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Successful treatment of a CLL associated IgM hyper-viscosity syndrome: A rare case

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ABSTRACT

In the context of chronic lymphocytic leukemia (CLL), Hyperviscosity Syndrome (HVS) typically arises from hyperleukocytosis, although it infrequently stems from IgM hyperparaproteinemia. We present a distinctive case of HVS induced by IgM hyperparaproteinemia in a patient experiencing relapsed CLL, marked by bulky disease and cytopenias upon progression. The patient exhibited new symptoms, including headache, dizziness, and confusion. Laboratory analysis revealed an elevated total protein level, and serum electrophoresis identified an elevated M spike at 4 g/dL with IgM on immunofixation. Suspecting HVS, prompt plasmapheresis was initiated, resulting in symptom resolution within two days.

A comprehensive literature review suggests that CLL patients with an elevated IgM level often face a poor prognosis, though HVS symptoms are not commonly observed. Our case underscores the significance of swiftly identifying HVS when IgM hyperparaproteinemia is detected in CLL patients. Notably, our patient not only achieved successful treatment for the acute presentation but also initiated second-line therapy for relapsed disease. In conclusion, effective management and stabilization of CLL patients with IgM-associated HVS are attainable, emphasizing the crucial role of prompt recognition.

1. Introduction

Viscosity is the measurement of the internal resistance of fluid to flow. Hyperviscosity syndrome (HVS) is caused by increased blood viscosity attributed to a pathological increase in either cellular or acellular components of blood. Increased cellular components include red blood cells (RBCs) as is often seen in polycythemia vera (PV); white blood cells (WBCs) as is seen in leukemias; and platelets as is seen in essential thrombocytosis. Increased viscosity due to acellular components of blood is typically due to an increase in the proteinaceous portion of the plasma and is largely due to accumulation of IgM protein. This pathological monoclonal or polyclonal expansion of IgM is often seen in cryoglobulinemia [1].

The clinical signs and symptoms of HVS include neurological dysfunction such as headaches, retinopathy, papilledema, stroke-like features, and seizures. These are mostly a result of the sluggish blood flow within the CNS vasculature. Lung, heart, kidney, and gastrointestinal involvement are also commonly encountered.

The diagnosis of HVS requires a high degree of clinical suspicion and requires careful assessment of the symptoms, clinical context (hematological disorder), and relevant laboratory tests. The laboratory testing that can aid in the diagnosis measures the serum viscosity relative to the viscosity of water, which is normally around 1.4–1.8 centipoise (cp). When the serum viscosity increases up to 4–5 cp, symptoms of HVS arise [2].

Treatment of HVS includes prompt recognition and early intervention in an attempt to thwart organ failure and reverse any potentially inflicted ischemic organ injury. The immediate treatment aims to remove either the cellular or acellular component, depending on the driving force. Removing the cellular components can be done via leukapheresis, a process which removes white blood cells from the blood. Removing the acellular components can be done via a process called plasmapheresis, which refers to the separation, removal, and collection of plasma from the blood. Plasmapheresis is relatively safe, can be done daily until symptoms resolve and has the potential to decrease the plasma viscosity by at least 20–30 % [3,4].

Long term solutions for HVS include treating the underlying etiology, which in a large majority of cases is due to hematologic disorders such as plasma cell dyscrasias and Waldenstrom's macroglobulinemia [1], and leukemias via chemotherapy and/or targeted therapy.

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HVS in the setting of CLL is a phenomenon that is more commonly due to hyperleukocytosis than hyperparaproteinemia [5,6]. Even in cases of hyperleukocytosis, with WBC count more than 100,000/mm3, not all patients will experience HVS. In fact, in one retrospective study, only 3/16 patients with a WBC count greater than 100,000/mm3 experienced HVS-related symptoms [7]. IgM-related HVS is considered a known occurrence, with the risk of developing symptoms increasing with IgM levels surpassing above 4 g/dl. This phenomenon is commonly seen in plasma cell dyscrasias, as well as Waldenström's macroglobulinemia [8,9].

We report a case of a patient with relapsed CLL, who while off treatment, presented with symptoms of HVS and an IgM paraproteinemia of greater than 4 g/dL. We describe the process of how we reached the diagnosis as well as our immediate and long term plans for treatment and stabilization.

2. Case

Our patient is a 53-year-old man who presented to the hospital with an enlarging neck mass and shortness of breath while lying down. His labs upon admission showed a WBC count of 9.6 (x10^3/mcl), hemoglobin (Hb) of 14.8 (g/dl), platelet count of 265 (x10^3/mcl), an absolute lymphocyte count (ALC) of 3.8 (x10^3/mcl), and a lactate dehydrogenase level of 735 units/L (Table 1 for full labs).

Computed tomography (CT) of the neck with IV contrast showed bulky bilateral multilevel cervical lymphadenopathy concerning for lymphoma. Positron emission tomography (PET) scan showed extensive bulky supradiaphragmatic and infradiaphragmatic lymphadenopathy. Most metabolically active disease was noted within the left neck, left retroperitoneum and inferior mesenteric lymph node below the aortic bifurcation (Fig. 1). Biopsies of a right neck cervical lymph node and a retroperitoneal lymph node were both consistent with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) based on the characteristic immunohistochemical profile, including positive for CD5, CD20, LEF1, BCL-2, and CD21, and absence of SOX-11. Neogenomic testing revealed TP53 wild type and IGHV3-11 × 05 unmutated status.

The patient was initiated on treatment with steroids and eventually transitioned to the Bruton tyrosine kinase (BTK) inhibitor Ibrutinib. He responded to ibrutinib within a few weeks, with shrinkage of his lymph nodes on imaging and normalization of his WBC count. Following six months of treatment with ibrutinib, CT scans showed near complete resolution of his retroperitoneal LAD, residual mesenteric LAD, and significant decrease in size of his axillary, mediastinal, supraclavicular, and cervical LAD. Later scans eventually showed complete resolution of his disease. The patient continued treatment with ibrutinib for two years without side effects and remained in complete remission (CR).

Unfortunately, three years after his diagnosis, his disease progressed, and he presented with enlarging bilateral cervical neck masses. Labs during that time showed an LDH of 947 units/ml, WBC count of 9.1 (x10^3/mcl), Hb of 14.4 (g/dl), platelet count of 172 (x10^3/mcl), and ALC of 4.5 (x10^3/mcl) with 12 % atypical lymphocyte percentage. CT neck, chest, abdomen, pelvis and PET/CT showed (Fig. 2) recurrence of his disease in the previously seen cervical, mediastinal, and mesenteric lymph nodes, with the largest mass measuring at 11.9 cm in the left cervical lymph node. He was suspected to have undergone a Richter transformation; however, a core biopsy of the left cervical lymph node showed CLL/SLL with lymphoma cells positive for CD20, PAX5 and LEF1, while negative for CD5, CD10, cyclin D1, SOX11, P53 or c-MYC (<40 %) thus confirming disease relapse. There was no evidence of any lymphoplasmacytic differentiation seen on the pathology slides.

Due to the cytopenia, bulky disease and progression on ibrutinib, the patient was planned to begin treatment with second line obinutuzumab/venetoclax based on the CLL 14 protocol [10].

Prior to starting this new regimen, he was admitted to the hospital due to headache, dizziness, and confusion. CT brain without contrast was negative for acute hemorrhage, mass, or evidence of infarction. Significant laboratory findings during this admission showed a WBC count of 16.6 (x10^3/mcl), and an elevated protein level of 11.8. A plasma cell dyscrasia workup was pursued and revealed a serum protein electrophoresis with an M spike of 3.2 g/dl; IgM level of 4715 mg/dL (40–230); IgA 43.2 mg/dL (70–400), IgG 943 mg/dL (700–1600); Free Kappa 36.46 mg/dL (0.33–1.94); Free lambda 1.16 mg/dL (0.57–2.63); F k/l ratio: 31.431 (0.26–1.65). which were suggestive of a monoclonal IgM kappa paraprotein.

Due to the elevated levels of IgM combined with neurological symptoms, HVS was suspected. He was started on steroids and underwent therapeutic plasma exchange (TPE)/plasmapheresis for two consecutive days, until his IgM level decreased to 2492 mg/dL with subsequent resolution of the neurologic symptoms. He then went on to receive chemotherapy consisting of cyclophosphamide 750 mg/m2 and vincristine 1.4 mg/m2 to ensure disease control and prevent further increase in IgM levels. The patient was stabilized and discharged home to start treatment with obinutuzumab/venetoclax as an outpatient regimen. Unfortunately, he developed disease progression after the fourth cycle of venetoclax/obinutuzumab and had to switch therapy to pirtobrutinib. Currently, he remains in pirtobrutinib for 4 months and has achieved a partial response with improvement of the lymphadenopathy.

Table 1
Lab results.

	Presentation	Relapse	Reference range
WBC (x10^3/mcl)	9.6	9.1	4–10.5
Hb (g/dl)	14.8	14.4	13.3–16.3
Platelet (x10^3/mcl)	265	172	140–400
Absolute lymphocyte count (ALC) (x10^3/mcl)	3.8	4.5	1.1–2.7
Creatinine (mg/dl)	1.10	1.30	0.66–1.25
Total protein (g/dl)	7.5	8.2	6.3–8.2
Albumin (g/dl)	4.2	4.8	3.9–5
Total bilirubin (mg/dl)	0.5	1.1	0.2–1.3
AST (unit/l)	34	45	15–46
ALT (unit/l)	24	29	21–72
LDH (unit/l)	735	947	313–618

3. Discussion

The presence of elevated IgM levels in CLL is rare. The limited IgM-associated CLL cases have been studied in the literature [11], and are associated with poor prognosis and shorter overall survival [12]. In a retrospective study conducted by Yin et al. [13], the authors describe 26 patients with untreated CLL and a median IgM level of 5.9 g/dl. Interestingly, none of those patients experienced symptoms pertaining to HVS, which speaks to the lower likelihood of any clinical manifestation despite high paraprotein levels.

Cases of HVS in the setting of elevated IgM-associated CLL are rarely encountered in current literature. In our review, we identified two cases of a suspected occurrence of HVS in the setting of hyper-IgM associated with CLL. The first case reported in 2018 discusses an atypical CLL patient with an elevated IgM level of 5.3 g/dl. Although no symptoms were reported, work up revealed retinal hemorrhages and evidence of chronic vascular disease on CT angiogram of the brain, which may have been attributed to the patient's long-standing hypertension vs asymptomatic HVS. At that time, the diagnosis was presumed secondary to Waldenström's macroglobulinemia but later confirmed to be atypical CLL. The patient declined treatment and opted for hospice care [14]. Another case by Martini et al. [15], describes a patient with atypical CLL treated with rituximab, however at progression of his disease, his blood work showed an increasing IgM level from 53 to 6550 mg/dL. At that point, the patient clinically progressed and was treated with idelalisib first then ibrutinib. After starting ibrutinib, IgM levels further increased,

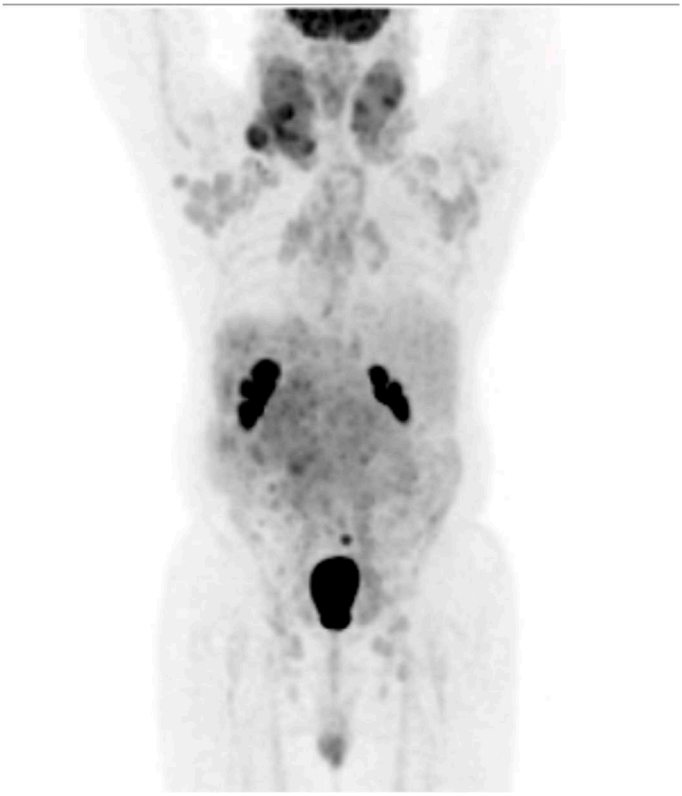

Fig. 1. Initial PET/CT scan showed extensive bulky supradiaphragmatic and infradiaphragmatic lymphadenopathy. Most metabolically active disease was noted within the left neck, left retroperitoneum and inferior mesenteric lymph node below the aortic bifurcation.

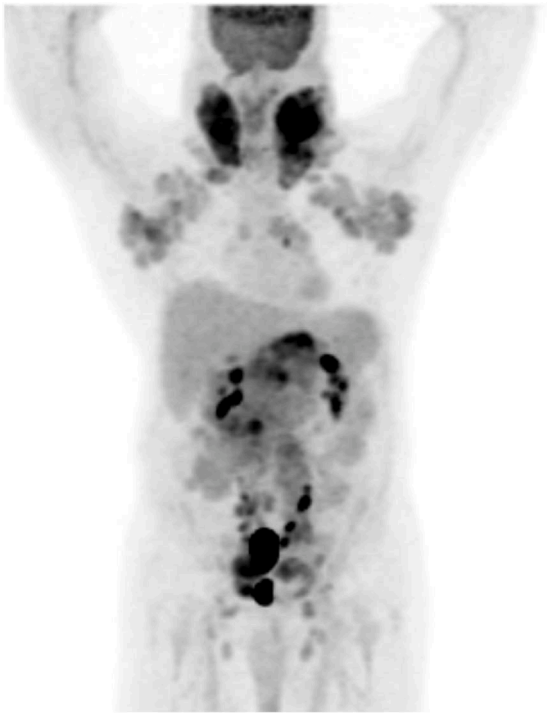

Fig. 2. PET/CT scan at the time of relapse showed interval increase in size with similar metabolic activity of previously seen cervical, mediastinal, and mesenteric lymphadenopathy and significant decrease in retroperitoneal lymphadenopathy.

and the patient reported nasal bleeding and visual disturbances that were eventually attributed to HVS. TPE and chemotherapy were initiated, however the patient continued to deteriorate and died of septic shock. More cases also described IgM paraproteinemia and HVS in CLL patients treated with Rituximab [16], a treatment which is suspected to cause paraproteinemia. These cases are worth mentioning, but are important to distinguish from non-treatment induced paraproteinemia.

To our knowledge, our patient case is the first report of a relapsed CLL/SLL presenting with enlarged LAD and elevated IgM levels at 4.715 g/dL in the context of HVS. This also represents a first case of successful treatment of HVS with resolution of symptoms by employing TPE and one round of cytotoxic chemotherapy. Treatment success was proved clinically in the form of a decrease in the IgM levels to 2.8 g/dl and concurrent dissolution of the HVS associated neurological symptoms. Despite not measuring the actual viscosity of his blood, the resolution of his symptoms after TPE confirms that they were attributable to those of HVS. The remarkable recovery made it possible for the patient to start his next line of treatment without further delay.

In contrast to the cases described earlier, ours was not an atypical CLL case, which makes it more unique. Cases of IgM-associated HVS have not been routinely reported in typical CLL. It also seems that the context of the paraproteinemia was not treatment induced as the patient had been off treatment for several months at the time of his relapse. This is important to shed light on as there have been many other well-described cases where rituximab based regimens had induced an IgM flare, not a very unexpected phenomenon [17].

The approach that we adopted was inspired by the same approach towards HVS in Waldenstrom's macroglobulinemia cases. Although we did not test for the *MYD88* L265P mutations, the lack of lymphoplasmacytic differentiation seen on pathology would make the diagnosis of WM less likely. In addition, a subset of CLL cases are also reported to express the *MYD88* L265P mutation [18]. The immediate danger that the patient was in gave us no time but to attempt to lower his IgM levels

rapidly. Screening for immunoglobulin levels and paraproteinemia is not routinely tested during the initial evaluation of CLL. This case serves to show that IgM-associated HVS could certainly occur in the context of CLL, and that treatment is possible. TPE, as discussed earlier, is safe to use and can significantly lower the paraprotein burden in the blood.

4. Conclusion

CLL-associated HVS in the form of IgM hyperparaproteinemia is a rare phenomenon. As such, our case describes a patient with relapsed CLL presenting with elevated IgM and HVS symptoms. Treatment with TPE and chemotherapy proved to successfully lower IgM levels and resolve the patient's symptoms. Not only did this help the patient avoid major life-threatening complications, but ultimately allowed him to start second-line therapy for his disease soon after resolution of his HVS.

Written consent

We have written consent from our patient which we will provide in the event that it becomes necessary.

CRediT authorship contribution statement

Toufic Tannous: Writing – original draft, Conceptualization. **Gil Hevroni:** Writing – review & editing, Conceptualization. **Raiyan Islam:** Writing – review & editing. **Georgios Pongas:** Writing – review & editing, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

G.P is a shareholder of Amgen, Eli Lily, Crispr Therapeutics and equity holder of Mevox ltd.

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