Daratumumab-Based Therapy for IgM Multiple Myeloma With Hyperviscosity Syndrome: A Case Report

Case report

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Clinical Practice Points

- IgM-multiple myeloma (IgM-MM) is a rare hematologic malignancy accounting for 0.5% of all myelomas. The differential diagnosis with Waldenström macroglobulinemia (WM, which shares the same IgM-isotype monoclonal component) is of critical importance, since their therapeutic approaches greatly differ.
- Hyperviscosity syndrome (HVS) secondary to hypergammaglobulinemia is more frequent with WM, but it can occur with MM.
- We reported the case of a 60-year-old patient with IgM-MM presenting with anemia, bone lesions and HVS due to hypergammaglobulinemia who underwent urgent plasmapheresis and was safely and successfully treated with a 4-drug induction regimen with daratumumab, bortezomib, cyclophosphamide and dexamethasone plus autologous stem-cell transplantation.

KEYWORDS: multiple myeloma, IgM, hyperviscosity syndrome, daratumumab, plasmapheresis

Introduction

IgM multiple myeloma (MM) is a rare hematologic malignancy accounting for 0.5% of all myeloma cases.[1] While IgM paraprotein is the hallmark of Waldenström macroglobulinemia (WM), it can be produced by various types of B-cell malignancies, ranging from marginal zone lymphoma to MM.[2] IgM MM and WM are two distinct hematologic disorders that share the same immunoglobulin heavy chain as well as some clinical features, thus making the differential diagnosis potentially challenging. Considering the different management and prognosis between MM and WM, a proper diagnosis in patients presenting with an IgM paraprotein is imperative.[3] Hyperviscosity syndrome (HVS) is characterized by neurological and cardiovascular symptoms, visual abnormalities and mucosal bleeding caused by increased serum viscosity, in the majority of cases due to the presence of monoclonal hypergammaglobulinemia. HVS is a common clinical feature of WM (40-90%) as opposed to MM, in which HVS is rarely described (2-6%).[4] HVS is mostly observed in the presence of an IgA or IgM paraprotein, due to their higher molecular weight (160 kilodaltons [kDa] and 925 kDa, respectively), as compared to IgG (150 KDa), and their tendency to polymerize.[4,5] Given the rarity of both IgM-MM and HVS in MM patients, most data about IgM-MM and its treatment come from case reports and small case series. Herein we report the case of a patient diagnosed with IgM-MM presenting with HVS treated with plasmapheresis and a 4-drug, daratumumab-based induction therapy.

Case report

A 60-year old Caucasian woman without relevant medical history, except for arterial hypertension, was admitted at the emergency department with progressively worsening fatigue, visual disturbance and dizziness. She also reported unintentional weight loss and upper back pain in the previous month. Physical examination and vitals were normal. Laboratory findings (Table I) revealed moderate anemia (Hb 7.5 g/dL), normal platelets and white blood cell count, as well as normal serum calcium and creatinine levels. The serum immunofixation showed an IgM-kappa monoclonal component, representing the 52.8% (5600 mg/dL) of total serum proteins as shown by serum electrophoresis in the gamma region. Kappa free light chain (κ FLC) was 2.34 mg/dL; urine immunofixation and Bence–Jones protein were negative. The low-dose whole-body computed tomography (CT) scan showed diffuse osteolytic lesions in skull, vertebrae, sternum, ribs and hips, without signs of nodal or parenchymal involvement or plasmacytomas. All lesions were positive by fluorodeoxyglucose positron emission tomography (FDG-PET/CT) (standardized uptake value [SUV] max 2.75). Bone marrow biopsy revealed 60% of monoclonal plasma cells CD38+/CD138+/CD56-/CD19/CD20- by immunophenotyping performed on bone marrow blood via flow cytometry with intracytoplasmic κ-restricted light chains. Plasma cells were negative for high-risk cytogenetic abnormalities [del(17p), t(4;14), t(14;16), amp(1q)] by fluorescent in situ hybridization (FISH) analysis. The assessment of MYD88 L265P mutation was negative by digital droplet polymerase chain reaction (ddPCR).

In light of the clinical findings suggestive for HVS and the elevated IgM levels, plasmapheresis was started together with a short course of high-dose dexamethasone (20 mg for 4 days); a rapid amelioration of symptoms was obtained after 2 plasmaphereses. The patient was enrolled in the EMN18 clinical trial (NCT03896737) and randomized to receive induction therapy with daratumumab (D, 16 mg/kg on days 1, 8, 15 and 22 for the first 2 cycles, and on days 1 and 15 thereafter), bortezomib (V, 1.3 mg/m^2 on days 1, 8, 15 and 22), cyclophosphamide (C, 300 mg/m^2 on days 1, 8, 15, and 22) and dexamethasone (D, 40 mg on days 1, 8, 15 and 22) for four 28-day cycles. Given the lack of data on the use of monoclonal antibodies such as daratumumab in MM patients presenting with HVS and the risk of IgM flare reported with the use of rituximab in patients with IgM levels >5000 mg/dl, we performed plasmapheresis along with the administration of VCD on day 1 of cycle 1, followed by the first

daratumumab infusion on day 2. Neither daratumumab infusion-related reactions (IRRs) nor IgM flare occurred. After the first D-VCD cycle, the monoclonal component dropped from 5600 mg/dl to 2293 mg/dl (partial remission). A total of 4 induction cycles with D-VCD were administered, followed by hematopoietic stem-cell mobilization with cyclophosphamide (3 g/m^2) as per protocol, with a total of $15.7x10^6$/Kg harvested CD34+ cells. Pre-transplant disease assessment showed the absence of M-component on both serum electrophoresis and immunofixation; the bone marrow aspirate showed the absence of aberrant plasma cells; and minimal residual disease (MRD) assessed by next-generation flow cytometry (NGF, EuroFlow Consortium) was negative at a sensitivity of 10^{-6}. FDG-PET/CT was also negative. High-dose melphalan (200 mg/m^2) followed by autologous stem-cell transplantation (ASCT) was then performed. Consolidation with 2 cycles of D-VCD has been recently completed and the patient is currently in complete remission from MM, with a MRD-negative status.

Discussion

The presence of an IgM-monoclonal component immediately raises the suspicion of WM, although it can also be attributed to IgM-MM, chronic lymphocytic leukemia or marginal zone lymphoma.[6] Furthermore, HVS was reported not only in WM patients, but also in patients with IgM-MM, thus suggesting that HVS is most likely related to the chemical-physical properties of the IgM, rather than to the underlying hematologic disorder.[3] IgM-MM is a rare hematologic malignant condition and data regarding the safety and efficacy of novel agents for its treatment are scarce. Moreover, the differential diagnosis between WM and IgM-MM can be particularly challenging. In our case, the diagnosis of IgM-MM was supported by the results of flow cytometry and immune histochemistry analyses on bone marrow cells (CD138+, CD20-, CD56-), by the absence of MYD88 L265P mutation,[7] and by the observation of multiple lytic lesions without lymphadenopathy, hepatomegaly or splenomegaly.[6]

Once the diagnosis is established, treatment must be initiated. The short-term goal of treatment is directed at rapidly reducing the excess immunoglobulin in order to decrease the serum viscosity and revert hyperviscosity-related symptoms; the long-term goal aims at controlling the underlying MM clone associated with the IgM production. While the former goal can be pursued through the use of plasmapheresis, the latter requires the prompt initiation of anti-MM treatment.[4] In our case, 2 consecutive plasmaphereses decreased IgM levels (5600 mg/dl to 3580 mg/dl) enough to significantly reduce hyperviscosity-related symptoms. Recently, the anti-CD38 monoclonal antibody daratumumab has been added to all the standard induction regimens recommended for the treatment of newly diagnosed MM patients, thus becoming a backbone in this setting for both ASCT-eligible patients (daratumumab-bortezomib-dexamethasone plus either thalidomide [D-VTd] or lenalidomide [D-VRd]) and ASCT-ineligible patients (daratumumab plus either lenalidomide-dexamethasone [D-Rd] or bortezomib-melphalan-prednisone [D-VMP]).[8] Having considered the young age and fitness of our patient, we offered her to participate in a clinical trial for ASCT-eligible patients with the opportunity of receiving daratumumab as part of the upfront treatment. To the best of our knowledge, there is neither a clinical trial investigating the efficacy of plasmapheresis in association with systemic therapy in MM nor data about the use of daratumumab in patients with HVS. Pre-emptive plasmapheresis prior to rituximab administration is recommended in WM patients with IgM levels ≥4000 mg/dl to avoid IgM flare and hyperviscosity.[9] Therefore, to avoid such risks (which, however, have not been previously described in MM), we planned a pre-emptive plasmapheresis on the first day of cycle 1, while daratumumab was safely administered the following day (C1D2) without IRRs or IgM flare.

Data regarding the safety and efficacy of approved anti-MM therapies in patients with IgM-MM are scarce, mainly coming from case reports or small-case series, and do not allow any specific treatment recommendation. However, a retrospective analysis on 134 IgM-MM patients

variably treated with conventional chemotherapy, novel agents and ASCT showed that IgM-MM patients exhibited similar responses and survival outcomes to those observed in other more frequent MM conditions.

Conclusion

In conclusion, we reported the first case of an IgM-MM presenting with HVS that was successfully treated with a daratumumab-based induction regimen in combination with plasmapheresis, showing that such strategy was safe and effective in reverting HVS symptoms and in inducing a deep remission.

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Table I. Main clinical and laboratory findings

Laboratory tests	Diagnosis	After plasmapheresis	After 1st cycle of Dara-VCD	After 4th cycle of Dara-VCD	After consolidation
Hemoglobin (g/dL)	7.5	9.9	10.1	11.6	11.4
Thrombocytes (x10^9/L)	525	266	286	478	56
Leukocytes (x10^9/L)	5.3	5.65	4.38	1.92	3.71
Neutrophils (x10^9/L)	2.9	5.36	2.89	0.90	2.50
Calcium (mmol/L)	2.06	2.31	2.33	2.15	2.15
Albumin (g/dL)	1.6	-	4	3.7	-
Creatinine (mg/dL)	0.4	0.66	0.75	0.62	0.66
M-protein (mg/dL)	5600	3580	2296	164	0
Paraprotein (mg/dL)	positive	positive	positive	negative	negative
IgM	5800	3456	3560	151	13
IgA	116	44	76	31	17
IgG	360	205	301	338	504
ß2-microglobulin (mg/L)	1.7	-	-	-	-
Kappa FLC (mg/dL)	2.34	-	1.62	0.98	0.46
Lambda FLC (mg/L)	0.61	-	0.69	0.81	0.35
Ratio FLC	3.84	-	2.35	1.21	1.31
Bence–Jones urinary protein	negative	-	negative	negative	negative
BM aspirate (plasma cells %)	15%	-	-	MRD negative	MRD negative
PET scan	positive	-	-	negative	negative

Abbreviations. Dara, daratumumab; V, bortezomib; C, cyclophosphamide; D, dexamethasone; FLC, free light chain; BM, bone marrow; PET, positron emission tomography; MRD, minimal residual disease.

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