CASE REPORT

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Immune Thrombocytopenic Purpura in a Patient Receiving Pomalidomide Treatment

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ABSTRACT Multiple myeloma (MM) is a clonal stem disease. Immune thrombocytopenic purpura is an autoimmune disease that is chronic and resistant to immunsupresive drugs. Pomalidomide is an immunomodulatory agent used in the treatment of MM. Pomalidomide used by our patient to treat myeloma could cause bone marrow supression. On the other hand, immune system dysregulation that may be seen with immunomodulatory agents used to treat MM may trigger some immunological events. MM and immune thrombocytopenic purpura (ITP) coexcistence is very rare. Herein, we aimed to share our experience with a patient with multipl myeloma who developed ITP during pomalidomide treatment.

Keywords: Purpura; thrombocytopenic; idiopathic; multiple myeloma; pomalidomide

Multiple myeloma (MM) constitutes approximately 1.8% of all cancers and approximately 13% of all hematological malignancies.[1,2] MM presents with monoclonal protein secretion into serum and/or urine, which is coupled with end-organ injury manifested by anemia, renal dysfunction, hypercalcemia, and bone involvement resulting from the clonal proliferation (>10%) of malignant plasma cells in bone marrow.[1] İmmune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by reduced thrombocyte count resulting from reduced thrombocyte production and increased thrombocyte breakdown.[3] Although anemia, leukopenia and thrombocytopenia can result from the treatment regimens used to treat MM, concomitant autoimmune thrombocytopenia and MM have been rarely reported. Herein, we aimed to present a patient with ITP that developed during the course of MM treatment.

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A 78-year-old Caucasian man was diagnosed with International Staging System stage II non-secretory MM manifested solely by bone involvement in October 2010.[4] All biochemical tests and the complete blood count of the patient were in the normal range; there was no monoclonal band in serum immune electrophoresis and urine immune electrophoresis. Since a very good partial response according to the International Myeloma Working Group's consensus report was achieved after four cycles of bortezomib-dexamethasone chemotherapy, high-dose chemotherapy with peripheral stem cell support was planned, although it was not possible to administer it as the cardiology department deemed patient high-risk due to ischemic heart disease.[5,6] During pomalidomide dexamethasone treatment, there was no use of drugs other than atenolol and clopidogrel for ischemic heart disease. Bortezomib-dexamethasone treatment then

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was continued to complete eight cycles. Afterwards, the patient was followed untreated. In December 2013, when his bone pain intensified, a positron emission tomography-computed tomography (PET-CT) revealed diffuse bone involvement with concomitant monoclonal plasma cell infiltration in bone marrow biopsy. Hence, he was considered to have relapsed disease, for which lenalidomide-dexamethasone treatment protocol was begun.[7] After a 9-month course of retinal detachment treatment, his bone pain re-intensified, for which he underwent a fluoro-18-deoxyglucose/PET, which showed signs of progressive bone involvement. Thus, carfilzomib-dexamethasone (Cd) regimen was started after his cardiologist's approval of the regimen.[8] Cd treatment was continued for 18 months, while intermittent PET CT evaluations during that time window showed signs of regression of bone lesions. As bone pain re-started at the 24th month of Cd treatment, the patient was considered to have progressive disease and begun on pomalidomide-dexamethasone treatment.[9] At the 14th month of the pomalidomide treatment, he suddenly developed epistaxis, gum bleeding and diffuse petechial skin bleeding. His blood tests at that time showed thrombocytopenia (thrombocyte count 13,800/mm^3 (N: 150,000-40,000/mm^3), which was confirmed by a peripheral blood smear examination using light microscopy. Apart from the patient's pomalidomide-dexamethasone treatment, he was using clopidogrel, atenolol, atorvastatin for ischemic heart disease. Epstein-Barr virus polymerase chain reaction (PCR) and cytomegalovirus PCR tests were performed for viral infections due to reasons that may cause secondary immunothrombocytopenia, and antinuclear antibody test was performed for collagen tissue diseases. No pathology was detected in these examinations. No hepatosplenomegaly was detected in abdominal ultrasonography. Thrombotic microangiopathic thrombocytopenia and other causes of thrombocytopenia were excluded. A bone marrow biopsy showed a normocellular bone marrow with an increased megakaryocyte count but no plasma cell infiltration and no signs of dysplasia were detected (Figure 1). The patient was thus considered to have acute immune thrombocytopenic purpura; the pomalidomide-dexamethasone treatment was stopped and methylprednisolone 1 mg/kg/day was started. Since the patient had marked thrombocytopenia after the steroid dose had been reduced, 1 g/kg/day intravenous immunoglobulin (IVIG) was administered intermittently for two days. The cardiology department did not allow splenectomy due to his coronary artery disease. Therefore, the patient was first administered vincristine (2 mg/week, four weeks). Since his thrombocyte count remained stable at approximately 50,000-100000/mm^3 after these treatments, pomalidomide-dexamethasone treatment was resumed. In July 2019, his thrombocyte count reduced to <20,000/mm^3 with recurrent bleeding. The etiology of thrombocytopenia was re-investigated with various tests, including a bone marrow biopsy. He was begun on eltrombopag 50 mg, which elicited a partial response; however, despite dose increment, the response was lost, which led to stopping the treatment in January 2020 and followed by rituximab (375 mg/m^2/day four weeks). After four courses of rituximab treatment, there wasn't adequate response obtained. Danazol treatment was started; however, no response could be obtained with an 8-week treatment, which made us stop danazol and switch to azathio-

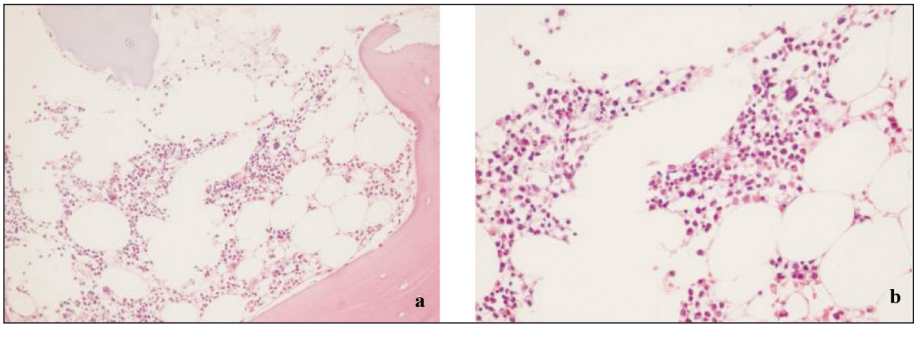

FIGURE 1: Bone marrow biopsy image of the patient. Here, the absence of atypical cell infiltration and dysplasia and the normal number and morphology of the megakaryocytes were evaluated as compatible with ITP (Microscopic examination was performed at H&E, x100 magnification).

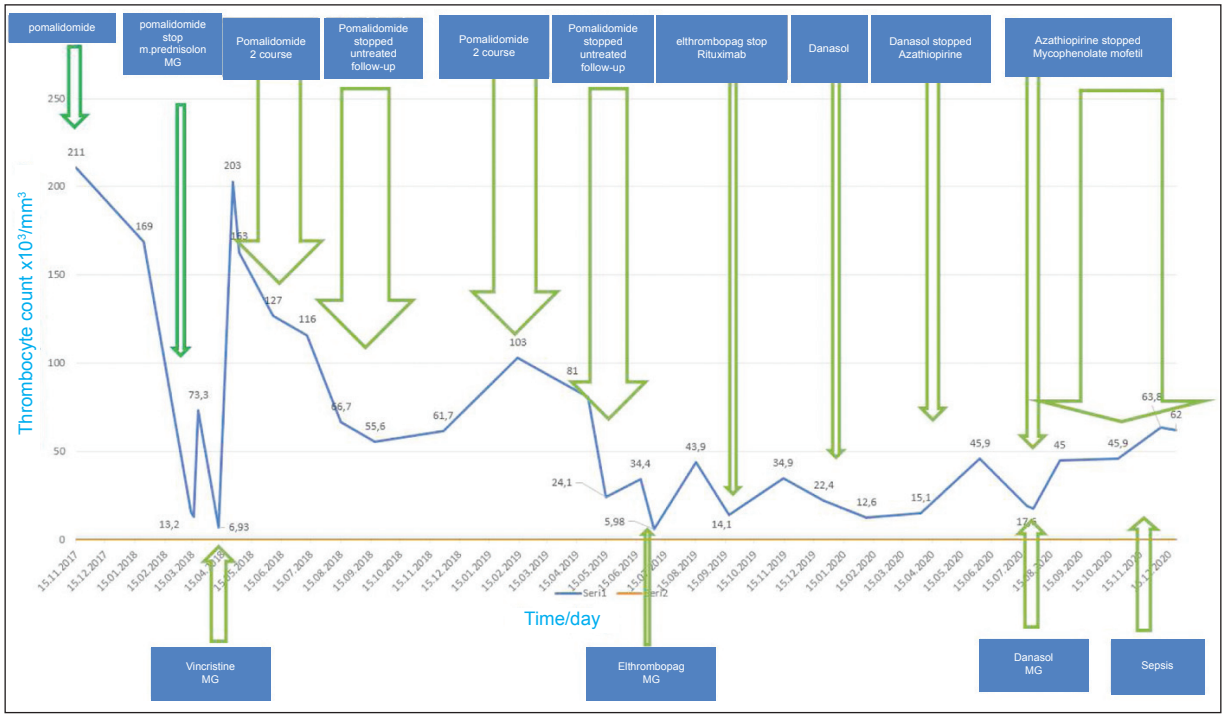

FIGURE 2: The platelet count of the patient and the treatments applied are given in graphic form.

prine treatment. After an 8-week course of the latter, thrombocyte count was measured 15,000/mm^3, and severe weakness, skin disorders, and balance problems emerged, which led to the cessation of azathioprine, too. In July 2020, mycophenolate mofetil was started at a dose of 250 mg/day, which was increased 500 mg/day later. The course of the patient's platelet count during the entire treatment process is given in the graphic (Figure 2). Although he had thrombocyte counts of 30,000-50,000/mm^3 while on treatment, he was succumbed to urosepsis during follow-up. The patient's consent was obtained for this case study.

DISCUSSION

Immune thrombocytopenia is a clinical condition that is frequently observed in lymphoproliferative diseases, such as chronic lymphocytic leukemia and non-Hodgkin lymphoma. Clinical signs of ITP are expected to be eliminated by corticosteroids and treatment of the underlying disorder.[10] Immune thrombocytopenic purpura is diagnosed by the lack of other causes of thrombocytopenia, such as infection and drug use, as well as the signs of diseases causing organomegaly and microangiopathic hemolytic anemia (thrombotic thrombocytopenic purpura-hemolytic uremic syndrome-diffuse intravascular coagulation).[3]

Our patient had MM. Since pomalidomide used by our patient to treat myeloma could potentially suppress the bone marrow, a bone marrow biopsy was performed, which revealed a normocellular marrow, an increased megakaryocyte count and a clonal plasma cell percentage of 4%. In the light of these findings, both pomalidomide-induced myelosuppression and thrombocytopenia secondary to the primary disease were eliminated, and ITP was considered the primary cause. A review of the literature on patients with concomitant MM and ITP shows an extremely low number of case reports in which MM and ITP were simultaneously diagnosed, or MM was diagnosed in a patient already having ITP.[11,12] Pomalidomide is an immune modulatory agent. There are reports that immune modulators may modulate the immune response. For example, a case of autoimmune thyroiditis during thalidomide treatment was

reported.[13] It is not entirely clear how immune modulators trigger autoimmune events. These agents may impair T cell proliferation and function. One of the possibilities is that T cell dysfunction induced by an immune modulator like lenalidomide directs latent autoreactive T cells straight to thrombocyte antigens and other antigens.[14] We decided to stop pomalidomide treatment considering that our patient had thrombocytopenia secondary to pomalidomide because he developed ITP during that treatment; however, thrombocytopenia did not improve despite that strategy. As recommended by others for corticosteroid resistant patients with ITP, we administered IVIG, vincristine, rituximab, eltrombopag, danazol, azathioprine and mycophenolate mofetil treatments, respectively.[3] Mycophenolate mofetil finally achieved a stable thrombocyte count of 30-50x10^3/L. During that treatment, no sign of myeloma relapse was detected at three-monthly controls. Adults with ITP have a 1.3-2 times higher mortality rate than the general population due to cardiovascular diseases, infection, and bleeding episodes.[3]

In conclusion, while it is extremely challenging to simultaneously manage two resistant diseases, i.e., MM and ITP that develops during pomalidomide treatment to treat the former, intense immunosuppressive treatment regimens that have to be administered may cause severe infections, as in our patient.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

REFERENCES

1. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-48. [Crossref] [PubMed]
2. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(5):548-67. Erratum in: Am J Hematol. 2020;95(11):1444. [Crossref] [PubMed]
3. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23): 3829-66. Erratum in: Blood Adv. 2020;4(2): 252. [Crossref] [PubMed] [PMC]
4. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-20. Erratum in: J Clin Oncol. 2005;23(25):6281. Harousseau, Jean-Luc [corrected to Avet-Loiseau, Herve]. [Crossref] [PubMed]
5. Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al; International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-73. Erratum in: Leukemia. 2006;20(12):2220. Erratum in: Leukemia. 2007;21(5):1134. [Crossref] [PubMed]
6. Rosi-ol L, Oriol A, Mateos MV, Sureda A, García-Sánchez P, Gutiérrez N, et al. Phase II PETHEMA trial of alternating bortezomib and dexamethasone as induction regimen before autologous stem-cell transplantation in younger patients with multiple myeloma: efficacy and clinical implications of tumor response kinetics. J Clin Oncol. 2007;25(28):4452-8. [Crossref] [PubMed]
7. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al; Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007;357(21):2123-32. Erratum in: N Engl J Med. 2009;361(5):544. [Crossref] [PubMed]
8. Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120(14):2817-25. [Crossref] [PubMed] [PMC]
9. Miguel JS, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(11):1055-66. [Crossref] [PubMed]
10. Zent CS, Kay NE. Autoimmune complications in chronic lymphocytic leukaemia (CLL). Best Pract Res Clin Haematol. 2010;23(1):47-59. [Crossref] [PubMed] [PMC]
11. Gupta V, Hegde UM, Parameswaran R, Newland AC. Multiple myeloma and immune thrombocytopenia. Clin Lab Haematol. 2000;22(4):239-42. [Crossref] [PubMed]
12. Verdirame JD, Feagler JR, Commers JR. Multiple myeloma associated with immune thrombocytopenic purpura. Cancer. 1985;56(5): 1199-200. [Crossref] [PubMed]
13. Erdem F, Gundogdu M, Kiki I, Capoğlu I. Autoimmune thyroiditis during thalidomide treatment. Am J Hematol. 2006;81(2):152. [Crossref] [PubMed]
14. Herold CI, Gasparetto C, Arepally GM. Lenalidomide-Associated ITP. Case Rep Hematol. 2011;2011:638020. [Crossref] [PubMed] [PMC]