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Case Report

Bilateral Bulky Adrenal Plasmacytomas with Very Good Response to Daratumumab-Based Therapy

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Abstract

Extramedullary myeloma disease represents an infrequent but aggressive variant of multiple myeloma (MM), and it is associated with a poor prognosis. An optimal treatment strategy for this clinical subset has not yet been clarified. In this report, we demonstrate a patient with MM with the uncommon manifestation of plasmacytomas with a very high burden in the bilateral adrenal glands at diagnosis, which were treated successfully with daratumumab-based second-line therapy.

Keywords: Adrenal plasmacytoma, daratumumab, extramedullary plasmacytoma, multiple myeloma

Introduction

Extramedullary myeloma disease (EMD) represents an uncommon but aggressive variant of multiple myeloma (MM), characterized by the development of bone marrow-independent myeloma clones. Most cases develop at the time of relapse, with a reported incidence rate from 3.4% to 10%. As an initial presentation of MM, it occurs in only 0.5%–4.5% of patients, frequently in the skin and soft tissue.[1] Treatment remains challenging, and the presence of EMD still confers a poor prognosis despite dramatically improved survival in patients with MM in the era of novel agents. Here, we report a case of *de novo* MM unusually presenting as bilateral giant adrenal plasmacytomas, which were managed successfully with a second-line, daratumumab-containing regimen.

Case Report

A 58-year-old male with a history of hypertension and diabetes presented with bilateral huge suprarenal tumors discovered incidentally by abdominal sonography. The tumors were 13.5 cm × 10.5 cm on the left side and 12 cm × 10.5 cm on the right, with increased attenuation at 35–50 Hounsfield units in unenhanced computed tomography. Kidney magnetic

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resonance imaging (MRI) displayed their heterogeneous hyperintense signals in T2-weighted images, marked restricted diffusion, with an internal fibrous structure [Figure 1]. Apart from an increased creatinine level of 1.86 mg/dL noted in the clinic, he had no complaints of pain or other symptoms and no relevant family history. Laboratory tests, including hemogram, lactate dehydrogenase, serum protein, electrolytes, and hormonal profile, were all within normal values. Due to an inconclusive core needle biopsy result, he underwent exploratory laparotomy. Intraoperative frozen section biopsy indicated a plasmacytoma, which stained positive for CD138 and predominantly lambda light chain. The intended resection was therefore canceled.

A diagnosis of MM was then evident. A bone marrow biopsy revealed infiltration of 10% lambda-restricted plasma cells. The presence of immunoglobulin (Ig) D lambda monoclonal gammopathy was confirmed by serum and urine electrophoresis, with a high level of serum IgD at 1963 IU/mL and free lambda light chain (FLLC) at 2197 mg/L with a significantly decreased ratio at 0.004. The serum β2-microglobulin level was 3.88 mg/L. He had a normal bone marrow karyotype, but 17p deletion was detected by fluorescence *in situ* hybridization. There were no osteolytic lesions, but his renal function further deteriorated. The patient was finally diagnosed with IgD-λ MM, Revised International Staging System stage III, with 17p deletion and extensive extramedullary plasmacytomas in bilateral adrenal glands.

The patient received 21-day cycles of bortezomib, thalidomide, and dexamethasone (VTd), the standard first-line regimen approved in Taiwan for transplant-eligible MM patients. Despite the initial efficacy of VTd in achieving negative serum immunofixation and renal function recovery, his serum IgD and FLLC levels began to increase just before the fourth cycle of treatment, indicating progressive disease. His adrenal tumors had regressed but remained at 9 cm in diameter. Therefore, he commenced second-line therapy with daratumumab, bortezomib, and dexamethasone (DVd). This regimen was used in the CASTOR trial, and it demonstrated comparable survival improvements with a lenalidomide-based regimen for relapsed/refractory high-risk myeloma.[2,3] The first treatment cycle showed a significant effect with undetectable serum IgD and a normalized free light chain (FLC) ratio. Follow-up MRI after three 21-day cycles of DVd demonstrated a substantial reduction in the adrenal tumors with only minimal residuals on the right side and 4.5 cm in diameter on the left side [Figure 2]. With the daratumumab-containing regimen, he sustained a very good partial response with negative serum immunofixation and only a 3.5 cm left adrenal plasmacytoma at 15 months after the initial diagnosis. An autologous stem cell transplant was planned but deferred due to COVID-19 infection.

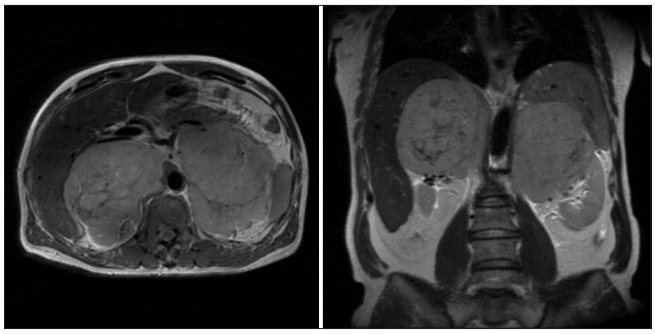

Figure 1: Large enhancing suprarenal masses with heterogeneous T2 hyperintensity and internal fibrous structure, up to 13.5 cm in size, shown in the horizontal section (left) and coronal section (right) of T2-weighted kidney MRI. MRI: Magnetic resonance imaging

Discussion

Extramedullary plasmacytoma involving bilateral adrenal glands is very rare, making it a diagnostic challenge. To date, only 13 cases of adrenal plasmacytoma at diagnosis have been reported, most of which were solitary plasmacytomas diagnosed after tumor resection [Table 1].[4-16] The presence of plasmacytoma of considerable size in patients with newly diagnosed MM has also rarely been reported in the literature, and therefore, information about optimal management is limited.

EMD is an independent adverse prognostic factor for MM and is prone to harbor high-risk cytogenetics such as deletion 17p, nuclear expression of p53, and translocation (4;14).[17] Nevertheless, there is currently no standard treatment specifically for EMD. We chose second-line DVd for our patient based on data derived from high-risk myeloma without knowing its efficacy in EMD. In addition to the lack of prospective trials on this uncommon subset of patients, most phase III trials of MM have not included EMD as a predefined subgroup. Data regarding the treatment efficacy, particularly of newer agents, are limited, heterogeneous, and predominantly derived from retrospective studies. Analysis from the European Society for Blood and Marrow Transplantation showed a trend of better progression-free survival with bortezomib-based induction versus nonbortezomib regimens.[18] Beksac *et al*. reported a 57% overall response rate (ORR) in favor of immunomodulatory drugs compared with proteasome inhibitors and chemotherapy.[19] While in phase II clinical trial of pomalidomide plus dexamethasone (Pd) for relapsed refractory MM, there were only four responders among the

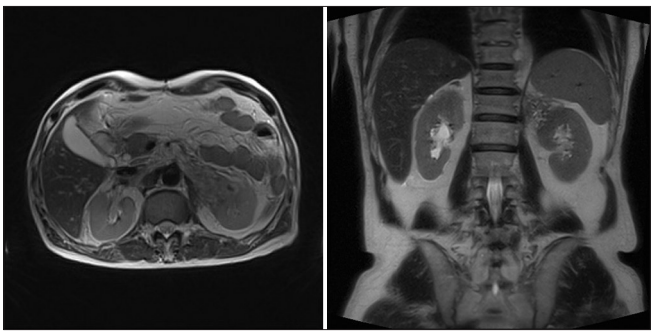

Figure 2: MRI after three cycles of DVd revealed a significant reduction in the adrenal tumors. MRI: magnetic resonance imaging

Table 1: Patient's demographics, disease characters, diagnosis, and treatment of previous case reports

Study	Age	Gender	Symptoms	Serum monoclonal protein	Side; size (cm)	Diagnosis	Treatment	Follow-up (months); treatment response
Kahara *et al*.[4]	52	Male	Nil	IgG λ	Right; 4	Surgery	Surgery + RT + chemotherapy (VAD)	12; CR
Fujikata *et al*.[5]	77	Male	Back pain	IgG λ	Right; 10	Surgery	Surgery + RT	12; CR
Rogers *et al*.[6]	75	Female	Abdominal pain	Absence	Right; 3.5	Surgery	Surgery + RT	N/A
Li *et al*.[7]	64	Female	Back pain	Absence	Right; 6, left; 4	Surgery	Surgery + RT	N/A
Ahmed *et al*.[8]	47	Male	Nil	IgG κ	Right; 8, left; 8	Biopsy	Chemotherapy (VAD-EDAP) + ASCT	50; CR
Blanco Antona *et al*.[9]	76	Female	Abdominal pain	N/A	Left; 6	Surgery	Surgery + RT	40; CR
Cao *et al*., 2014[10]	26	Male	Flank pain	Absence	Right; 4.5	Surgery	Surgery	72; CR
Cao *et al*., 2016[11]	35	Male	Flank pain	Absence	Right; 3.5	Surgery	Surgery	24; CR
Townend *et al*.[12]	57	Male	Abdominal pain	κ light chain	Right; 5.5, left; 9.5	Biopsy	Surgery	N/A
Chennoufi *et al*.[13]	50	Female	Abdominal pain	λ light chain	Left; 13.5	Biopsy	Chemotherapy + RT	3; died
Khan *et al*.[14]	19	Female	Fever	Absence	Left; 8	Biopsy	Surgery	60; CR
Choudhury *et al*.[15]	68	Male	Hip pain	Presence*	Left; N/A	Biopsy	N/A	N/A
Mathew *et al*.[16]	64	Female	Back pain	Presence*	Left; 1.5	Biopsy	Chemotherapy (VCRd) + ASCT	Progressive disease

*The last two reports were the only cases diagnosed with MM, but their serum monoclonal proteins were not specified. RT: Radiation therapy, ASCT: Autologous stem cell transplant, N/A: Not available, CR: Complete response, VAD: Vincristine, doxorubicin, and dexamethasone, EDAP: Etoposide, dexamethasone, Ara-C, and cisplatin, VCRd: Bortezomib, cyclophosphamide, lenalidomide, and dexamethasone, MM: Multiple myeloma

13 patients with EMD (31%).[20] Moreover, to overcome the negative prognostic effect of EMD, an intensive combination incorporating cisplatin, doxorubicin, cyclophosphamide, and etoposide with backbone regimens as first-line treatment has been proposed by expert consensus, particularly for bulky EMD.[1,17,21] However, the high incidence of treatment-related adverse events limits its application.

More recently, daratumumab, a monoclonal antibody targeting CD38 antigen approved in 2015, has also demonstrated a degree of efficacy for EMD in relapsed/refractory settings in a few small-scale studies. Jelinek *et al*. reported an ORR of 57.7% in a retrospective study composed of 41 relapsed MM patients with soft tissue or bone-related plasmacytomas treated with daratumumab, lenalidomide and dexamethasone (DRd).[22] A subgroup analysis of the Icaria-MM trial, which prospectively evaluated the efficacy of isatuximab, another anti-CD38 agent, plus pomalidomide and dexamethasone in 14 patients, also resulted in a 50% ORR, compared with 10% responders in the Pd arm. Of note, regarding extramedullary lesions, only one patient achieved complete remission, and another had a significant reduction.[23] In brief, adding CD38-targeted agents in the backbone regimens may also be a choice for EMD.[1] Nevertheless, despite improvements in response and progression-free survival, the efficacy for extramedullary lesions *per se* and long-term survival outcomes still require more investigations.

In conclusion, our case demonstrates not only a rare manifestation of MM but also the promising efficacy and durability of a daratumumab-containing regimen for such a high-burden EMD. Its progressive nature and poor prognosis with conventional treatment options also indicate an urgent need for novel therapeutic strategies. The role of daratumumab in the treatment of EMD warrants further evaluation.

Declaration of patient consent

The patient has been informed and has given his consent for his images and other clinical information relating to the case to be reported in a medical publication. He understands that his name will not be published and that every attempt will be made to ensure anonymity, but complete anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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