentrations can result in a ‘flare phenomenon’, producing a transient rise in the paraprotein and a worsening hyperviscosity syndrome, as was detected in our patient and could be explained by lower VWF levels and pronounced bleeding symptoms.⁷ It is important to delay rituximab until IgM levels are <3–4 g/dl. Second, although some good responses have been reported with Bortezomib-based regimens, toxicity consisting of peripheral neuropathy can be seen in 46% (grade ≥ 3 in 7%, and some series up to 30%).¹⁰ Our patient experienced a partial response with initial treatment, but VWF levels did not change; in addition, she presented high-grade toxicity that was difficult and only partially reverted. Although low neurotoxic effects have been reported with reduced frequency administration of bortezomib, it compromised response rates.^{4,11}

Ibrutinib is approved for WM treatment in monotherapy or associated with rituximab obtaining a major response rate of 73% (including minor response rates up to 90.5%).^{12–14} One of the main safety concerns related to ibrutinib is the increased bleeding risk, due to the platelet antiaggregant effect caused by interference of platelet-VWF-collagen binding and by inhibition of platelet signalling pathways. Inhibition of Bruton tyrosine kinase reduces the expression of several platelet transmembrane receptors, including the

platelet-collagen receptor glycoprotein VI and the platelet-VWF receptor glycoprotein Ib (GPIb).¹⁵ This causes frequent mucocutaneous low grade bleeding (>50% of patients on ibrutinib will have a bleeding event after 3 years of follow-up). Major bleeding cases have been reported in up to 3% of patients.^{13,16}

Because of this, there are very few reports of WM and AVWS treated with ibrutinib in the literature.¹² Castillo and colleagues mentioned five cases without further information about response, median time to response or impact in bleeding symptoms. Among the four patients with AVWS in the series of Treon and colleagues, three had normalized VWF levels after starting ibrutinib.^{2,13} In our case, 2 months after starting ibrutinib, our patient only reached a partial response similar to that of bortezomib, but showed a total normalization of VWF markers and cessation of epistaxis and haematomas.

Our patient experienced a faster and intense VWF response to ibrutinib, compared with patients treated with bortezomib (2 *versus* 6 months).¹⁷ The reversal in factor levels after starting ibrutinib – achieving a similar degree of IgM reduction as with bortezomib – was far more remarkable. Even more interesting, during the 20-day discontinuation of ibrutinib, the IgM rise was only minimal but the drop in factor levels was dramatic.

As previously stated, there is an inverse relation between VWF and serum IgM levels. However, it seems that control over the monoclonal protein is not the only mechanism that explains the good response, improvement of the bleeding symptoms and VWF levels. We suggest that this significant increase in VWF levels after ibrutinib administration can be explained because of the reduced GPIb receptor expression and the consequent VWF increase in peripheral blood, leading to an increase in FVIII and improving secondary haemostasis.

It is also important to bear in mind that ibrutinib discontinuation can result in a transient rise in monoclonal IgM leading to the reappearance of bleeding symptoms, and not to mislabel this fact as disease progression.¹⁸

Conclusion

This case suggests that AVWS does not confer a contraindication for ibrutinib treatment in patients with WM with underlying AVWS, but could be associated with better outcomes. Due to few cases having been reported, we recommend a close clinical follow-up during the first weeks of treatment. On the whole, the effect of ibrutinib appears to be very rapid, and not directly related to the degree of IgM reduction. Larger studies should be carried out to obtain further information about these phenomena in this subgroup of patients.

Author contributions

MP, RÍ and IZ have written the case report. SR, RA and AJ-U treated the patient. JM-L and AJ-U collaborate with the manuscript correction.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Ethical approval

This case report does not require the approval of an ethics committee. The authors confirm that patient consent has been obtained.

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