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Case Report

Multiple Myeloma Presenting with Cytopenias

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Abstract

Multiple myeloma is characterized by neoplastic proliferation of a single clone of plasma cells in the bone marrow producing a monoclonal immunoglobulin and ultimately causing various complications including: anemia, renal dysfunction, bone disease and infections. The median ages of multiple myeloma at diagnosis in North America and Europe are 70 to 72 years respectively. Over the last 10 years, management of multiple myeloma has dramatically changed due to the introduction of several novel therapies that have improved the disease outcome and prognosis.

The diagnosis of multiple myeloma below the age of 30 years is rarely encountered. Also having cytopenias other than anemia at disease presentation is a rare event. We are reporting two cases of multiple myeloma presenting with cytopenias. The first one presented with bicytopenia at the age of 26 years, while the other one was found to have asymptomatic neutropenia during her investigations as a possible donor for allogeneic stem cell transplantation. Both cases were successfully managed and received autologous stem cell transplantations at King Fahad Specialist Hospital in Dammam, Saudi Arabia.

Keywords: Multiple myeloma; Cytopenias; Hematopoietic stem cell transplantation; Maintenance therapy

Introduction

Multiple Myeloma (MM) is a plasma cell neoplasm characterized by neoplastic proliferation of a single clone of plasma cells in the Bone Marrow (BM) producing a monoclonal immunoglobulin and causing anemia, renal failure, bone destruction and infectious complications [1-4]. MM is the second most commonly diagnosed Hematologic Malignancy (HM) and it accounts for approximately 10% of all HMs [1,3,5]. The median age of MM at diagnosis is about 70 years in the United States of America (USA) and approximately 72 years in Europe [6-8].

MM is usually preceded by an asymptomatic phase of paraprotein secretion termed Monoclonal Gammopathy of Unknown Significance (MGUS) [9,10]. Patients with MM generally present with fatigue, bone pains, osteolytic bone lesions, anemia, hypercalcemia, high serum creatinine level, elevated Erythrocyte Sedimentation Rate (ESR), elevated serum protein level, Extramedullary Disease (EMD) and Monoclonal (M) protein in the serum or urine in addition to normal, low or high White Blood Cell (WBC) as well as Platelet (PLT) counts [10,11].

Case Presentation

Case 1

A 26 year old Saudi male with no previous medical illnesses was referred to KFSH in Dammam on 17/06/2008 as a possible case of acute leukemia. He presented to the local hospital with 2 week history of fever, sweating, epistaxis, weight loss in addition to leukocytosis, anemia and thrombocytopenia. Upon admission to KFSH, his physical examination revealed: pallor and few ecchymotic areas over the limbs, but no external palpable lymphadenopathy, jaundice or leg edema. His chest was clear and his cardiovascular and neurological examinations revealed no abnormality. He had no abdominal tenderness or palpable organomegaly. Complete Blood Count (CBC) revealed: WBC count of 17.1 x 10^9/L, Hemoglobin (Hb) of 6.9 g/L and PLT count of 24 x 10^9/L. Peripheral Blood Film (PBF) showed: thrombocytopenia, rouleaux formation and few plasma cells. His serum creatinine was 127µmol/L, total protein: 177g/L, serum Lactic Dehydrogenase (LDH) level: 211units/L, Beta 2 Microglobulin (B2M): 11.1 mg/L and serum IgG: 96.2g/L. His BM Examination (BME) revealed: hypercellular marrow with 42% monoclonal plasma cells, decreased erythroid precursors and no increase in megakaryocytes. Cytogenetic analysis showed 17 p deletion and skeletal survey revealed multiple lytic lesions.

After establishing the of MM, IgG lambda, stage *III*, the patient was commenced on VAD (vincristine, doxorubicin and dexamethasone) regimen of chemotherapy as novel therapies were not yet available at KFSH in Dammam in addition to monthly doses of zolendronic acid 4mg intravenously (*IV*). After receiving 6 cycles of VAD chemotherapy, the patient achieved complete response of his disease then he was referred to King Faisal Specialist Hospital and Research Center (KFSH/RC) in Riyadh for autologous Hematopoietic Stem Cell Transplantation (HSCT). He received his autologous HSCT on 21/01/2009. As the patient had High-Risk (HR) MM, he was commenced on thalidomide maintenance therapy, but he was not compliant with this medication.

In November 2010, he presented to KFSH in Dammam with relapse of his myeloma. He was given 6 cycles of VRD (bortezomib, lenalidomide and dexamethasone) regimen of therapy, following which he achieved Very Good Partial Response (VGPR), so he was planned for a second autologous HSCT. He received cyclophosphamide and Granulocyte-Colony Stimulating Factor (G-CSF) for stem cell mobilization. After stem cell collection by apheresis, he received melphalan conditioning therapy followed by

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Table 1: Causes of pancytopenia.

1-	**Megaloblastic anemia and nutritional deficiency**
2-	**Bone Marrow Failure (BMF) syndromes:** - Aplastic anemia - Myelodysplastic syndromes - Other congenital and acquired BMF syndromes: Fanconi anemia, dyskeratosis congenital, Diamond-Blackfan syndrome, Schwachman-Diamond syndrome and paroxysmal nocturnal hemoglobinuria.
3-	**Hematological malignancies:** Acute myeloid leukemia, acute lymphoblastic leukemia, hairy cell leukemia, lymphoma, multiple myeloma, plasma cell leukemia, Waldenstrommacroglobulinema and malignant histiocytosis.
4-	**Hypersplenism:** Congestive splenomegaly, portal hypertension, liver cirrhosis, tropical splenomegaly, myelofibrosis and thalassemia.
5-	**Metastatic carcinoma:** Neuroblastoma
6-	**Infectious diseases:** Malaria, disseminated tuberculosis, leishmaniasis, enteric fever, viral hepatitis and septicemia.
7-	**Storage diseases:** Neimann-Pick disease and Gaucher's disease.
8-	**Myelosuppressive therapies:** Cytotoxic chemotherapies, immunosuppressive agents, antimicrobials [sulfonamides, chloramphenicol, linezolid and ganciclovir], anticonvulsants, anti-thyroids, diuretics and non-steroidal anti-inflammatory agents.

infusion of HSCs on 20/01/2013. His engrafted his neutrophils, with G-CSF, on day 10 and his PLTs on day 14 post-HSCT respectively. Thereafter, he received bortezomib-based consolidation therapy followed by maintenance therapy composed of bortezomib and dexamethasone every 2 weeks for a total duration of two years. Later on, he continued to have regular follow-up at our institution. He was last seen at our out-patient clinic in late January 2018. He was asymptomatic; his physical examination revealed no abnormality and his laboratory investigations were within normal limits. No new medication was commenced and he was given a new follow-up appointment.

Case 2

In January 2012, a 53 year old Saudi female with history of hypertension, complicated by subdural hematoma that was evacuated 12 years earlier, was evaluated at KFSH in Dammam as a possible donor for allogeneic HSCT. She was totally asymptomatic and her physical examination revealed no abnormality. Her CBC showed: WBC of 3.76 x 10^9/L with 20% neutrophils, Hb of 13.4 g/L and PLT count of 204 x 10^9/L. PBF showed: neutropenia, no dysplastic changes and no abnormal infiltration. Her renal and hepatic profiles were normal. Viral and autoimmune screens were negative. Her serum calcium and thyroid function tests were normal. Serum protein was 85g/L, serum LDH was 315units/L and B2M was 2.4mg/L. Serum IgA was 10.4g/L, serum free light chain kappa was 59.4mg/L and serum protein electrophoresis revealed an IgA kappa monoclonal band. Her BME revealed a cellular marrow with no dysplastic features. There were > 20% monoclonal plasma cells and cytogenetic analysis showed no abnormality. Skeletal survey revealed osteopenia and several lytic lesions in the skull and femoral bones.

After establishing the diagnosis of IgA kappa MM, the patient received 4 cycles of bortezomib and dexamethasone in addition to monthly doses of *IV* zolendronic acid. Re-staging evaluation showed < 5% plasma cells with no monoclonal band on serum protein electrophoresis. Later on, she was planned for autologous HSCT. In Early August 2012, autologous HSCs were harvested by apheresis then she received HD melphalan followed by HSC infusion on 30/08/2013. Her autograft was successful and her early post-HSCT was uneventful apart from mild engraftment syndrome.

Re-staging evaluation performed 3 months post-HSCT showed clinical, hematological, biochemical and radiological evidence of complete response. She developed localized herpes zoster infection that was treated with acyclovir one year post-HSCT. Thereafter she continued to have regular follow-up at the out-patient clinic. She was last seen in late February 2018. She was very well and all her laboratory tests were normal, so a new follow-up appointment was given.

Discussion

The peak incidence of MM is between 60 and 70 years of age [12]. The disease is uncommon below the age of 40 years [12,13]. MM in patients younger than 40 years of age accounts for only 2% of all myeloma cases [7,12,14]. However, several studies have been performed in patients with MM ≤ 40 years of age [12,13,15,16]. MM in patients younger than 30 years of age accounts for only 0.3% of all myeloma patients [14,17,18]. Also, several studies reported the occurrence of MM in patients younger than 30 years of age [7,8,17-19]. The clinical and laboratory manifestations in patients with MM ≤ 40 years of age include: fatigue, bone pains, renal impairment, infections, EMD, hypercalcemia, elevated serum LDH level and thrombocytopenia [13,16]. Studies have shown that compared to older patients, patients with MM who are younger than 40 years of age have higher rates of: renal failure, plasma cell leukemia, EMD, Bence Jones proteinuria, and bone disease [12,14,15].

Age is a strong prognostic factor in MM as studies have shown that survival declines continuously by each decade particularly in patients older than 60 years of age [6,20]. Regarding survival in younger patients with MM, there have been conflicting reports. It had previously been reported that survival in younger patients with MM was longer than that in older subjects [13,14,16,17]. However, more recent studies have shown that the median Overall Survival (OS) in younger patients with MM is shorter than that in older patients even if autologous HSCT is performed [12,15]. So, it is recommended to develop specific therapeutic strategies for younger patients with MM in order to improve their survival further [12,13].

Peripheral blood pancytopenia is the simultaneous presence of anemia, leucopenia and thrombocytopenia [21-26]. Pancytopenia is not a disease by itself but the reduction in blood elements below the normal reference values may result from various disease processes

[21-24,26]. The causes of pancytopenia are included in (Table 1) [21-33]. In patients presenting with cytopenias, if no obvious cause is found with the initial investigations such as peripheral blood film as well as infection and autoimmune screens, BM examination becomes mandatory to reveal the cause of cytopenia [27-30,34].

In patients with MM, pancytopenia may be due to: (1) heavy BM infiltration by plasma cells causing BM failure, (2) drugs causing myelosuppression such as cytotoxic chemotherapy and antimicrobials, (3) infections such as septicemia or leishmaniasis, (4) renal failure induced erythropoietin deficiency, (5) cytokine-mediated BM failure, (6) fasligand-mediated apoptosis, and (7) associated: Myelodysplastic Syndrome (MDS), aplastic anemia, vitamin B-12 deficiency and autoimmune disorders such as idiopathic thrombocytopenic purpura, Evan's syndrome, autoimmune hemolytic anemia and pernicious anemia [3,4,34-37]. In patients with MM, anemia is a common presentation, while bicytopenia or pancytopenia are less frequently encountered at the diagnosis of myeloma [3,11,38]. As pancytopenia is a quite unusual finding at the presentation of MM, the diagnosis of MM in patients presenting with pancytopenia may be delayed [3].

Neutropenia at the presentation of MM can be either disease-related or autoimmune in type [39,40]. Later on, neutropenia evolves as a consequence of medications such as lenalidomide or disease progression [41]. Early mortality in patients with MM is usually attributed to the combined effects of active disease or comorbid factors [40]. A large study that included > 300 patients with MM treated in the United Kingdom between 1980 and 2002 showed the following results: (1) 10% of MM patients died within 60 days of establishing the diagnosis of MM, (2) infection and renal failure were the main causes of early mortality, and (3) 45% of early deaths were attributed to infection, but neutropenia was present in only 7.4% of patients who died because of infectious complications [40].

Autologous HSCT is the standard of care for patients with MM who are younger than 65 years of age [42-46]. Results of randomized clinical trials comparing high-dose therapy plus autologous HSCT with conventional chemotherapy alone have shown that transplantation improves Progression-Free Survival (PFS) and OS [45-48].

The recent development of novel therapies has improved the depth of responses and has prolonged survival in patients with MM for many years [49,50]. The widespread use of autologous HSCT and the introduction of several novel agents into clinical practice have significantly contributed to major advances in the therapy and prognosis of MM [50]. Examples of the novel therapies that have recently been introduced into the treatment of MM include: (1) proteasome inhibitors such as bortezomib, carfilzomib and ixazomib, (2) immunomodulatory agents such as thalidomide, lenalidomide and pomalidomide, (3) monoclonal antibodies such as daratumomab and elotuzumab, and (4) histone deacetylase inhibitors such as panobinostat, in addition to other classes of medications that can also be used in the treatment of MM such as: (a) glucocorticoids, (b) DNA alkylating agents, and (c) doxorubicin, cisplatinum and etoposide [10,49,50].

Prior to autologous HSCT, it is essential to administer effective induction chemotherapy in the form of a combination regimen that incorporates novel agents such as bortezomib [46,50]. Different conditioning agents before autologous HSCT, but high-dose melphalan remains the most commonly used conditioning therapy [10,46]. Consolidation and maintenance therapies in the form of thalidomide, lenalidomide or bortezomib can improve and prolong disease response to transplantation and can delay relapse of MM [46,50].

MM is an incurable disease as studies have shown that almost all patients with MM will relapse at some stage following initial therapy, the majority within 3 years of an autologous HSCT [45,47-49,51]. Patterns of relapse in patients with MM include: (1) 66% as clinically symptomatic disease, (2) 18% as asymptomatic disease characterized by an increase in monoclonal proteins, (3) 14% as EMD, and (4) 2% as plasma cell leukemia [43]. In patients with relapsed MM, the available therapeutic options include: (1) additional chemotherapy, (2) second autologous HSCT, (3) allogeneic HSCT in highly selected patients, and (4) clinical trials with investigational agents [42,52].

A second autologous HSCT is a feasible and a safe therapeutic option for patients with MM who either progress or relapse after the first autologous HSCT [42,48,52]. A timely second autologous HSCT should be considered in patients with MM who fail to achieve a Very Good Partial Response (VGPR) or better responses after the first autologous HSCT [50]. The outcome of the second autologous HSCT can be predicted by: (1) time to progression after the first autologous HSCT, and (2) the interval between the first and the second autologous HSCTs [42]. Factors that are associated with improved OS and PFS in patients with relapsed MM subjected to a second autologous HSCT include: (1) younger age, (2) beta-2-microglobulin < 2.5mg/L at diagnosis, (3) duration of remission > 9 months from the first autologous HSCT, and (4) greater partial remission in response to their first autologous HSCT [48]. Studies have shown that a second autologous HSCT in patients with relapsed MM is associated with superior OS and PFS compared to conventional chemotherapy offering a potential consolidative option for selected patients [42,48]. However, a meta-analysis of data pooled from controlled clinical trials failed to show superior OS with double or tandem autologous HSCT [50].

The patients presented had various cytopenias at presentation. The first patient had bicytopenia in conjunction with leukocytosis as well as a symptomatology compatible with that of acute leukemia while the second patient presented with asymptomatic neutropenia and was diagnosed to have MM during investigations for stem cell donation. The first patient, whose myeloma presented at a relatively very young age, was found to have a HR-MM that relapsed after the first autologous HSCT and needed salvage therapy and a second autologous HSCT followed by maintenance therapy. The initial impression regarding the second patient was in favor of myelodysplastic syndrome as she was in her fifties and as she had neutropenia. However, both patients were thoroughly evaluated and they treated successfully with chemotherapy, novel therapies in addition to autologous HSCT.

Conclusion

MM can present with cytopenias other than anemia. Presentation can range from being asymptomatic to an aggressive picture that

may mimic acute leukemia. In certain parts of the world, MM can be diagnosed in patients younger than 30 years of age. MM presenting at young age may be having an aggressive course.

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