Large plasmacytoma occupying the upper limb in a myeloma patient

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Abstract

Extramedullary disease (EMD) is an issue for patients with multiple myeloma (MM), since extramedullary spread of MM is associated with an aggressive course and a poor prognosis. Moreover, the mechanism of EMD development is uncertain. Here, we present extensive extramedullary plasmacytoma occupying the left upper limb of a 66-year-old female patient with MM with an extremely aggressive course and multiple visceral organ involvement without bone marrow infiltration or plasma cell leukemia. EMD of this large size is extremely rare and this case may provide a clue for better understanding of clinical features of EMD in MM.

Introduction

As dramatic progress has been made in the therapeutic strategies for multiple myeloma (MM), in particular the development of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), extramedullary disease (EMD) is observed with increasing frequency.[1] To date, visceral organ involvement of spleen, liver, kidneys, lymph nodes, and cutaneous tissue has been reported.[2] The prognosis of MM patients with extramedullary relapse is very poor.[3] EMD is often associated with high serum lactate dehydrogenase levels,[4] plasmablastic cell morphology, and complex cytogenetic abnormality.[5]

In the largest retrospective analysis of relapse patterns following autologous hematopoietic stem cell transplantation for MM, Alegre *et al*. reported that increased EMD was evident both at diagnosis and after therapy.[6] Also they found that the risk of extramedullary relapse was not significantly increased after the use of PIs and IMiDs.[6] However, it has been suggested that PIs and IMiDs may increase the incidence of EMD by attenuating the biology of MM.[7-9]

The mechanism of EMD development is elusive, but it is suggested that oncogenes,[10,11] instability of chromosomes,[12] cell adhesion molecules,[7,8,13] and tumor microenvironment[14] may have important role.

Here, we report a surprisingly large tumor mass occupying the left upper limb in the course of MM treatment including PIs and IMiDs. EMD of this large size has not been reported before, and this case may provide a clue to understand the features of EMD in MM.

Case Report

A 66-year-old woman developed pain in her left shoulder and was diagnosed with pathological fracture. Her serum IgG was elevated to 3811 mg/dL and IgG-lambda type M-protein was detected by serum immunoelectrophoresis assay. She had 19.6% of bone marrow plasmacytosis with normal cytogenetics. The diagnosis of ISS stage 1 IgG-lambda type MM was established. No other bone lesion, anemia or kidney injury was found. Her left upper extremity was treated with 8 Gy single fraction using a 4MV photon beam by parallel opposed portals, prior to the conventional vincristine/adriamycin/dexamethasone (VAD) induction therapy. After the three courses of VAD treatment, she was switched to a bortezomib/dexamethasone (BD) regimen because of a Helicobacter cinaedi bacteremia developed in the third course of VAD. After the completion of 3 courses of BD regimen, her bone marrow plasmacytes was decreased to 0.4%, however, a tumor of 1×1 cm large developed in her left arm. With a clinical diagnosis of plasmacytoma, second course of radiotherapy with 8 Gy irradiation (left upper extremity was treated with 8 Gy single fraction using a 4MV photon beam by parallel opposed portals), was performed, after which the patient underwent lenalidomide/dexamethasone therapy. Lenalidomide/dexamethasone was effective, and her EM nodule decreased in size to visually undetectable level; however, 6 months later, after 4 courses of Lenalidomide/dexamethasone treatment the nodule enlarged again. There were 15×15 mm tumor in flexor side of her left arm and 20×20 mm tumor in her extensor side of forearm. MRI revealed those tumors were not connected to cortical bones, in addition, no other tumors in her left arm were found. A needle biopsy of a tumor in her left arm was performed and an accumulation of atypical plasmacytes were detected. As a third line therapy, 2 courses of bortezomib/cyclophosphamide/dexamethasone regimen, followed by melphalan/thalidomide/prednisolone (MPT) was administered, however, during the 6th course of MPT, the extramedullary plasmacytoma occupied her left upper limb.

Then, pomalidomide/dexamethasone as a fourth line was started, which was initially effective; the size of the tumor mass decreased, and the vessels on the surface of the bulk of the tumor appeared to be reduced. However, in the 3rd course of pomalidomide treatment, the EMD enlarged again and extended to her left forearm and back of the hand (Figure. 1). On the contrary, there were only scarce MM cells in the bone marrow (3.6%). Those MM cells were morphologically plasmablastic and harbored complex cytogenetic abnormality. She died of severe respiratory failure. Pleural and pulmonary tumor infiltration was suspected. Post-mortem examination revealed extensive MM involvement of multiple organs, including not only the left upper limb, but also lung, liver, kidney,

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Key words: Multiple myeloma; Extramedullary diseases; Tumor heterogeneity.

Contributions: JT and SH committed the clinical practice and wrote the paper. KO and TI evaluated the post-mortem examination. DN and KN contributed essential advice regarding clinical practice and writing the article. SH and KN supervised the study.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 10 February 2015.
Revision received: 11 January 2017.
Accepted for publication: 10 February 2017.

Rare Tumors 2017; 9:5866
doi:10.4081/rt.2017.5866

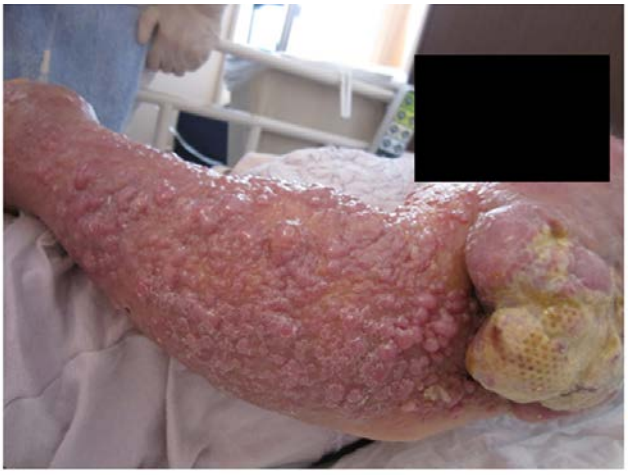

Figure 1. Large plasmacytoma occupying the left upper limb in a female myeloma patient.

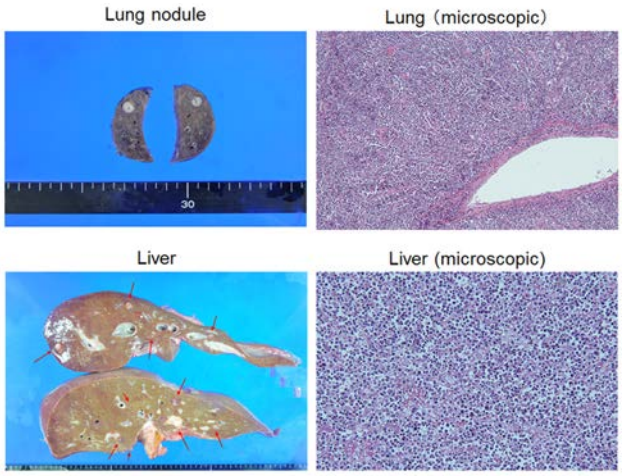

Figure 2. Extramedullary diseases developed in lung and liver

stomach, and thyroid (Figure 2). However, the bone marrow had only scattered patchy myeloma cells.

Discussion

We demonstrate a remarkably large plasmacytoma developing in the left arm of a patient with refractory MM. The presence of this large extramedullary plasmacytoma may be rare; so far, no cases of EMD of a similar size have been reported.

Consistent with prior reports, the patient had plasmablastic MM cells, complex karyotype, elevated LDH, and presented a very aggressive course. Although MM cells were seen to invade multiple organs, including lung, liver, and kidney, there was no evidence of plasma cell leukemia, and only 3.6% bone marrow plasmacytosis was detected. This dissociation between bone marrow and peripheral blood findings and aggressive visceral organ invasion may be significant. The difference between marrow and visceral organ involvement has been reported. For example, in the largest retrospective analysis of relapse patterns following autologous hematopoietic stem cell transplantation for MM, Alegre *et al*. found that 14% of cases that relapsed were EMD and were not associated with BM infiltration.[6]

Also this dissociation may indicate the heterogeneity of MM; for a long time, it has been recognized that not all tumor cells are identical.[15] For example, tumors are heterogeneous in their proliferative ability and only a subset of tumor cells have long-term renewal potential.[15] In addition, it has been noticed that clonal evolution, in which tumor cells accumulate mutations, some of which confer increased fitness and survival advantage can occur.[16]

Furthermore this dissociation may imply there are biological difference between myeloma homing in bone marrow and myeloma forming EMD. Regarding the biology of EMD formation, genetic abnormalities[10,11,12] decreased cell adhesion molecules expression, down regulation of chemokine receptors,[7,8,13] and tumor microenvironment[14] may have important role.

In the courses of the pomalidomide treatment, the vessel pattern in the bulk of the tumor had reduced. This is compatible with the widely recognized phenomenon that IMiDs antagonize tumor angiogenesis.

Conclusions

We discussed an extremely large EMD developing in a patient with refractory MM. MM cells extensively invaded multiple organs without significant bone marrow infiltration. This case may provide clues for a better understanding of the EMD.

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