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A Secondary B Acute Lymphoblastic Leukemia in Known Case of Multiple Myeloma Treated with Lenalidomide- A Rare Case Report

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Abstract

Therapy-related or secondary acute myeloid leukemias in Multiple Myeloma (MM) are well documented; however, secondary B-acute lymphoblastic leukemia (B-ALL) in MM is rarely reported. Chromosome 11q23 abnormality is frequently seen in secondary acute myeloid leukemia; but secondary-ALL without 11q23 abnormality is extremely rare and associated with poor survival. Although, the role of lenalidomide causing secondary malignancies in MM has not been fully understand and explained, we are presenting a case of secondary B-ALL in known case MM treated with Lenalidomide without association of 11q23 abnormality. A 52-years old lady, a diagnosed and treated case of MM with Lenalidomide achieved a complete remission (CR). She was on routine follow and presented with fever and reduced appetite. Complete blood count (CBC) showed thrombocytopenia & peripheral-blood-smear (PBS) examination showed 60% blasts. Blasts were negative for cytochemical myeloperoxidase (MPO). Flowcytometric immunophenotyping (FCI) of blasts population showed B ALL phenotype. Cytogenetics evaluation did not reveal translocations involving 11q23, the *KMT2A* gene locus. Although extremely rare, secondary-ALL is one of the therapy-related neoplasms in MM without translocations involving 11q23, the *KMT2A* gene locus. In addition to CR with lenalidomide therapy in our patient, and absence of B-ALL clone at the time of initial diagnosis by FCI indicates that the secondary B-ALL was de novo disease. Chronic lenalidomide use in the treatment of MM may have resulted in the development of s-ALL, however, the exact association between MM, chronic therapy with lenalidomide and s-ALL in this patient remains unknown and needs further work up.

Keywords: Secondary B acute lymphoblastic leukemia; Multiple myeloma; Lenalidomide

Introduction

Therapy-related or secondary acute myeloid leukemias (AML) in multiple myeloma (MM) are well documented; however, secondary B acute lymphoblastic leukemia (B-ALL) in MM is rarely reported [1]. The frequently found chromosomal abnormality in secondary AML as well as secondary B-ALL is translocations involving 11q23, the *KMT2A* gene locus. Secondary B-ALL without 11q23 abnormality is extremely rare and associated with poor survival. In addition to that there are only a few published reports describing occurrence of secondary B-ALL in MM patients. We report a case of secondary B-ALL in known case MM treated with Lenalidomide without association of 11q23 abnormality who had achieved complete remission.

Case Presentation

A 52-years old lady, presented with fatigue and lower backache and being investigated for the same. Meanwhile MRI spine was done and it revealed wedge compression of D8 vertebra. Serum immunoelectrophoresis showed abnormal electrophoretic pattern with presence of monoclonal band IgG/lambda (1.4 G/dl) type. The renal function test and complete blood count (CBC) levels were within normal ranges except for anemia with hemoglobin (Hb) of 7 gm/dL (range: 13-17 gm/dL). Serum calcium was 9.2 mg/dL (range: 8.5-10.2 mg/dL) and beta-2 microglobulin was 3.8 mg/L (< 2 mg/L). The bone marrow (BM) aspiration revealed 38% plasma cells and infiltration in sheets by plasma cells in trephine biopsy. FCI of BM aspiration revealed clonal plasma cells. Skeletal survey showed many lytic lesions of the skull and lumbar-sacral area. A diagnosis of MM was made in 2010. After that she was treated with Lenalidomide, dexamethasone and zolendronic acid for two years. She had achieved complete remission in 2012 and was on routine follow up till July 2014. Subsequently, she presented with fever, weakness and reduced appetite. CBC revealed total leukocyte count (TLC) - $5.42x10^9$/L (range: $4\text{-}11x10^9$/L), Hb - 12.4 gm/dL (range: 13-17 gm/dL), and platelets - $7x10^9$/L (range: $150\text{-}410x10^9$/L). Peripheral-blood-smear (PBS) examination showed 60% blasts and was negative for cytochemical myeloperoxidase (MPO) staining.

Cytogenetic analysis was performed by using common B ALL probes and includes *BCR/ABL1* by using Locus Specific Identifier (LSI) *BCR/ABL1* dual fusion translocation probe, *KMT2A* by using LSI *KMT2A* (11q23) break apart rearrangement probe, *TCF3/PBX1*; t(1;19) and *ETV6/RUNX1*; t(12;21) fusion translocation probes and

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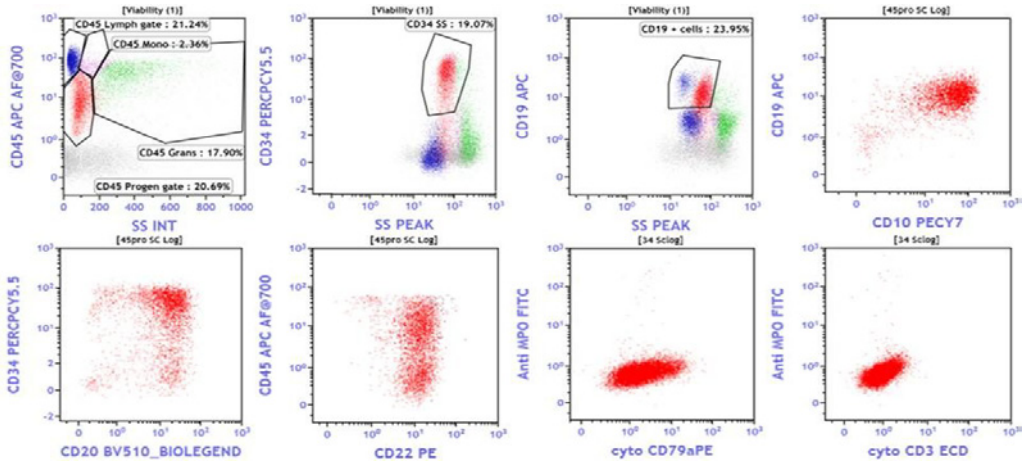

Figure 1: Immunophenotypic analysis of bone marrow specimen. The dot plots show blasts (red dots) with positive expression for CD10, CD19, CD20, CD34, co-expression of CD22 and cytoplasmic CD79a. The blasts were negative for cytoplasmic CD3 and myeloperoxidase.
Abbreviations: B-ALL: B-acute lymphoblastic leukemia; MM: Multiple Myeloma; CBC: Complete Blood Count; CR: Complete Remission; FCI: Flowcytometric Immunophenotyping; PBS: Peripheral-Blood-Smear; MPO: Myeloperoxidase; AML: Acute Myeloid Leukemias; Hb: Hemoglobin; BM: Bone Marrow; TLC: Total Leukocyte Count; PBS: Peripheral-Blood-Smear; LSI: Locus Specific Identifier; FDA: Food and Drug Administration

Table 1: Different studies published in the literature.

Study	No. of cases	Treatment Received		Latency period (Years)	*KMT2A* (11q23) aberration
		Alkylating agent	Lenalidomide		
[7]	1	Yes	No	One	Detected
[9]	1	Yes	No	One	Not detected
[8]	1	Yes	No	Nine	Not detected
[10]	1	No	Yes	Two	Not available
[11]	2	Yes	No	Five to six	Not detected
[12]	3	No	Yes	Two	Not available
[13]	3	Not available	Yes	Two to seven	Not detected
Present study	1	No	Yes	Four	Not detected

revealed negative results for all these translocation, however showed tri-tetrasomy of chromosomes 1, 4, 9, 10, 11, 17, 19 & 22 in 90-95% cells and ploidy analysis revealed triploidy in 100% of cells. In addition to this, no other common MM related abnormalities were detected.

BM specimen was further processed for FCI using a lyse-stain-wash technique and a comprehensive eight-color antibody-panel for acute leukemia on Navios (Beckman Coulter; BC) and analyzed using kaluza-1.3 software (BC). The acute leukemia panel included monoclonal antibodies against CD1a, CD2, CD3, CD4, CD5, CD8, CD10, CD11b, CD13, CD15, CD16, CD19, CD20, CD22, CD33, CD34, CD38, CD45, CD56, CD58, CD117, CD123, HLADR, cytoplasmic CD79a, cytoplasmic CD3 and cytoplasmic MPO. Data were collected and analyzed using a CD45–side scatter based gating strategy and it revealed 21% of lymphoblasts. These blasts express moderate CD19, CD20, CD34, CD38, HLADR and CD58, dim CD10, sCD22, CD45, and CD123. They were also positive for cytoplasmic CD79a but negative for cytoplasmic myeloperoxidase and other myeloid/T cell markers (Figure 1). Further she was planned for chemotherapy ALL protocol but she succumbed to death after one week of diagnosis.

Discussion

Therapy-related acute leukemia is a heterogeneous disease that may occur especially after treatment with chemotherapy (alkylating agent/topoisomerase II inhibitor) or radiotherapy [1]. These alkylating agent-related acute leukemias are mostly AML with antecedent myelodysplasia with a mean latency period of 5 to 7 years [1-3]. On the other hand, secondary leukemias caused by DNA topoisomerase II inhibitors had relatively short latent periods (1-5 years) without antecedent myelodysplasia [1-3]. Translocations involving 11q23, the *KMT2A* gene locus are the most common characteristic chromosomal aberrations seen in therapy-related or secondary acute myeloid leukemias [4]. Incidence of therapy-related acute lymphoblastic leukemias is very much less than that of the therapy related AML and represents approximately 12% of all therapy-related acute leukemias and 1.2% to 4% of adult ALLs [4,5]. However, similar to that of therapy related AML chromosomal abnormalities in *KMT2A* gene (11q23) being the commonest ones. The risk of developing secondary AML in MM patients after treatment with alkylating agent therapy has been calculated to be 3-5% at 3 years and 10-15% at 10 years [6] while that of secondary ALL is extremely rare, about 0.5-1% of treated patients [6]. There were few case reports of treated MM cases terminated into s- B ALL published in the literature [7-13] and very few of them had documented absence of 11q23 cytogenetic abnormality (Table 1). Chen, et al. [11] also showed that, s-ALL cases with an 11q23 abnormality compared to cases without

an 11q23 abnormality had a longer latency period (median, 36 vs. 19 months). There is an increased risk of developing secondary malignancies including ALL after the chronic use of lenalidomide to treat MM have been reported by Food and Drug Administration (FDA) [12] and also showed the median time span to develop the secondary malignancy was 2 years. Recently, Palumbo, et al. [14] also showed similar findings and stated that increased risk of developing hematological second primary malignancies after use of lenalidomide in newly diagnosed MM patients.

Our patient had received only a lenalidomide in MM treatment and developed secondary BALL with a no detectable translocations involving 11q23, the *KMT2A* gene locus. The latency period was four years from diagnosis of MM and was comparable with the mean latency period described in the literature for secondary ALL related to lenalidomide treatment [12,14] (Table 1).

Conclusion

Although extremely rare, secondary ALL is one of the therapy-related neoplasms in MM without translocations involving 11q23, the *KMT2A* gene locus. In addition to CR with lenalidomide therapy in our patient, and absence of B-ALL clone at the time of initial diagnosis by FCI indicates that the secondary B-ALL was de novo disease. Chronic lenalinomide use in the treatment of MM may have resulted in the development of s-ALL, however, the exact association between MM, chronic therapy with lenalidomide and s-ALL in this patient remains unknown and needs further work up. Detailed immunophenotypic and cytogenetics evaluation is important for further categorization and risk stratification of such cases.

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