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Case Report

Extensive Extramedullary Involvment in Patient with IgD Multiple Myeloma Progressive Disease: Efficacy of the Novel Agents

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Abstract

The treatment of patients with Multiple Myeloma is dramatically evolving. At the present, multiple classes of agents with distinct mechanisms of action are available and the current strategies improved significantly the outcome of Myeloma Multiple patients. Nevertheless, subsets of patients with aggressive disease and shorter survival are still present. Indeed, immunoglobulin D Myeloma is an aggressive condition associated with poor outcome and the extramedullary disease is a clinical high-risk characteristic, which remains incurable even in the era of the novel agents.

Here we present a patient with Immunoglobulin D Myeloma Multiple who was refractory to a first-line bortezomib-based treatment and developed a progressive disease characterized by extensive extramedullary involvement in a large muscle area. The patient was treated, as second line of therapy, with Daratumumab associated to Lenalindomide and Dexamethasone obtaining a stable biochemical complete remission and the complete cure of the large extramedullary disease, as documented by the Magnetic Resonance Image.

Daratumumab is the first-in-class human monoclonal antibody against CD38 cells and is currently approved for the treatment of patients with relapsed/refractory Myeloma who have failed previous lines of treatments. So far, limited data support the efficacy of monoclonal antibody therapy in patients with extramedullary disease or with IgD Myeloma Multiple and the data mainly described patients in advance relapse who were previous heavily treated with more than two lines of therapy.

This challenging case-report with the associated images highlights the efficacy of Daratumumab when used as the second-line therapy even in patients with aggressive disease.

Keywords: Multiple Myeloma; Extramedullary Disease; Daratumumab; IgD

Introduction

The treatment of patients with Multiple Myeloma (MM) is dramatically evolving. The advent of new agents such as proteasome inhibitors, immunomodulatory drugs and more recently monoclonal antibodies improved significantly the outcome of MM patients. Nevertheless, subsets of patients with aggressive disease and shorter survival are still present. Indeed, Immunoglobulin (Ig) D MM is a rare subtype of MM accompanied with aggressive course and poor outcome. Extramedullary Disease (ED), defined by the presence of extraskeletal (i.e. soft-tissue or visceral) clonal plasma cells infiltrates, is reported to affect more frequent the IgD MM patients and is a clinical high-risk characteristic, which remains incurable even in the era of the novel agents. Here we report a challenging case of IgD MM characterized by progressive disease with extensive extra osseous involvement and successfully treated by Daratumumab, in the second line of therapy.

Case Report

A 77-year-old male presented with anemia and pathological fracture to the femoral bone in 2017. Serum Immu¬Nofixation Electrophoresis (sIFE) and Bence-Jones immu¬nofixation on urine (urine IFE) evidenced the presence of an IgD λ monoclonal component and λ light chains respectively. Protein electrophoresis showed a monoclonal spike (M spike) with an IgD λ M component of 150mg/L; the immunoglobulin dosage showed immunopharesis. Renal function was conserved, but relevant proteinuria (2.19 gr/die) was documented. The determination of serum Free Light Chains (FLC) detected a high level of lambda at 392 mg/L with a significantly decreased ratio at 0.04. The calcium level was normal and hemoglobin value was 10.5 g/dL, but the patient is carrier for beta-thalassaemia trait. Bone marrow biopsy confirmed the presence of 30% plasma cell infiltration lambda restricted. Convectional skeletal radiography showed osteolytic lesions in the skull, on the right radium bone and a large osteolytic lesion on the right femur bone. Therefore, IgD-λ MM was diagnosed and the International Staging System was II. The first line of therapy consisted of nine 35-day cycles of bortezomib-melphalan-prednisone (VMP regimen) [1], from October 2017 to August 2018. A partial response was documented after 4 cycles of VMP. The evaluation at the end of cycle nine documented an

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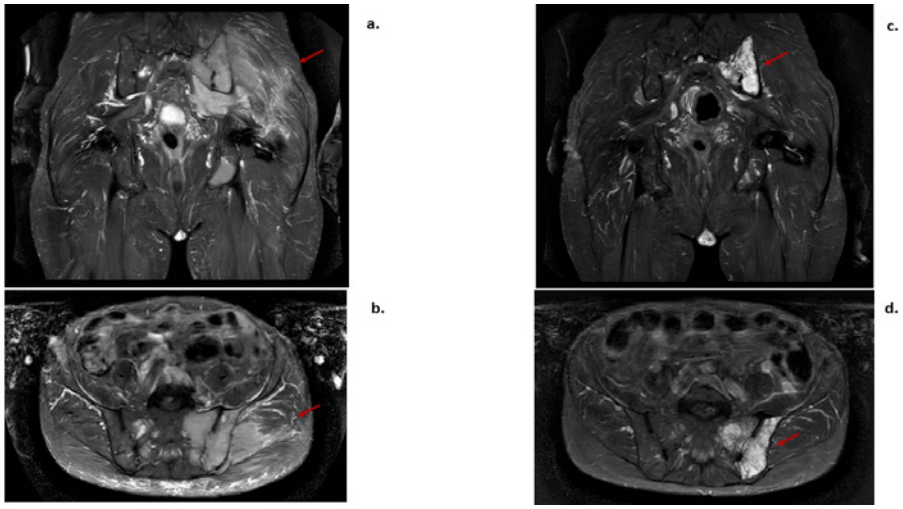

Figure1 : MRI images of the IgD Myeloma Multiple patient with aggressive and extensive extramedullary disease before and after the Daratumumab treatment. **a.** STIR coronal and **b.** STIR axial images before treatment. The images display a significant increased signal intensity on STIR at the left sacral ala, at the left iliac and ischiatic bone. A dramatically extensive hyperintense signal in T2-weigthed STIR image at the left gluteal and piriformis muscle detected an extensive area of extramedullary disease (red arrow). **c.** STIR coronal and **d.** Axial images after Daratumumab treatment, displaying a normal signal intensity in the gluteal muscle area due to reappearance of normal muscle in the gluteal area. There is a significant residual increased signal intensity on STIR images at the bone left sacrum, left iliac and ischial bone due to cystic involution of residual bone disease (red arrow).

IgD λ M component of 240 mg/dL, an increased level of the FLC measurements (sFLC κ/λ ratio 0.01) and marked increase of the proteinuria (4.14 gr/day). On September 2018, due to intense sacral pain, Magnetic Resonance Imaging (MRI) was performed. The T1-weighted and STIR (Short Tau Inversion Recovery) images detected a large hypointense and hyperintense image respectively involving the left sacral ala, the left iliac and ischiatic bones. Furthermore, a dramatically extensive hyperintense signal in STIR image at the left gluteal and piriformis muscle detected an extensive area of ED. According to International Myeloma Working Group (IMWG) criteria, the "progressive disease" was established and a new therapy attempt was discussed. At October 2018, we proposed a second line regimen with Daratumumab, Lenalidomide and Desamethazone (D-Rd). The patient received 28-day cycles of Lenalidomide (25 mg orally on Days 1 to 21 of each cycle) Dexamethasone (20 mg orally weekly) and Daratumumab (16 mg/kg intravenously weekly during Cycles 1 and 2, every 2 weeks during Cycles 3 to 6, and every 4 weeks thereafter until disease progression).

Daratumumab was well tolerated with no complication or infusion-related reaction.

The patient was regularly monitored with sIFE, urine IFE, FLC and M-spike measurements in order to assess the response to the treatment in addition to evaluation of other classical serological parameters, including β2 microglobulin, lactate dehydrogenase, Calcium and hemoglobin. Bone pain relief and a biochemical partial response were achieved after 2 cycles of D-Rd and, according to IWMG criteria, a biochemical complete remission was documented after 11 cycles: the protein electrophoresis detected ipogammaglobulinaemia, the IgD λ M component was undetectable, the urine IFE was negative for Bence-Jones protein, and the proteinuria was significant decrease to 0.42 gr/24 hours. The sIFE was negative for monoclonal IgD but detected a monoclonal component IgG kappa, a monoclonal antibody interference limited to Daratumumab as it has been described [2].

MRI was repeated on August 2019 after 12 cycles and documented a dramatic reduction of both the hypointense signal in T1-weighted images and the corresponding hyperintense signal in STIR images in the sacrum left region as for cystic involution of residual bone disease. Regarding the large muscle area, previously largely involved, was completed cured with no residual hyperintense signal image. As of January 2020, the patient is still on complete remission and on D-Rd treatment.

Discussion

IgD MM is an uncommon variant of MM with an incidence of about 2.0% [3-4]. It has been reported that IgD myeloma is associated with a relatively high incidence of high risk-features as Bence Jones proteinuria, renal failure, extra osseous disease, hypercalcemia, and amyloidosis [3-7]. The IgD MM patients have a poor outcome when compared with other subtypes, with a median survival between 13 and 21 months [3,6-7], although in the era of the novel agents, recent reports describe a similar outcome in comparison to the other type of immunoglobulin MM [8-9].

Among the high risk-features of the IgD myeloma, the ED, is observed with higher frequency in patients with IgD MM in comparison to other patients (19 to 63% *vs.* 13 to 19%) [3,7,10]. Indeed, in patients with MM disease, the reported rates of ED at relapse have ranged from approximately 3% to 30% [13-17]. Of note, the incidence of ED, both at diagnosis and during follow-up, has significantly increased in the more recent years [13] and the possible association with the expanding use of novel agents has been discussed [18-20]. Indeed, high dose treatment or novel agents seem not to directly increase the risk of ED, which might be related with the availability of more sensitive imaging techniques and the prolongation of patients' survival [13,18]. Regardless of such speculations, it is to note that the development of ED, at diagnosis or at relapse, is associated with more aggressive disease and shorter overall survival [13-17]. Indeed,

the reported survival is approximately 12 months in ED patients if the extramedullary mass is adjacent to the bone and less than 6 months if the myeloma mass of soft tissue is not linked to the skeletal involvement of MM [17]. Unfortunately, even in the era of the novel agents, extramedullary relapse remains incurable [9-10].

Daratumumab is a humanized monoclonal antibody targeting CD38 cells with a direct on-tumor and immunomodulatory mechanism of action. Tumor cell death is induced by Daratmumab *via* several CD38+ immune-mediate actions including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis, apoptosis and modulation of CD38 enzymatic activity. Daratumumab exhibits immunomodulatory effects as well through the reduction of CD38+ immunosuppressive cellular populations [19-20].

In 2015, the monoclonal Ab Daratumumab has been approved by the USA Food Drug Association as a single-agent treatment for patients with relapsed/refractory MM who have failed more than three lines of treatment regimens and revealed response rates of 31.1% [21-22]. An updated pooled analysis of these studies reported that 12% of patients had at least 1 extramedullary plasmocytoma [23]. Importantly, the overall response rates in patients with ED were significantly lower that which observed in the overall population (16.7% *vs.* 33.1%, respectively).

Subsequent efforts have focused on combining Daratumumab with other standard myeloma agents. In two randomized, open-label, active-controlled, phase 3 studies, CASTOR [24] and POLLUX [25], Daratumumab in combination with standard-of-care regimens (Lenalidomide and Dexamethasone [Rd] or Bortezomib and Dexamethasone [Vd]) respectively, demonstrated superior clinical benefit compared with Rd or Vd alone in patients with relapsed/refractory MM in term of overall response rate and risk of disease progression or death. However, the efficacy of these combinations in patients with ED has not been reported. At this time, limited data exist regarding the efficacy of Daratumumab, either alone or in combination, in patients with ED. Moreover, most of the data are represented by case reports describing patients heavily treated with more than one previous line of therapy [26-27]. Of note, since most of the patients recruited in clinical trials were IgG, IgA, or Bence Jones proteins MM, the efficacy of Daratumumab in patients IgD MM is not established and only an anecdotal case report describing the Daratumumab role in pluri-treated IgD MM patient [28].

To the best of our knowledge, this is the first case report demonstrating an example of IgD MM in progressive disease with an extensive ED responsive to Daratumumab. We believe that this case and the associated images are challenging to further evaluations regarding the Daratumumab role when used as second-line of therapy in ED and/or IgD MM patients.

Conclusion

IgD MM is an aggressive condition with poor outcome and shorter survival. It is frequently associated to EM involvement: a clinical high-risk characteristic, which remains incurable. We herein reported a clinical case documenting the efficacy of Daratumumab therapy in the management of IgD MM patient with extensive extramedullary progressive disease. The present observation is promising and warrants for further investigations on the role of Daratumumab in similar, high risk, clinical subsets.

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