Bleeding challenge in Waldenström Macroglobulinemia

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Introduction

- Waldenström Macroglobulinemia (WM) is a lymphoplasmacytic lymphoma with a monoclonal IgM protein characterized by anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and hyperviscosity (1).
- Abnormal bleeding can be seen in WM due to multiple underlying reasons: thrombocytopenia, hyperviscosity, cancer therapy and rarely acquired von Willebrand factor disease (aVWFD).
- Recent therapies targeting the inhibition of the Bruton's tyrosine kinase (BTK) have emerged as promising treatment options for patients with B-cell neoplasms, including WM (2).
- The hematologic adverse effects of BTK inhibitors include not only cytopenias, but also platelet aggregation abnormalities, therefore increasing the risk of bleeding complications (3).
- Diagnosing the underlying etiology of bleeding in WM can be challenging and we illustrate an example of a systematic approach to a case seen at our institution.

Case Presentation

HPI:

- An 80-year-old male with a 10-year history of WM who presented to the clinic with macroscopic hematuria.
- The patient described the hematuria as three episodes of multiple drops of blood in urine within the prior week.

PMH:

- He received multiple chemotherapy regimens in the last 10 years, including cyclophosphamide, rituximab, bortezomib and he was on ibrutinib for the last one year.

Case Presentation Con't

ROS:

- Review of systems was positive for fatigue and anxiety, but negative for any blood in stool, easy bruising, nose bleeding, gum bleeding and changes in vision.

PE:

- Vitals signs were within normal limits.
- Physical exam was unremarkable with normal findings.

LABS:

- Complete blood count showed Hemoglobin of 14.8 g/dL and Platelet of 220,000/mL.
- Urinalysis was positive for 25 red blood cells without any white blood cells.
- Serum protein electrophoresis with immunofixation showed a monoclonal IgM of 27 mg/dL.

FURTHER WORKUP AND MANAGEMENT:

- Ibrutinib was held due to its common side effect, bleeding.
- The patient was referred to Urology to rule out bladder cancer due to history of cyclophosphamide treatment.
- Cystoscopy demonstrated mildly elevated bladder neck, otherwise normal for any acute pathology to explain the hematuria.
- The benign bleeding was thought to be from the prostatic urethra irritation and patient was started on tamsulosin.
- In the follow-up appointment, patient had bleeding for 20 minutes from a venipuncture site for routine lab testing.
- The further evaluation for bleeding showed that patient had decreased vWF Ag (33%), vWF Activity (13%) and aVWFD was diagnosed.
- Meanwhile, patient's IgM increased to 778 mg/dL and ibrutinib was resumed.
- In the next follow-up, patient's bleeding symptoms were resolved and did not recur, his IgM decreased to 32 mg/dL and vWF Ag (229%), vWF Activity (204%) dramatically increased.

Discussion

- This case highlights the complexity of understanding the bleeding mechanisms in WM. Although there are several mechanisms for bleeding in WM, the systematic approach to evaluate will be key to elucidate the underlying diverse mechanisms.

Approach to Diagnosing Etiology of Bleeding in patients with Waldenström Macroglobulinemia	
Thrombocytopenia	<ul style="list-style-type: none">Can be secondary to WM, chemotherapy or consumption.Rule out with CBC.
Anatomical Causes	<ul style="list-style-type: none">If bleeding is site specific, rule out anatomical causes via appropriate imaging and procedures such as EGD, colonoscopy and cystoscopy.
Hyperviscosity Syndrome	<ul style="list-style-type: none">Can present with epistaxis, gingival bleeding and retinal hemorrhage (4).Seen in patients with very high IgM concentrations as high as 4000mg/dL (5).Diagnose with IgM levels, viscosity measurement is not required.
Chemotherapy side effects	<ul style="list-style-type: none">Can cause bleeding via thrombocytopenia.Remember cyclophosphamide as a cause of bladder cancer, stop the medication and consult urology for cystoscopy.
Ibrutinib	<ul style="list-style-type: none">Main side effects are bleeding, diarrhea and atrial fibrillation (6).Stop the medication when suspected, but can cause worsening of the disease.
aVWFD	<ul style="list-style-type: none">A rare cause of bleeding in patients with WM.Diagnose with decreased vWF Ag and vWF Activity levels (7).Depending on the severity, patients might require acute treatment such as IVIG, vWF concentrate or recombinant vWF.

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