

Case Report

Successful treatment with autologous peripheral blood stem cell transplantation for multiple myeloma concurrent systemic lupus erythematosus: a case report

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Abstract: Increased occurrence of monoclonal gammopathy in systemic lupus erythematosus (SLE) patients has been reported by early studies. There is strong association between SLE and malignant tumors, but SLE with concurrent multiple myeloma (MM) cases were seldom reported in literature. The current study reported one case of a 48-year-old male who was diagnosed MM with concurrent SLE. He was treated with combination chemotherapies and autologous peripheral blood stem cell transplantation. Continuous very good partial response (VGPR) was achieved for MM and SLE remained in inactive status after treatments. This is the first report of autologous peripheral blood stem cell transplantation to manage the complex of MM and SLE, and the experience in the present study will improve the clinical practice in such situation.

Keywords: Multiple myeloma, systemic lupus erythematosus, monoclonal gammopathy, autologous peripheral blood stem cell transplantation

Introduction

Multiple myeloma (MM) is a malignancy of plasma cells which could over produce monoclonal globulins. This disease manifests bone lesions, hypercalcemia, anemia or renal insufficiency clinically. The incidence of MM is 6.1/100,000 people per year in United States of America. As a kind of gerontal disease, the median age at diagnosis of MM is 71 years in whites and 67 years in blacks [1]. MM is considered an incurable disease, but several new drugs such as bortezomib, thalidomide and lenalidomide have improved the prognosis considerably [2]. High dose chemotherapy and autologous stem cell transplantation could improve complete remission rate and overall survival compared with standard therapy for transplant candidates [3]. Systemic lupus erythematosus (SLE) is a kind of diffuse connective tissue disease mediated by autologous immune reactions. The entity is characterized by multiple autologous antibodies in serum and multiple systems affected clinically. MM with concurrent SLE was seldom reported in literature and treatment of such

complications still remains unclear. This study reported a successful treatment with autologous peripheral blood stem cell transplantation for a patient with multiple myeloma and concurrent systemic lupus erythematosus, which could improve clinical practice of such complications.

Case presentation

A 48-year-old male was admitted to the Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, Zhejiang, China) on June 11, 2014, due to recurrent pain of multiple joints for half a year, and fever for 9 days. The patient suffered from pain of bilateral shoulders half a year before admission, and pain of bilateral elbows, knees, metacarpophalangeal joints, proximal interphalangeal joints gradually, as well as one hour's morning stiffness of bilateral hands. The patient took acetaminophen himself and the symptoms could be relieved a little. The pain of joints deteriorated with fever 9 days before admission, and the patient received intravenous cefuroxime in a

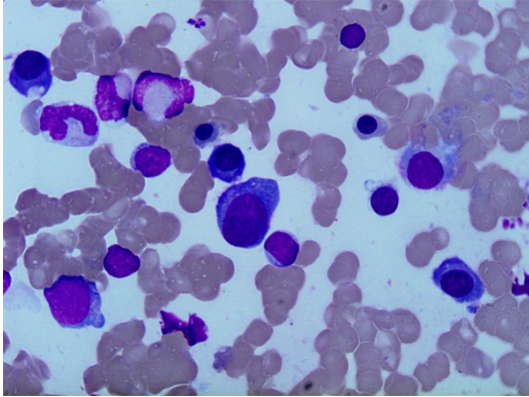


Figure 1. Bone marrow smear on January 29, 2015 showed increased plasma cells which accounted for 14% of nucleated cells, and 3% immature plasma cells. Olympus microscope CX31, Wright stain, original magnification $\times 1000$.

local hospital. The temperature restored normal but the pain of joints still existed, so the patient came to our hospital for further treatment. Physical examination showed pressing pain of bilateral temporomandibular joints, left shoulder, left elbow, left knee and left sacroiliac joint with decreased motion of these joints. Bilateral proximal interphalangeal joints were swollen with positive pressing pain. Pressing pain of chest vertebra was positive and ante flexion of the vertebra was limited. Bilateral Patrick signs were positive, but Lasegue signs were negative. No ulcers of mouth mucosa were found, and no enlarged superficial lymph nodes were touched. Blood routine test showed white blood cells $2.2 \times 10^9/l$ (normal range $4.0-10.0 \times 10^9/l$), hemoglobin 113 g/l (normal range 110-160 g/l), platelets count $259 \times 10^9/l$ (normal range $100-300 \times 10^9/l$). The alanine transaminase, aspartate aminotransferase, blood urea nitrogen and serum creatinine level were within normal ranges. Serum albumin was 32.9 g/l (normal range 35.0-52.0 g/l), globulin was 60.9 g/l (normal range 15.0-30.0 g/l) and albumin/globulin ratio was 0.54 (normal range 1.50-2.50). The erythrocyte sedimentation rate was as high as 111 mm/h (normal range <20 mm/h) and C reactive protein was 30.7 mg/l (normal range <10 mg/h). The immunoglobulin test showed IgG level was as high as 52.40 g/l (normal range 7.00-16.00 g/l) but IgA and IgM levels were decreased (<0.25 g/l and <0.15 g/l respectively, normal range 0.70-4.00 g/l and 0.40-2.30 g/l). Serum level of component C4 was decreased (73 mg/l, normal range 100-

400 mg/l). Immunofixation electrophoresis revealed monoclonal immunoglobulin of IgG/ λ . Autologous antibodies tests showed positive autoantibody to nuclear antigen (ANA) with the titer of 1:320, as well as positive anti-ribonucleoprotein antibody, anti-Smith antibody and anti SS-A antibody. Rheumatoid factors, anti-cyclic citrylated peptide antibody, anticardiolipin antibody and human leukocyte antigen B27 (HLA-B27) were all negative. The 24 hours urine protein was 56 mg (normal range 28-141 mg). The chest computed tomography scan revealed interstitial changes in dorsal parts of bilateral lungs. Emission computed tomography (ECT) discovered moderately increased nuclide uptake in posterior left eighth rib, and no abnormal signs were found in other bones. X-rays of cranium and pelvis were normal. Bone marrow smear showed 2% plasma cells in bone marrow. Diagnosis of systemic lupus erythematosus was confirmed, and intravenous methylprednisolone 40 mg per day was prescribed to control the symptoms. The dose of methylprednisolone was then tapered gradually and methotrexate 10 mg per week was added on September, 2014 to avoid recurrence of SLE. Re-examination of bone marrow smear on January 29, 2015 showed increased plasma cells which accounted for 14% of nucleated cells, and 3% immature plasma cells (**Figure 1**). Biopsy of bone marrow revealed increased plasma cells disseminated in the bone marrow, which suggested the plasma cell tumor. Re-examination of serum immunoglobulin showed IgG 32.40 g/l (normal range 7.00-16.00 g/l) and immunofixation electrophoresis revealed monoclonal immunoglobulin of IgG/ λ . Multiple myeloma was diagnosed and six cycles of CTD regimen chemotherapy (cyclophosphamide 0.4 g on days 1 to 4, dexamethasone 40 mg on days 1 to 4, and thalidomide 100 mg orally every night) were administered from February to August, 2015. Very good partial response (VGPR) was achieved after six cycles of chemotherapy according to Revised Uniform Response Criteria by the International Myeloma Working Group [4]. Methylprednisolone 8 mg per day was continued to control symptoms of SLE. Peripheral blood stem cells were collected on December 17 and 18, 2015 after high dose chemotherapy of cyclophosphamide 5.6 g (3 g per m^2 of body surface area). Preconditioning for autologous peripheral blood stem cell transplantation was started on February 26, 2016

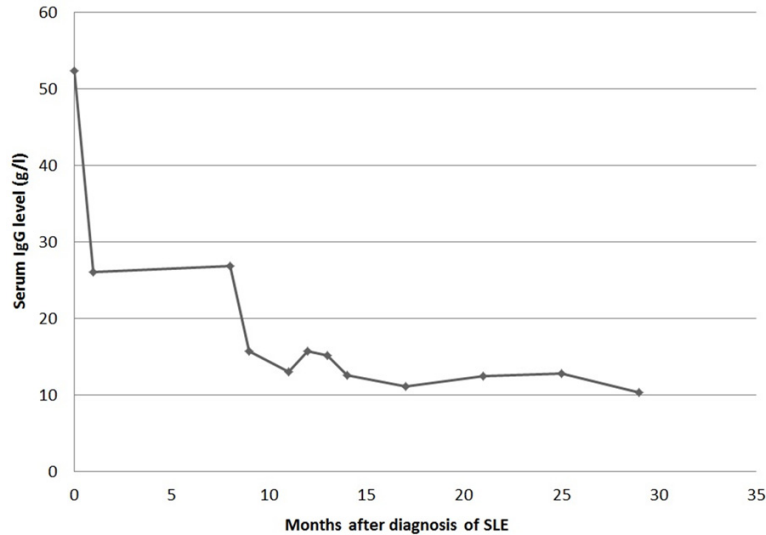


Figure 2. Changes of serum IgG level (g/l) of the patient from the diagnosis of SLE on June, 2014.

which contained semustine 350 mg on day -7, busulfan 211.2 mg (3.2 mg per kilogram of body weight) on days -6 to -4, and etoposide 660 mg on days -3 to -2 (10 mg per kilogram of body weight). 6.57×10^8 per kilogram of body weight mononucleated cells were transfused on day 0, after that the neutrophils engrafted on day +10 and the platelets engrafted on day +12. Blood routine test was normal during follow up on July 13, 2016 and IgG level was 12.87 g/l (normal range 7.00-16.00 g/l) while immunofixation electrophoresis was still positive (**Figure 2**). Autoantibody to nuclear antigen (ANA) was positive with lower titer of 1:20, and anti-ribonucleoprotein antibody, anti-Smith antibody and anti SS-A antibody turned negative. Bone marrow smear revealed well hematopoiesis with 1% plasma cells. The disease remained in continuous VGPR status and thalidomide 100 mg per night and methylprednisolone 4 mg per day were prescribed for maintenance therapy.

Discussion

The patient in the present study clinically manifested as lesions of peripheral joints with pain, tenderness and swelling, hematologic disorder with leukopenia and anemia, positive ANA, positive anti-ribonucleoprotein antibody and anti-Smith antibody, so the diagnosis of systemic lupus erythematosus was confirmed either according to the 1997 classification criteria of

American College of Rheumatology (ACR) or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [5, 6]. Monoclonal immunoglobulin of IgG/ λ was discovered by immunofixation electrophoresis for the patient. However, percentage of clonal plasma cells in bone marrow did not exceed 10% of nucleated cells, and no obvious bone lesions were found by ECT or X-rays. Diagnosis of multiple myeloma could not be established according to the classification criteria of International Myeloma Working Group on June 2014 [7]. Then glucocorticoid and subsequent

immunosuppressant methotrexate were given to the patient in order to control the symptoms of SLE. Routine re-examination of bone marrow smear seven months later revealed increased plasma cells which accounted for 14% of nucleated cells, and 3% immature plasma cells. Although no obvious bone lesions were found by ECT or X-rays, the patient suffered from anemia which could be a manifestation of MM, and monoclonal gammopathy, so diagnosis of MM could be established and chemotherapies were given to the patient then.

Early studies have reported the increased occurrence of monoclonal gammopathy in SLE patients. About 3.3% SLE patients were found to have monoclonal immunoglobulin in their serum [8]. In a recent study, 5.4% of SLE patients were identified with monoclonal gammopathy. No multiple myeloma was found in this cohort [9]. The author concluded that monoclonal gammopathy was more frequent in SLE patients than in the general population, but there were no differences in disease manifestations, treatment approaches, or malignancies between SLE patients with and those without monoclonal gammopathy [9]. However, there is strong association between SLE and malignant tumors, especially hematological neoplasms. In an international cohort study, the standardized incidence ratio (SIR) for non-Hodgkin's lymphoma in SLE patients was 3.64 (95% Confidence Interval 2.63-4.93), and near-

ly 11% of patients with MM were reported to have clinico-laboratory features of SLE [10, 11]. In another large SLE cohort, 5 cases of MM were found in 16, 409 SLE patients, and 4 of them were blacks [12]. Furthermore, the risk for MM was significantly elevated among individuals with a family history of SLE [13]. In a series of 12 case reports, the median age of 45 years at diagnosis of multiple myeloma in SLE was much younger than the median age of 64 years for multiple myeloma in the general population. The distribution of presenting symptoms, extramedullary manifestations, immunoglobulin type, response to therapy and prognosis did not appear to differ from isolated multiple myeloma [14].

The pathophysiology underlying the association between SLE and MM still remains unclear. It is plausible that continuous immune system activation in SLE could lead to proliferation of monoclonal B cells, and then develop to MM. Simultaneously; defective immune surveillance in SLE may promote the development of malignant tumors, such as MM. The increased risk for MM among individuals with a family history of SLE suggests possible genetic factors [13]. Immunosuppressive therapy or persistent Epstein-Barr virus infection in SLE patients may also contribute to an increased risk for malignancy [14]. Therefore, for SLE patients with monoclonal gammopathy such as the patient in the present study, bone lesions, level of monoclonal globulin and plasma cell counts in bone marrow should be monitored frequently, and chemotherapies should be performed at the time of confirmed diagnosis of symptomatic MM.

For most reported MM patients concurrent with SLE, corticosteroids and immunosuppressants such as cyclophosphamide, chloroquine or azathioprine were used for treatment of SLE. And for treatment of MM, most used chemotherapies were MP (Melphalan and corticosteroids) or VAD (vincristine, doxorubicin and dexamethasone) regimens [15]. The use of interferon for maintenance therapy in a MM patient with SLE should invite caution because it could lead to aggravation of SLE [16]. With the introduction of novel drugs such as proteasome inhibitors and immunomodulators, the prognosis of MM patients has improved considerably [2]. Fröhlich K et al reported successful use of

bortezomib in a patient with SLE and MM [17]. The effect of autologous peripheral blood stem cell transplantation in patients with MM and concurrent SLE has not been reported yet. In a MM patient with SLE, myasthenia gravis and non-familial diffuse palmoplantar keratoderma, partial remission was achieved by VAD and CHOP (cyclophosphamide, doxorubicin, vincristine and dexamethasone) regimen chemotherapy, but the physicians failed to collect sufficient numbers of CD 34+ cells for peripheral blood stem cell transplantation [18]. Bortezomib based regimen was suggested for the patient in present study after diagnosis of MM, but he refused to accept bortezomib because of its higher cost. Therefore CTD (cyclophosphamide, thalidomide and dexamethasone) regimen chemotherapy was administered and partial remission was achieved after 6 cycles of chemotherapies. Then consolidation autologous peripheral blood stem cell transplantation was successfully administered and the patient remains in remission period. The experience in the present study provided an effective choice to manage the complex of MM and concurrent SLE.

The current study reported a patient of multiple myeloma with concurrent systemic lupus erythematosus who was treated with chemotherapies and autologous peripheral blood stem cell transplantation. Increased occurrence of monoclonal gammopathy in SLE patients has been reported, and there is strong association between SLE and MM. Autologous peripheral blood stem cell transplantation could be an effective choice to manage the complex of MM and concurrent SLE.

Disclosure of conflict of interest

None.

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