CASE REPORT

International Journal of Myeloma 9(3): 19–23, 2019

Successful autologous stem cell transplantation for POEMS syndrome with an unusually large osteolytic lesion: A case report and literature review

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POEMS syndrome is a rare multisystemic disease related to monoclonal plasma cell proliferative disorder. Bone lesions in POEMS syndrome are usually sclerotic, and osteolytic lesions are uncommon. Although high-dose chemotherapy administration, followed by autologous stem cell transplantation (auto-SCT) is widely indicated for POEMS syndrome, the pathogenesis and treatment strategy in patients with osteolytic lesions are still unclear. In this report, we present the rare case of a patient with POEMS syndrome with a large osteolytic lesion who was successfully treated with auto-SCT. A 36-year-old man presenting with edema and difficulty in walking was diagnosed with POEMS syndrome based on peripheral polyneuropathy, hepatosplenomegaly, elevated levels of serum VEGF, and IgA-λ monoclonal protein gammopathy. FDG-PET/CT showed high FDG avidity on a large osteolytic lesion on the right pelvic bone, in addition to multiple osteosclerotic lesions. The patient was administered immunomodulatory drugs and a proteasome inhibitor, and subsequently underwent high-dose chemotherapy, followed by auto-SCT. Post transplantation, his symptoms improved gradually, and FDG avidity on the osteolytic lesion decreased. POEMS syndrome with osteolytic lesions indicates a large tumor burden and could be a more progressive disease. For long-term disease remission of POEMS syndrome with osteolytic lesions, an FDG-PET/CT-guided decision for treatment is necessary.

Key words: POEMS syndrome, osteolytic lesion, autologous stem cell transplantation, VEGF, FDG-PET/CT

Introduction

The polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a multisystemic disease related to monoclonal plasma cell proliferative disorder, first described by Bardwick et al. (1980) [1]. POEMS syndrome is also known as Takatsuki disease [2], Crow–Fukase syndrome [3], or osteosclerotic myeloma. The diagnostic criteria are based on a composite of clinical and laboratory features, including polyneuropathy, monoclonal plasma cell proliferative disorder, and major (Castleman disease, osteosclerotic lesions, and vascular endothelial growth factor [VEGF] elevation) or minor (organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, and thrombocytosis/polycythemia) criteria [4].

Although the POEMS syndrome pathogenesis is still unclear, aberrant monoclonal plasma cell proliferation is suspected to be a basis of this disease. In addition, patients have high levels of serum inflammatory cytokines, such as VEGF, interleukin-6, and tumor necrosis factor-α, which indicate the presence of various symptoms [5]. Therefore, POEMS syndrome is a paraneoplastic syndrome caused by monoclonal plasma cell proliferative disorder; however, its characteristics (younger

Received: July 15, 2019, accepted October 25, 2019
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age and better survival) are different compared to multiple myeloma (MM).

The incidence of bone abnormalities in patients with POEMS syndrome is reported to be up to 97% [6]. However, compared to MM, bone lesions in POEMS syndrome are usually sclerotic, and osteolytic lesions are uncommon [4]. Most bone lesions are small (diameter < 1 cm [7]), and no cases with large osteolytic lesions have been reported so far. In addition, few studies have reported the outcomes of osteolytic lesions after the treatment of POEMS syndrome [7, 8], while the long-term efficacy of treatment for osteolytic lesions is hardly known.

In this report, we present the rare case of a patient with POEMS syndrome who had a large osteolytic lesion and was treated successfully with high-dose chemotherapy (high-dose melphalan [HD-Mel]), followed by autologous stem cell transplantation (auto-SCT).

Case Presentation

A 36-year-old man with bilateral leg pain, difficulty in running, walking up and down the stairs, and lower extremity numbness and edema was referred to our institution for a detailed examination. On admission, he was unable to walk for a long distance without the help of a walking stick. A physical examination showed pitting edema in his lower extremities, but there were no signs of skin change or bone pain. A neurological examination revealed decreased strength of the proximal and distal muscles of his lower extremities and hyperalgesia of his distal limbs, and a nerve conduction study (NCS) showed a demyelinating polyneuropathy pattern.

Laboratory studies revealed elevated serum VEGF (5700 pg/mL; normal range < 680 pg/mL) and immunoglobulin A (IgA) (880 mg/dL; normal range = 110–410 mg/dL) levels. Serum immunofixation electrophoresis detected IgA-λ monoclonal protein gammopathy (Fig. 1A), while the ratio of the serum free light chains was normal. There was no anemia, hypercalcemia, or renal dysfunction. A hormonal study found elevated adrenocorticotropic hormone (203.0 pg/mL; normal range < 46.0 pg/mL), thyroid-stimulating hormone (7.043 μIU/mL; normal range = 0.350–4.940 μIU/mL), and estradiol (64 pg/mL; normal range = 11–44 pg/mL) levels, but free T3 and free T4 levels were within normal limit. Bone marrow analysis showed 1.4% of plasma cells. Skeletal X-ray and computed tomography (CT) scan revealed a 9-cm osteolytic lesion with a sclerotic rim on the patient's right pelvic bone and multiple osteosclerotic lesions on his spine and pelvis. Fluoro-2-deoxyglucose with positron emission tomography/CT (FDG-PET/CT) showed markedly aberrant FDG avidity on all bone lesions; in particular, the maximum standard uptake value (SUVmax) of the osteolytic lesion was 21.4 (Fig. 2, At diagnosis). A biopsy of the osteolytic lesion was technically difficult and was not performed. Chest and abdominal CT scans showed hepatosplenomegaly, but no pleural effusion or ascites. Based on all these symptoms and examination results, the patient was diagnosed with POEMS syndrome with a large osteolytic lesion.

Radiation therapy was first recommended for the osteolytic lesion. However, the patient did not agree for fear of delayed bone ossification due to radiation exposure. Instead, he agreed to receive thalidomide and dexamethasone (Td) therapy (Fig. 3). After one cycle of Td therapy, the patient's serum VEGF levels decreased to 2650 pg/mL, and the patient was subsequently administered bortezomib and dexamethasone (Bd) therapy. However, four cycles of Bd therapy failed to control

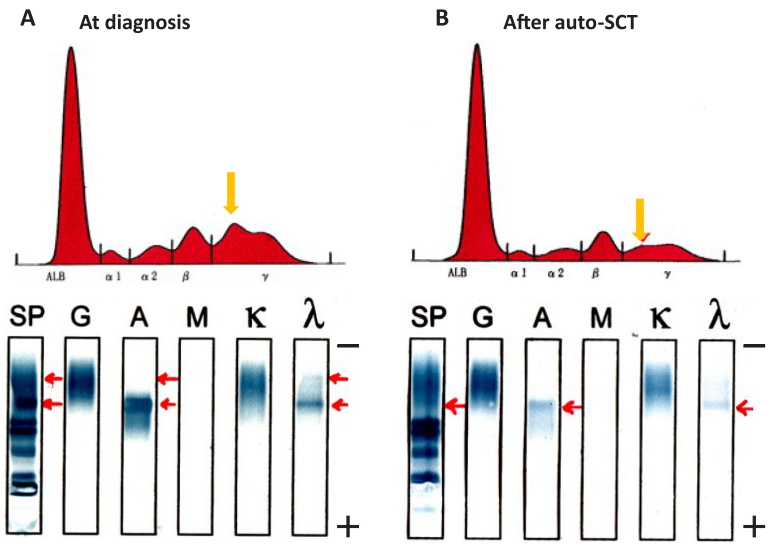

Figure 1. Immunofixation electrophoresis at diagnosis and one month after auto-SCT. IgA, immunoglobulin A; auto-SCT, autologous stem cell transplantation.

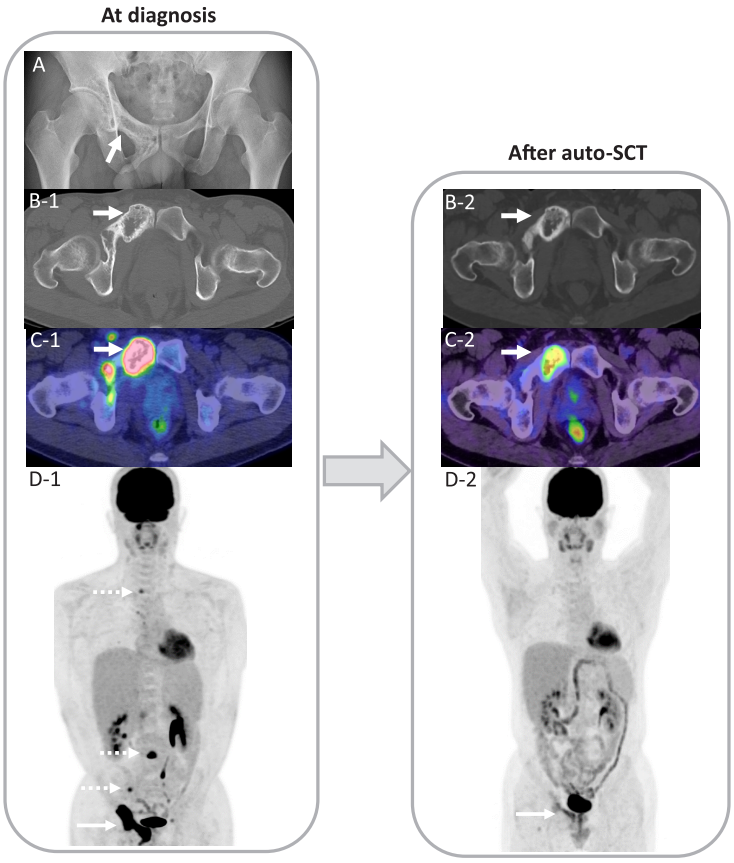

Figure 2. Radiological surveys at diagnosis and one month after auto-SCT. (A) Frontal skeletal X-ray of the pelvis. (B, C, D) Axial CT of the pelvis and fused PET/CT images. Arrows indicate osteolytic lesions, and dotted arrows indicate osteosclerotic lesions. CT, computed tomography; PET, positron emission tomography; FDG, fluoro-2-deoxyglucose.

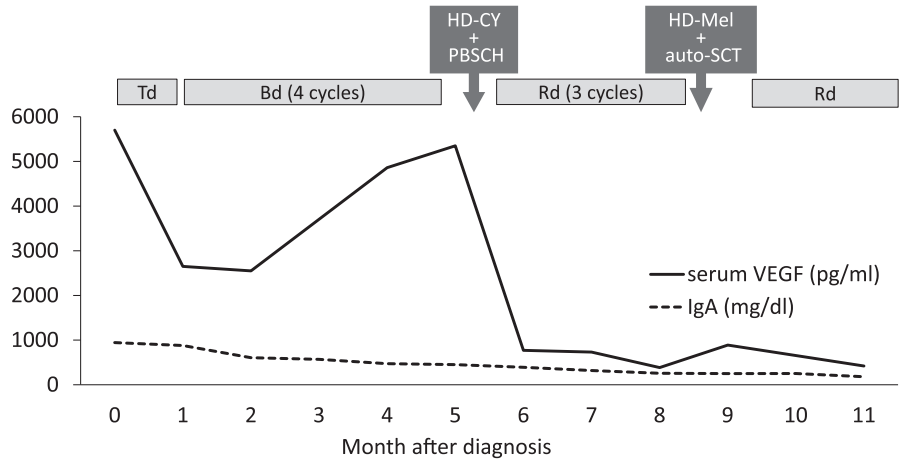

Figure 3. Clinical course of treatment and trend of serum VEGF and IgA levels after diagnosis. Td, thalidomide and dexamethasone; Bd, bortezomib and dexamethasone; HD-CY, high-dose cyclophosphamide; PBSCH, peripheral blood stem cell harvesting; Rd, lenalidomide and dexamethasone, HD-Mel, high-dose melphalan; VEGF, vascular endothelial growth factor; IgA, immunoglobulin A.

the symptoms, and the patient's serum VEGF levels increased to 5100 pg/mL. The patient underwent high-dose cyclophosphamide (2 g/m^2) therapy, followed by peripheral blood stem cell harvesting, mobilized by the granulocyte-colony stimulating factor. Subsequently, his serum VEGF levels decreased markedly to 771 pg/mL. After additional treatment with three cycles of lenalidomide and dexamethasone (Rd), the patient received HD-Mel (200 mg/m^2) followed by auto-SCT, eight months after diagnosis.

The number of transplanted CD34-positive cells was 2.86 × 10^6/kg. The patient achieved neutrophil engraftment on day 18 post transplantation, without any symptoms of pre-

engraftment immune reactions. He suffered from diarrhea and febrile neutropenia, but both were manageable. One month post transplantation, the patient's serum VEGF levels were found to be within the upper normal limit, indicating the achievement of a complete response in serum VEGF levels according to Mayo Clinic response criteria [4]. However, immunofixation electrophoresis could still detect the IgA-λ monoclonal protein (Fig. 1B). A CT scan showed no remarkable changes in the osteosclerotic lesions. FDG-PET/CT showed that FDG avidity on the osteosclerotic lesions had disappeared, but the osteolytic lesion could still be detected, with the SUVmax decreasing to 6.32 (Fig. 2, After auto-SCT), indicating improvement according to Mayo Clinic response criteria [4]. Therefore, the patient underwent consolidation therapy with Rd protocol post transplantation.

Five months post transplantation, the patient's leg strength showed gradual improvement, and he was able to walk without a walking stick. Nine months post transplantation, the patient returned to his job under Rd therapy. Twelve months post transplantation, FDG avidity on the osteolytic lesion still remained, and the patient continued Rd therapy. All the above treatments were approved by the ethical committee of the institutional review board, and written informed consent was obtained from the patient.

Discussion

An osteosclerotic lesion, so-called osteosclerotic myeloma, is one of the characteristics of POEMS syndrome, which is included in the diagnostic criteria and reportedly occurs in ~54%–95% of patients with POEMS syndrome [6]. Differential diagnoses for osteosclerotic lesions include a benign bone island and skeletal metastases of solid cancers. Why patients with POEMS syndrome develop osteosclerotic lesions is still unclear, but VEGF affects bone repair and regeneration [9] and is believed to play a key role in the pathogenesis of osteosclerotic lesions in POEMS syndrome.

Most osteolytic lesions in POEMS syndrome exhibit mixed sclerotic and lytic components, such as lytic central parts with sclerotic rims or a "soap-bubble appearance," and pure lytic lesions are extremely rare [7]. Differential diagnoses include aneurysmal bone cysts, non-ossifying fibroma, and fibrous dysplasia [4]. Unlike osteosclerotic sites, osteolytic sites reportedly have significantly increased plasma cells [10]. Therefore, patients with POEMS syndrome with osteolytic lesions are considered to carry a large tumor burden. However, as in this report, determining the precise number of plasma cells in an osteolytic lesion is often difficult. Instead, several diagnostic imaging techniques are helpful. Osteosclerotic sites in patients with POEMS syndrome are often smaller than 1 cm; therefore, nearly 30% of bone lesions were reportedly overlooked in a skeletal X-ray survey [7]. A CT scan on the bone window level is effective in detecting bone lesions in POEMS syndrome. A large osteosclerotic lesion tends to have a lytic site in its central part. An FDG-PET/CT scan is also helpful in detecting osseous sites because bone lesions in POEMS syndrome, especially osteolytic lesions, are FDG-avid [8, 11]. Neoplastic lesions, such as plasmacytomas and Castleman disease, can also be evaluated using FDG-PET/CT. The Mayo Clinic recommends treatment response criteria for POEMS syndrome using an FDG-PET/CT parameter [4]. In this report, the FDG-PET/CT response one month post transplantation indicated that the residual disease and response criteria of the Mayo Clinic are useful in assessing whether additional therapy is required.

Although a standard therapy for POEMS syndrome has not yet been established, most patients are treated according to the treatment strategy for other plasma cell neoplasms, such as MM. In the case of a localized disease, when a patient has only one or two bone lesions, radiotherapy is the most common treatment option [12]. On the other hand, most patients have a multifocal disease or bone marrow involvement, suggesting the need for systemic chemotherapy. Conventionally, melphalan and dexamethasone [13] or single corticosteroid therapy has been used, but recent studies have reported that novel agents, such as proteasome inhibitors (bortezomib [14]) and immunomodulatory drugs (thalidomide [15] and lenalidomide [16]), are highly effective. It is still unclear which proteasome inhibitors or immunomodulatory drugs are better in the treatment of POEMS syndrome. Misawa S et al. reported thalidomide was useful for auto-SCT ineligible POEMS syndrome patients [15]. Cai QQ et al. also reported that lenalidomide was effective for relapsed or refractory POEMS syndrome patients [16]. Therefore, immunomodulatory drugs are useful for newly diagnosed and refractory POEMS syndrome patients as well as multiple myeloma. In our bortezomib-refractory case, immunomodulatory drugs are highly effective. High-dose chemotherapy, followed by auto-SCT is expected to show a drastic improvement of polyneuropathy in patients younger than 65–70 years. Jaccard et al. first reported five successful cases treated with auto-SCT [17], and subsequently, several studies have reported that auto-SCT is effective for POEMS symptoms, especially polyneuropathy [18–21]. A recent report from our institute, as well as another study, on long-term follow-up showed ~90% of 5-year overall survival and ~65% of 5-year progression-free survival [22–25].

Bone lesions are also improved by treatment for POEMS syndrome. Glazebrook et al. reported that the treatment response shows, on the CT scan, a decrease in the size and

number of osteosclerotic lesions or increased sclerosis in osteolytic lesions [7]. On the other hand, Pan et al. reported that FDG-avid bone sites show a decreased SUVmax, but the appearance of bone lesions on CT scans does not change post treatment [8]. Studies have reported that patients with POEMS syndrome who do not achieve complete metabolic response post transplantation have significantly poor prognosis and tend to have osteolytic sites [24]. In contrast, Wang et al. reported that there is no correlation between serum marker levels and bone lesion patterns [26]. In this report, auto-SCT decreased the disease activity of bone lesions, as assessed by an FDG-PET/CT scan, not by a CT scan; however, the remaining FDG avidity post transplantation suggested the risk of progression. Focal irradiation might have been a treatment option, but because the patient refused radiation therapy, we decided to administer additional consolidation chemotherapy, which successfully controlled the patient's disease activity.

In summary, we successfully treated the patient with POEMS syndrome with a large osteolytic lesion using high-dose chemotherapy, followed by auto-SCT. Treatment efficacy for the osteolytic lesion was evaluated using an FDG-PET/CT scan. POEMS syndrome with osteolytic lesions indicates a large tumor burden and could be a more progressive disease. Therefore, an FDG-PET/CT-guided treatment decision is crucial for long-term disease remission of POEMS syndrome with osteolytic lesions.

Disclosure of Conflicts of Interest

The authors declare no competing financial interests.

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