A case of a Young Multiple Myeloma Patient With Poor Prognostic Cytogenetics

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ABSTRACT: Multiple myeloma is a hematologic malignancy and a subtype of plasma cell dyscrasias, which accounts for 13% of all hematologic malignancies. It mainly affects older adults and is diagnosed in only 2% of the young population under the age of 40 years. This report presents a 33-year-old man diagnosed with Multiple myeloma with 4 poor prognostic specifications consisting of amplification of the 1q21, Translocation of t(4;14), deletion of the 6q21 and 13q14, along with decreased chromosome count to 44, X,-Y. Even though the combination of 4 poor prognostic cytogenetics in young patients is rare, he responded significantly to the Bortezomib regimen. He was selected as a candidate for bone marrow transplantation. The treatments get interrupted 2 days after the first session of the fifth cycle due to an undesirable COVID-19 infection. After 20 days, the symptoms return, and paraclinical findings show signs of MM relapse.

KEYWORDS: Multiple myeloma, young, poor prognostic, COVID-19

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Introduction

Multiple myeloma (MM) is a hematologic malignancy and a subtype of plasma cell dyscrasias, which accounts for 13% of all hematologic malignancies.[1] MM mainly affects older adults and is diagnosed in only 2% of the young population under the age of 40 years.[2] Prognosis in MM depends on 4 key factors; disease staging, the patient's general features, the biology of the disease, and the response rate to treatment.[3] Cytogenetic abnormalities are among the biological features of the disease.[4] Infections are one of the prevalent complications and the leading cause of mortality in MM patients.[5] In this report, a 33-year-old man diagnosed with MM with poor prognostic cytogenetic characteristics is presented, on the verge of complete remission and bone marrow transplantation, gets COVID-19 infection, experiences relapse of MM, and is deceased.

Case Presentation

The patient was a 33-year-old man admitted to the rheumatology ward with severe low back pain commencing in the past 3 months. The pain was mainly in the lumbar and sacroiliac vertebra and sternum, and movement and rotation exacerbated it and woke him up at night. He mentioned 12 kg weight loss. He had a history of non-pasteurized dairy consumption in the past 3 months and no history of trauma, nausea, blurred vision, or fever. Also, no smoking history was mentioned, and he had no family history of hematologic diseases. Different types of NSAIDs were prescribed for back pain, which over time proved ineffective. In physical examination, tenderness was evident in the sternum, right lower ribs, lumbar, and right sacroiliac joint. Also, a decrease in flexion and lateral bending was detected, deep tendon reflexes and muscle forces were normal, and the Babinski test was negative in both limbs.

His young age and chief complaints led to the diagnosis of brucellosis, the endemic disease of the region. Other differential diagnoses were propounded, such as tuberculosis, ankylosing spondylitis, and malignancy. The list of laboratory results is shown in the Table 1.

Abdominopelvic ultrasonography showed mild spleen enlargement (splenic span of 136 mm). Cranial radiography showed several lytic lesions of different sizes, accompanied by a slight increase in the cranial bone thickness. Thoracolumbar magnetic resonance imaging (MRI) study showed multiple abnormal lesions in vertebral bodies of the thoracolumbar spinal column. In addition, in the pelvis and thoracolumbar MRI, diffused abnormal bone marrow signal intensity was noted in favor of MM (Figure 1).

Serum protein electrophoresis (SPEP) showed a peak in beta-1. The urinary protein electrophoresis (UPEP) showed a significant increase in free light chains, IgG/IgA, mixed tubular and glomerular, and Bence Jones proteinuria. Bone marrow aspiration and biopsy (BMA and BMB) were performed for him. Histopathologic examination showed that more than 80% of all nucleated cells were plasma cells or plasmablasts (Figure 2).

Immunophenotyping of BMA by flow cytometry shows a predominantly abnormal plasma cell population that is positive for CD38, CD138, and CD56 and negative for CD19. In the cytogenetic study, 44,X,-Y,der(1)del(1)(p13,3p22)del(1)(p31,3p33),del(2)(q13),der(3)t(1;3)(q12;q27),del(6)(q13q27),-8,del(12)(p11,2),-13,-18,+mar×2[8]/45,sl,+mar[10]/44,sl,del(1)(q12q25), add(16)(q13)[2] was present.

Table 1. Laboratory results.

LABORATORY PARAMETER	NORMAL RANGE	RESULTS			
		TIME OF DIAGNOSIS	END OF THE FOURTH CYCLE	COVID-19	RELAPSE
WBC count, count/mm	4000-10 000	2500	7600	3600	4600
Neutrophil count, count/mm	2500-8000/mm^3	1375	4712	1210	2162
Lymphocyte count/mm	1000-4000/mm^3	1000	1900	900	1932
Hemoglobin, mg/dl	14-18	8	11.9	11.7	11.7
MCV, fl	80-96	92	94	93	94
MCH, Pgr	26-32	30	32	31	30
Platelet, count/mm	150 000-450 000	41 000	69 000	57 000	78 000
LDH	0-500		181	410	
Urea, mg/dl	15-45	12	23	28	25
Cr, mg/dl	0.5-1.4	0.9	0.7	0.7	0.8
CRP	-	-	-	3+	-
ESR, mm/h	Age/2	130	23	80	75
INR	1-1.4	2.3			
PTT, s	30-45	54			
Calcium, mg/dl	8.2-10.7	11.5		7.9	
Phosphorus, mg/dl	2.5-5	4.8		3.7	
25-hydroxy vitamin D, ng/ml	>30	14.5			
B2M	-	>6	3.8	3.8	3.9
Albumin, g/dl	3.5-5.5	3.6		3.3	
PTH, pg/dl	15-68	1.5			
TSH, micIU/ml	0.35-4.94	2.39			
AST, IU/l	<41	13			
ALT, IU/l	<41	22			
ALP, IU/l	80-306	137			
Urine analysis		Proteinuria			
Wright	-				
2-ME	-				
RF	-				
HLA-B27	-				

In Fluorescence in situ Hybridization (FISH) report, he had 74% amplification of 1q21, 89% deletion of 6q21, 97% deletion of 13q14.3, 81% positive IGH break, and 81% t(4;14) (p16;q32) FGFR3/IGH. Therefore, the final diagnosis of high-risk MM was made based on the available findings.

Treatment started with a VRD regimen which includes bortezomib 1.3 mg/m^2 (days 1, 4, 8, 11, 22, 25, 29, 32), lenalidomide 25 mg, and dexamethasone 40 mg. His back pain decreased after the fourth session of treatment. In the BMA and BMB that were taken on the last session of the fourth cycle, plasma cell counts decreased to 3%, contributing to complete remission. Regarding the adequate response, he was selected as a candidate for autologous bone marrow transplantation.

2 days after the first session of the fifth cycle, he was admitted to the emergency department with an abrupt fever of 40°C, anosmia, anorexia, weakness, Mild dyspnea, and reduction in

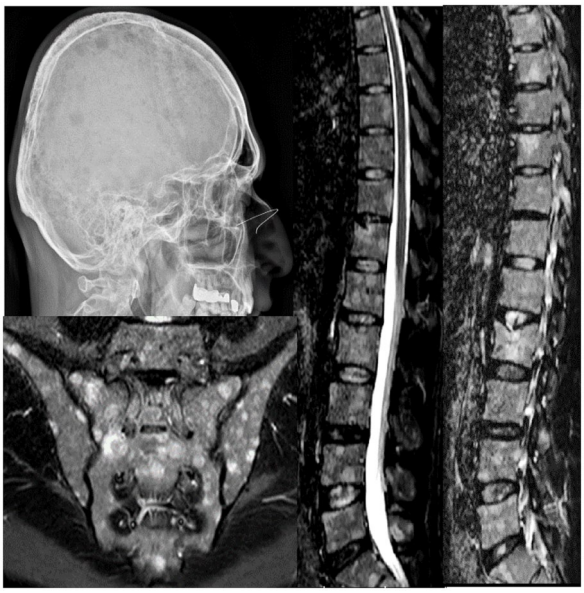

Figure 1. Several lytic lesions with different sizes in the skull, vertebras, sacroiliac, and pelvic bones.

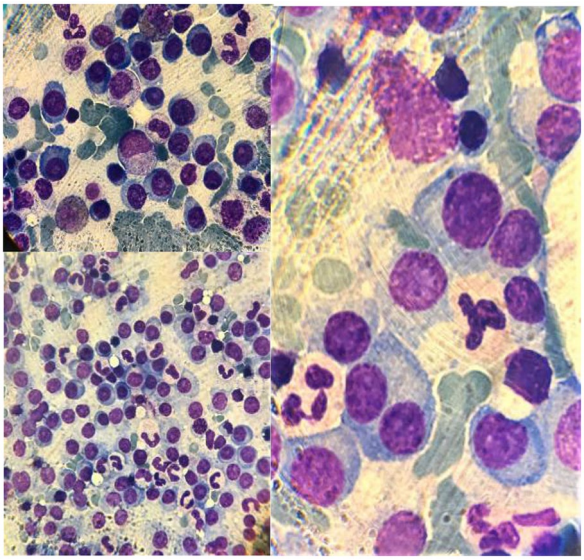

Figure 2. BMA and BMB of the patient showed an excessive number of oval-shaped plasma cells with basophilic cytoplasm, a round and eccentric nucleus, and bi- and multi-nucleated plasma cells in some fields.

oxygen saturation (91% without oxygen). Laboratory studies and spiral chest computed tomography (CT) were requested. Multiple peripheral patchy ground-glass opacities were unveiled in the CT scan (Figure 3). The coexistence of positive reverse transcription-polymerase chain reaction (RT-PCR) made a definite diagnosis of COVID-19 infection. He was admitted to the infectious disease ward for isolation and treatment, and his chemotherapy session was postponed. After 2 days, the fever subsided. During treatment, he showed no sign of dyspnea or respiratory distress, and oxygen saturation was above 94%. He was discharged from the hospital without any complications. Approximately 20 days after discharge, a vague pain started in his feet and back. The pain intensity increased, and on the day

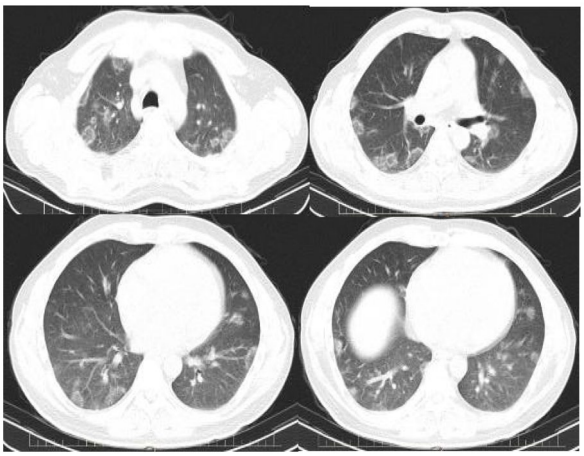

Figure 3. Spiral chest CT demonstrates peripheral patchy ground-glass opacities by the COVID-19 infection disease.

of negative RT-PCR, he was admitted with excruciating pain in the lower limbs and his back, which was resistant to regular analgesic drugs. SPEP, which became normal before COVID-19, showed a peak in beta-1, and MM relapse diagnosis was confirmed. Afterward, he received different treatments such as a repeat VRD regimen, Bortezomib/Cyclophosphamide/Dexamethasone (VCD), Pegylated liposomal Doxorubicin/Bortezomib and Bendamustin containing regimen but non showed any acceptable results.

Discussion

MM is a disease of elderly patients. Various studies demonstrate that the survival rate for patients 65 years old and younger is 2-fold more than for older patients.[6] In this case, according to the 2014 International Myeloma Working Group diagnostic criteria,[7] the diagnosis was made with the presence of end-organ damage (hypercalcemia, anemia, bone lesions) and more than 80% plasma cells in bone marrow samples as well as multiple bone lesions in MRI.

MM patients are often referred to the hospital with various complaints, mostly related to plasma cell infiltration in organs or their over-productions. The MM presentations are anemia in 73%, bone pain in 58%, elevated creatinine in 48%, fatigue and generalized weakness in 32%, hypercalcemia in 28%, and weight loss (approximately 9 kg) in 24% of patients.[2] It is less common in young MM patients to present with beta2-microglobulin (B2M) of 3.5 and more and low hemoglobin.[8] In our case, severe bone pain was the first presentation, but the intensity was higher than in regular MM patients. Moreover, B2M was high, and low hemoglobin was detected, which is exceptional.

Although metaphases occur in a small number of MM cells, almost 20% to 30% of patients have detectable cytogenetic abnormalities.[9] Among cytogenetics with poor prognosis, amplification of the 1q21 is detectable in 43% of newly diagnosed MM and 72% of patients with relapsed MM.[10] Translocation of t(4;14) has the highest prevalence in IgH translocations in MM and is more significant in ages less than

65 years (15% vs 14.3%).[11] In addition, the deletion of the 6q21[12] and 13q14 are predictors of poor prognosis.[13] Even though the combination of 4 poor prognostic cytogenetics in young MM patients is rare, it has occurred in the presented case.

It is anticipated that in patients with 1q21 amplification, only 3 copies and 20% plasma cells suffice to develop Bortezomib resistance.[14] Patients with the rest of the mentioned cytogenetic abnormalities show improvement in outcome with Bortezomib treatment.[15] Even though our patient had poor prognostic cytogenetics, he responded to the VRD regimen in the first line. However, after recurrence, it has become resistant to the treatments performed so far, and the disease has not subsided.

In a study by Chari et al, an association of MM patient's clinical features with COVID-19 outcome is discussed and Age of higher than 60, high-risk MM, and renal disease are suggested as poor prognosis factors. Additionally MM patients with complete remission showed better prognosis.[16] According to cytogenetic abnormalities, our patient was categorized as high risk and associated with poor prognosis but he responded well to COVID-19 treatment. However, prolonged survival and overcoming adverse prognosis could be acquired by tandem ASCT post Induction treatment. COVID-19 infection and temporary cessation of therapy have led to the recurrence of the disease and failure to respond to various treatments.

Due to the lack of information on the association between COVID-19 infection and malignancies, the authors have no comment about the possibility of continuing various antineoplastic therapies (chemotherapy, immunotherapy, monoclonal antibody therapy, etc.) during non-severe COVID-19, especially in High-risk malignant patient.

Conclusion

Although MM is a disease of elderly patients, it should be considered a differential diagnosis in young patients with clinical and laboratory findings. Apparently, in malignancies, COVID-19 may not show severe respiratory manifestations, and the possibility of continuing antineoplastic treatment of patients during infection still needs further investigation.

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Authors' Contributions

EI visited the patient in the hospital daily, checking and revising the manuscript. SM and MN drafted the manuscript.

Ethics' Approval

This article has been approved by the ethics committee of Ardabil University of medical sciences (IR.ARUMS.REC.1400.262)

Consent to Participate

Written informed consent was obtained from the patient for his participation in this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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