Case Report

Ixazomib Treatment of IgA Multiple Myeloma With Hyperviscosity Syndrome

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Clinical Practice Points

- IgA-κ multiple myeloma (MM), although rare, can clinically manifest as hyperviscosity syndrome with cardiopulmonary symptoms and without other classic signs.
- Treatment with ITD (ixazomib, thalidomide, dexamethasone) can provide long-term control of disease activity in patients with MM.
- Ixazomib appears to be a promising therapeutic oral agent for the treatment of hyperviscosity syndrome in patients with MM.

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Introduction

Multiple myeloma (MM) accounts for 10% of all hematologic malignancies. Most patients with MM will present with anemia, bone pain, and elevated creatinine levels.[1] Although very rare in patients with MM, symptoms of hyperviscosity can occur, including mucosal bleeding, loss of vision, and neurologic abnormalities.[2] Therapeutic apheresis has been the standard of care for treating hyperviscosity syndrome (HVS).[3] Both bortezomib-based[4] and carfilzomib-based[5] strategies have been reported to demonstrate a rapid decline in serum immunoglobulins. However, to the best of our knowledge, information regarding the use of ixazomib (an oral proteasome inhibitor) in patients with MM and HVS is lacking. In the present report, we have described, to the best of our knowledge, the first case of an elderly woman with HVS as a result of IgA MM who was successfully treated with ITD (ixazomib, thalidomide, dexamethasone). Moreover, the mechanisms of HVS have been briefly discussed in the context of previous reported cases.

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Case Report

A 71-year-old white woman with a history of hypertension and a total hip replacement had presented with deterioration of physical fitness, dyspnea, and angina pectoris in the absence of visual disturbances. She also complained of lower back pain and pain in the right thigh of several weeks' duration. The patient appeared responsive at examination. Her blood pressure was 183/103 mm Hg, heart rate was 82 beats/min, and her respiratory rate was 16 breaths/min. Physical examination only demonstrated petechiae on both legs without signs of edema.

The laboratory findings demonstrated the following: hemoglobin, 6.2 mmol/L; platelet count, 319 × 10^9/L; albumin, 26 g/L; total protein, 121 g/L; creatinine, 72 μmol/L; and calcium, 2.65 mmol/L. Protein electrophoresis and immunofixation showed a monoclonal IgA of > 75 g/L, with an increased κ-free light chain of 653 mg/L. An electrocardiogram revealed sinus arrhythmia without signs of ischemia. Serum viscosity was elevated to 6.8 centipoise (cP; normal, ≤ 1.5 cP). All laboratory data are listed in Table 1. Additionally, a computed tomography scan revealed multiple osteolytic lesions in C6 and T8-T10, sacral bone, ilium, head of the femur, and head of the humerus, highly suggestive of MM. No signs of pulmonary edema or embolism was found on the computed tomography scan. The soft tissue and other organs appeared normal, without signs of plasmacytoma. Bone marrow aspirate showed κ-light chain-restricted plasma cells. Additional cytogenetic analysis revealed a translocation t(4;14) with a hyperdiploid karyotype without the loss of 17p13.1/TP53 or t(14;16).

Because of signs compatible with hyperviscosity, including symptoms of shortness of breath and angina pectoris, together

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Table 1 Laboratory Features of Our Patient

Laboratory Test	At Presentation	After Plasmapheresis	After 1 Cycle of ITD	After 5 Cycles of ITD	After 9 Cycles of ITD
Hemoglobin, mmol/L	6.2	7.1	6.9	8.2	8.2
Hematocrit	0.33	0.35	0.36	0.42	0.42
MCV, fL	98	95	93	93	98
Thrombocytes, $\times 10^9$/L	319	182	408	252	232
Leukocytes, $\times 10^9$/L	6.5	8.7	8.0	10.8	8.6
Neutrophils, $\times 10^9$/L	4.2	6.2	5.7	8.2	6.2
APTT, s	30	–	–	–	–
PT, s	12	–	–	–	–
Fibrinogen, g/L	2.9	–	–	–	–
D-dimer, µg/mL	0.72	–	–	–	–
Urea, mmol/L	7.2	–	–	–	–
Uric acid, mmol/L	0.61	–	–	–	–
Calcium, mmol/L	2.65	2.19	2.16	2.30	2.12
Phosphate, mmol/L	1.34	–	–	–	–
Albumin, g/L	26	42	30	32	30
Glucose, mmol/L	6.7	7.6	–	–	–
Creatinine, µmol/L	72	63	59	72	65
MDRD, mL/min	>60	>60	>60	>60	>60
Total protein, g/L	121	–	–	–	–
M-protein, g/L	63	7	6	<1	<1
Serum viscosity, cP	6.8	1.5	1.5	–	–
Paraprotein, g/L					
IgA	>75	10.60	4.38	1.41	1.19
IgG	2.98	–	–	–	–
IgM	0.16	–	–	–	–
β_2-Microglobulin, mg/L	7.9	–	–	–	–
κ-FLC, mg/L	653	–	49.8	14.4	8.24
λ-FLC, mg/L	5.25	–	6.76	9.69	8.63
FLC ratio	124.38	–	7.37	1.49	0.96

Abbreviations: APTT = activated partial thromboplastin time; cP = centipoise; FLC = free light chain; ITD = ixazomib, thalidomide, dexamethasone; MCV = mean corpuscular volume; MDRD = Modification of Diet in Renal Disease; PT = prothrombin time.

with a serum viscosity of 6.8 cP, therapeutic plasma exchange was immediately started. The removed plasma was replaced by a combination of 5% albumin and 0.9% saline with a prescribed volume of 50 to 60 mL/kg body weight of plasma removal. After 1 plasmapheresis treatment, her HVS had resolved in < 2 days. Subsequently, she was treated with 9 monthly cycles of ixazomib (4 mg on days 1, 8, and 15 of a 28-day cycle) and thalidomide (100 mg on days 1-21 of a 28-day cycle), combined with dexamethasone (40 mg weekly; ITD regimen according to the HOVON 126 study [Hemato-Oncologie voor Volwassenen Nederland; Hematology-Oncology for Adults in the Netherlands]). In that study, patients with newly diagnosed MM not eligible for autologous stem cell transplantation were treated with 9 cycles of ITD, followed by maintenance therapy with ixazomib. After this therapy, a rapid decrease in monoclonal IgA (Table 1) was observed in our patient, with a final result of a very good partial response (IgA after 9 cycles of ITD, 1.19 g/L; Table 1). The serum hemoglobin level had normalized within 2 months. The treatment was well tolerated, apart from complaints of nausea and first-degree peripheral polyneuropathy.

Discussion

Viscosity is the result of friction between molecules moving through a tube (ie, blood vessel) and is usually measured in units of centipoise (cP). The degree of viscosity depends on the temperature, shear, driving pressure, and vessel radius.[6] Because MM affects multiple constituents of the blood, viscosity could be affected.[7] Increased serum viscosity, determined by proteins, causes impaired blood flow, especially in the microvasculature, resulting in HVS. Typically, HVS will be characterized by the classic triad of mucosal bleeding, visual disturbances, and neurologic abnormalities, including dizziness, headache, hearing loss, nystagmus, and retinal hemorrhage. Although uncommon, pulmonary blood flow obstruction can result in shortness of breath, as was the case for our

Table 2 Clinical and Laboratory Features of 20 Patients With Multiple Myeloma and Hyperviscosity Syndrome

Investigator	Sex	Age, y	Paraprotein	Serum Viscosity[a]	Treatment	Survival, mo
Kopp et al,[18] 1967	M	52	IgG-κ	6.0	TPE + CP + RT	NR
Benninger et al,[19] 1971	M	80	IgG-λ	11[b]	TPE	0.6
Dine et al,[20] 1972	M	74	IgA, NR	5.2	TPE + melphalan for 1 y; CP thereafter	NR
Sugai,[21] 1972	F	48	IgA-κ	10.5	TPE + CP + prednisone	2
Wolf et al,[22] 1972	F	54	IgG-κ	3.5	Melphalan + prednisone + RT	13
	M	62	IgG-κ	31.7[c]	TPE + melphalan	28
Lindsley et al,[23] 1973	M	56	IgG-κ	18	TPE + melphalan + prednisone + RT	20
Tuddenham et al,[24] 1974	F	72	IgA-λ	7.8	TPE + CP	3
	M	55	IgA-λ	3.9	TPE + CP + prednisone + RT	NR
	F	68	IgA-λ	10	TPE + RT	1
	M	49	IgA-κ	3.2	TPE + melphalan + CP	NR
Virella et al,[25] 1975	M	59	IgA-κ	6.0	TPE + CP + prednisone	24
	F	55	IgA-λ	9.5	TPE + CP + prednisone	NR
Proctor et al,[26] 1984	F	66	IgE, NR	NR	TPE + CHOP	27
Coppell,[27] 2000	M	58	IgG-κ	9.3	TPE + melphalan + chemotherapy, NOS + aHCT	NR
Chiang et al,[28] 2000	M	57	IgG-κ	3.1	TPE + chemotherapy, NOS	NR
Park et al,[29] 2005	F	68	IgG, NR	5.2	CP + prednisone	>25
Santos et al,[30] 2012	F	65	IgA-κ	NR	TPE + dexamethasone	NR
Golesic et al,[31] 2015	M	44	IgG, NR	3.0	TPE + CP + bortezomib + dexamethasone + aHCT	NR
Present patient	F	71	IgA-κ	6.8	TPE + ixazomib + thalidomide + dexamethasone	>48

Abbreviations: aHCT = autologous hematopoietic cell transplantation; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CP = cyclophosphamide; F = female; M = male; NOS = not otherwise specified; NR = not reported; RT = radiotherapy; TPE = therapeutic plasma exchange.
[a]All measurements were performed at 37°C, unless otherwise stated.
[b]Serum viscosity measured at 22°C.
[c]Serum viscosity measured at 13°C.

patient.[8] Owing to microcirculatory obstruction, patients might present with thrombotic complications. In contrast, an excess of paraproteins could lead to impairment of hemostasis, resulting in bleeding. Our patient had had petechial hemorrhages with a normal platelet count. This could have resulted from the inhibition of the polymerization of fibrin monomers by paraproteins, which is a required for fibrin formation,[9] or acquired von Willebrand syndrome.[10]

The causes of hyperviscosity can be classified into monoclonal hyperglobulinemia, which has been frequently observed in Waldenström macroglobulinemia (WM),[8] polyclonal hyperglobulinemia, and marked red blood cells (polycythemia vera) or white blood cells (chronic myeloid leukemia).[3] However, in rare circumstances, monoclonal hyperglobulinemia caused by MM can also lead to symptomatic HVS, with an incidence of 2% to 6%.[2]

In MM (and WM), serum viscosity reflects the amount and properties (molecular size) of the paraprotein.[11] Physicochemical differences exist between the subclasses of immunoglobulins. IgG, the most abundant isotype in serum, is a monomer with a molecular weight of 150 kD. Monomeric serum IgA is the second isotype in serum and has a molecular weight of 160 kD. IgM is a large star-shaped pentamer with a molecular weight of 925 kD[12] and has the greatest effect on serum viscosity. For comparison, albumin has a molecular weight of 65 kD. Although HVS has occurred uncommonly in patients with MM, those patients with the IgG3 subclass are more likely to develop HVS compared with patients with other subtypes owing to concentration-dependent aggregation.[13] HVS with the IgA subtype, as was the case for our patient, can occur because this paraprotein is subject to a high degree of polymerization.[14] Symptoms of HVS will usually appear when the serum viscosity has exceeded 4.0 to 5.0 cP, which corresponds to a serum IgM of ~3 g/dL, serum IgG of 4 g/dL, and serum IgA of 6 g/dL. However, the level at which patients become symptomatic has varied.[2] Our patient had become symptomatic at a plasma viscosity of 6.8 cP.

In the case of symptomatic HVS, therapeutic plasma exchange should be started immediately to quickly reduce the blood viscosity by removing excess immunoglobulins from the circulation. In general, the use of therapeutic plasma exchange is a safe and well-tolerated treatment of hyperviscosity.[15] For our patient, only 1 plasma exchange was needed, which resulted in a decline in serum viscosity from 6.8 to 1.5 cP. Also, the paraprotein level had decreased from 63 to 7 g/L (Table 1). As suggested by our findings, treatment with ixazomib can contribute significantly to symptom improvement. Recurring clinical manifestations of hyperviscosity can be prevented by keeping the serum viscosity to less than the symptomatic threshold of the patient.

Disease-specific cytoreductive therapy will often be started just after therapeutic plasma exchange. At present, the most effective frontline therapies in the nontransplant setting include Dara-VMp (daratumumab, bortezomib, melphalan, prednisone), DRd (lenalidomide, low-dose dexamethasone, daratumumab), and VRd (lenalidomide with low-dose dexamethasone plus bortezomib).[16] More recently, ixazomib, a second-generation orally available proteasome inhibitor, has been approved for the treatment of relapsed or refractory MM.[17]

It has not yet been confirmed in clinical studies whether control of hyperviscosity prolongs overall survival or only reduces the morbidity that results from the underlying malignancy. Furthermore, no clinical trials have been performed to determine the effectiveness of systemic therapy for HVS in the context of underlying MM. A PubMed search was performed for studies describing HVS in patients with MM. Studies were excluded from the present study if they had reported light chain myeloma, monoclonal gammopathy of undetermined significance, smoldering MM, and/or WM. Although rare, HVS has been reported previously in patients with MM.[18-31] Because previous reports of HVS dated back > 50 years[18] and owing to its low incidence, the clinical characteristics of HVS remain largely unknown. A total of 19 additional cases of HVS in association with MM reported between 1967 and 2015 were identified. The details are presented in Table 2, including the present patient (n = 20 patients). The median age at the diagnosis of HVS with MM was 58 years (range, 44-80 years), and most patients were men (n = 11; 55%). In contrast to a large reported myeloma cohort,[1] the IgA paraprotein frequency in the present study was 53% (vs. 21%). Four patients had had a diagnosis of IgA κ, four patients had had a diagnosis of IgA λ, and for one patient, the light chain isotype was not described. IgG paraprotein frequency was observed in 45% of the patients (n = 9) compared with 52% in the MM cohort.[1] Of these 9 patients, 6 had had a diagnosis of κ as the light chain isotype; the subtype for the 3 remaining patients was not described. IgE MM had been diagnosed in 1 patient (5%) without a reported light chain isotype. The mean serum viscosity measured at 37°C (n = 16) was 6.1 (range, 3-18). In 2 patients,[19,22] the serum viscosity was measured at 22°C and 13°C, and in 1 report,[26] the viscosity level was not specified. Of the 20 patients, 17 (85%) had received plasma exchange therapy to lower the serum viscosity quickly. Most patients (n = 17; 85%) were treated with adjuvant systemic therapy. The most frequently used treatment regimen was cyclophosphamide and prednisone (n = 6; 32%). Melphalan was used in 6 patients (30%) and combined with prednisone for 2 patients. Two patients had undergone autologous hematopoietic cell transplantation. One patient was, as was the present patient, also treated with a proteasome inhibitor (bortezomib) combined with the cyclophosphamide and dexamethasone regimen, followed by autologous hematopoietic cell transplantation. To date, no studies describing the effect of ixazomib combination therapy have been reported. Heterogeneous and incomplete reporting of outcome measures in the reported studies precluded the possibility of drawing conclusions regarding the efficacy of these treatment strategies.

Conclusions

The findings from the present case report have shown that IgA-κ MM can clinically manifest as HVS with cardiopulmonary symptoms without the other classic signs of HVS, including mucosal bleeding and visual and neurologic abnormalities. The standard of care for treating HVS is plasmapheresis. In addition, treatment with ITD can provide long-term control of disease activity in patients with MM. The decline of the paraprotein with this triple combination induction regimen that includes ixazomib raises the possibility of ixazomib as a treatment of HVS in patients with MM. Because of the low degree of toxicity, ixazomib appears to be a promising therapeutic oral agent suitable for all patient groups.

Disclosure

The authors have stated that they have no conflicts of interest.

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