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Unveiling the Uncommon: B-ALL Emerging in a Landscape of Multiple Myeloma- A Case Report

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Abstract

Patients suffering from Multiple Myeloma (MM) have improved survival with current available therapies. However, there remains a long-term enhanced risk of developing treatment-associated second primary malignancies. Here we present a case of a patient with IgG Lambda MM who underwent treatment for refractory disease who was noted to have new onset bicytopenia. For his MM, he had previously received Immunomodulatory (IMiD) agents in induction as well as maintenance. A peripheral blood smear showed circulating abnormal lymphoid cells, and a bone marrow examination along with flowcytometry revealed B-cell acute lymphoblastic leukaemia (B-ALL). He was administered an age-appropriate induction chemotherapy regimen but he eventually succumbed. Secondary B-ALL is a rare occurrence in patients with MM, with exposure to alkylating agents and IMiD being potential risk factors.

Keywords: Multiple myeloma; Leukaemia; Carcinogenesis; Immunomodulatory agents; Lenalidomide

Introduction

Current available therapies in the armamentarium have shown dramatic improvement in survival rates for patients with multiple myeloma (MM). There is a reported relative 5-year OS of over 60% for patients who are younger than 65 years old [1]. However, there has been an increased awareness and concern for the development of second primary malignancies (SPMs) as a result of improved survival. Lenalidomide is an immunomodulatory agent which is commonly used during induction and as a long-term maintenance therapy prior to or after autologous stem cell transplant (ASCT). Lenalidomide maintenance until progression is shown to be associated with a better progression-free survival compared to no maintenance in patients with MM. However, it has been associated with an enhanced risk of haematological SPMs like acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) [2]. However, B- cell acute lymphoblastic leukaemia (B-ALL) as an SPM has been reported very rarely in patients with MM. Routinely, in our clinical practice, we observe occurrence of cytopenias in patients with MM while on treatment with a broad differential diagnosis; however, the development of a haematological SPM should promptly be considered. Here we report a case of a patient with IgG Lambda Multiple myeloma who developed bicytopenia while on treatment for relapsed disease, initially suspected to be a plasma cell leukaemia, later found to have B-ALL.

Case Presentation

A 62-year-old male, a native of Uttar Pradesh, India and a farmer by occupation with no comorbidities was initially diagnosed with IgG Lambda MM in the setting of renal insufficiency, lytic bone lesions in the humerus and pelvis, monoclonal gammopathy with 5.14 g/dL M-protein, and 25% monotypic plasma cells by bone marrow biopsy.

Se. Immunofixation revealed IgG Lambda MM with Lambda Free light chain being 542 (Kappa: Lambda- 0.038). Baseline cytogenetic studies did not reveal any significant abnormalities. He was initiated on treatment with bortezomib, thalidomide and dexamethasone. He received 6 cycles of the same following which myeloma assessment revealed a partial response (PR). Thereafter, thalidomide was replaced by lenalidomide and he received 10 cycles of the same. Subsequently, he developed a very good partial response (VGPR) to the therapy and was counselled for Autologous HSCT. However, patient was unwilling for the same and was initiated on lenalidomide maintenance at 10mg/day which was later increased to 15 mg/day. After 2 years of maintenance, lenalidomide

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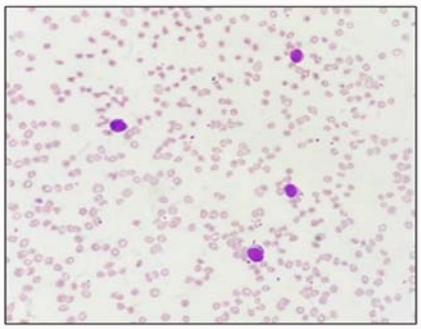

Figure 1: Peripheral blood smear showing circulating atypical cells (blasts).

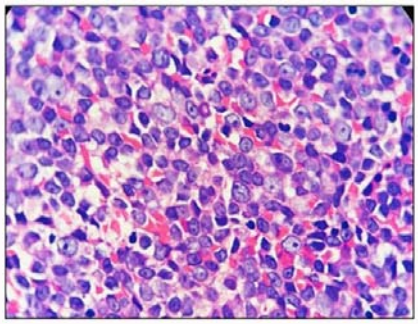

Figure 2: Bone marrow core biopsy depicting infiltration by blasts.

was discontinued and patient was kept on a 3 monthly follow up.

Subsequently, patient presented with complaints of generalized weakness, increased fatiguability, cough with minimal expectoration and a low-grade fever in the past 2 weeks. HRCT thorax revealed multifocal consolidation in bilateral upper lobes and ground glass opacities suggestive of an infective etiology. Sputum AFB and gene Xpert for tuberculosis was negative. He was started on an antibiotic course. At that time, his complete blood count showed a white blood cell count of 6000 cells/mcL, haemoglobin of 7.8 g/dL and a platelet count of 60×10^9 cells/L. Lambda light chains had decreased to 12.7 mg/L with a kappa:lambda ratio of 0.89, and the M-protein was not detected on electrophoresis. A peripheral blood smear examination and a bone marrow evaluation was advised.

Investigations

His peripheral blood smear showed presence of small to medium sized atypical cells with round to irregular nucleus, clumped chromatin, prominent nucleoli and moderate amount of basophilic cytoplasm (Figure 1). These findings indicated a possibility of circulating plasma cells as seen in plasma cell leukemia or a distinct lymphoproliferative disease.

His bone marrow core biopsy showed a hypercellular marrow (Overall cellularity- 95%) It was nearly entirely replaced by sheets of blast cells with scant cytoplasm, hyperchromatic nucleus and prominent nucleoli (Figure 2). Trilineage hematopoiesis was suppressed. Virtually, no plasma cells were detected either morphologically or by flow cytometry.

Flow cytometry, however, identified a blast population comprising 68% of total that was Positive for nTDT, CD19, cCD79a, CD34, CD38, CD10, CD123, CD304, CD 22, CD86 (dim), CD 73 (dim) while being negative for cMPO, cCD3, CD7, CD73, CD13, CD25, TSLPR, CD138, CD20, CD56, CD117, CD27, CD81, CD3, CD4, CD8, CD5, Kappa and lambda.

Flowcytometry findings were consistent with B-Cell acute lymphoblastic leukemia (Figure 3).

Fluorescence in situ hybridisation analysis was positive for the deletion of TP53 gene on the short arm of chromosome 17 i.e. (17p13) and negative for t(12;21)/ETV6::RUNX1 fusion, t(9;22)/BCR::ABL1 fusion, KMT2A (MLL) gene rearrangement, IgH gene rearrangement, and CRLF2 gene rearrangement. Karyotype was normal i.e, 46,XY.

Treatment

The patient was diagnosed as a case of B-ALL and was admitted to the hospital for stabilisation. In view of baseline fungal pneumonia with superadded bacterial infection, he received antibiotics and antifungal therapy for 14 days. A repeat HRCT thorax showed clearing of GGOs. He was later initiated on induction therapy with Dana-Farber Cancer Institute (DFCI) ALL consortium Protocol (For Age >60 years). Diagnostic lumbar puncture was performed with cytology and flow cytometry negative for malignant lymphoblasts. He thereafter received two doses of prophylactic intrathecal methotrexate during induction. Bone marrow biopsy after the initial induction therapy showed a hypocellular regenerating marrow with scattered blasts. Measurable residual disease (MRD) assessment by flow cytometry detected an abnormal immature clone of B-cell population comprising 2.74% of nucleated cells.

Outcome and Follow-up

Patient subsequently developed drug induced liver injury (DILI) secondary to methotrexate and L-asparaginase. He later developed Grade 4 Hepatic encephalopathy with aspiration pneumonitis and eventually succumbed.

Discussion

With the introduction of novel agents like immunomodulatory agents, proteasomal inhibitors and more recently, monoclonal antibodies like Daratumumab, MM usually follows a chronic course with remissions and relapses requiring multiple lines of treatment, therefore, increasing the risk for the development SPMs in myeloma survivors [3]. The use of alkylating agents like high-dose melphalan as a conditioning regimen prior to ASCT in myeloma can significantly contribute to the development of myeloid malignancies [4]. Maintenance therapy with lenalidomide has also been independently associated with an increased risk of SPMs. A meta-analysis of three randomised controlled trials revealed that lenalidomide maintenance in comparison to placebo was associated with an increased HR of 1.71 (95% CI 1.04 to 2.79) for the development of solid tumours and an increased HR of 2.03 (95% CI 1.14 to 3.61, p=0.015) for development of haematological malignancies [2].

However, the International Myeloma Working Group recommends the use of lenalidomide in the maintenance setting, given its survival benefit [5].

B cell-acute lymphoblastic leukemia is a rare SPM occurring in patients with MM. In the CALGB 100104 trial of lenalidomide versus placebo maintenance following ASCT, in which 460 patients with MM were included, B-ALL was initially identified in a single patient on lenalidomide and none in the placebo group after a median follow-up of 34 months [6]. After a median follow-up of 91 months,

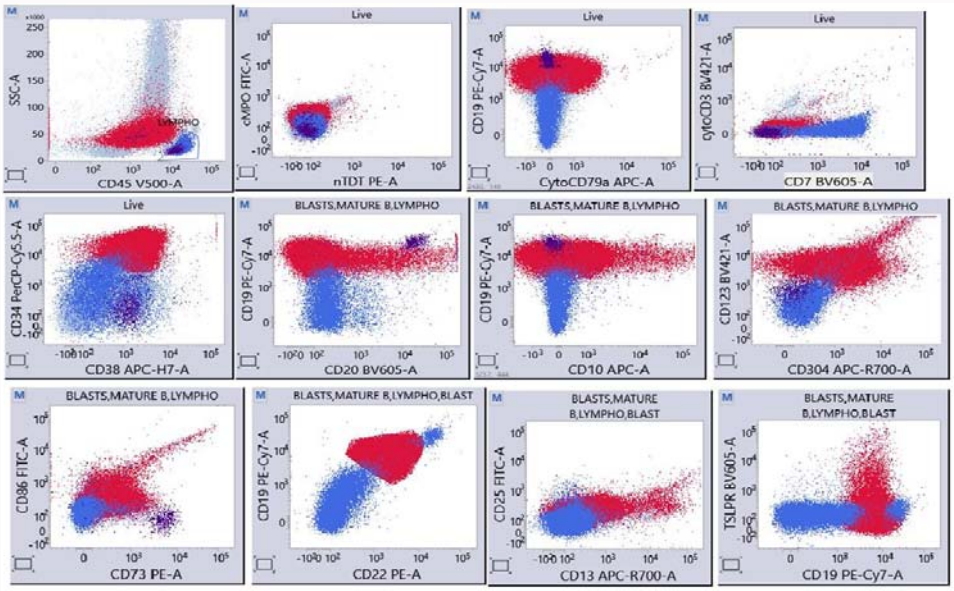

Figure 3: Shows Flowcytometry findings performed on the bone marrow aspirate sample.

however, B-ALL had been identified in six patients on lenalidomide and two patients on placebo, demonstrating the potentially longer follow-up time needed to observe cases of secondary B-ALL [7]. In our case, the patient was found to have B-ALL at 9 months after discontinuation of lenalidomide, having received a cumulative exposure of approximately 40 months of IMiD-containing therapy throughout his MM course.

In the current available literature, similar treatment strategies as those used in patients with de novo B-ALL have been used with very limited case reports of successful allogeneic stem cell transplantation in such cases [8,9].

The prognosis for haematological SPMs in patients with MM is very poor. A single-centre study of 47 patients with myeloma diagnosed with therapy-related myeloid neoplasms showed a median overall survival of only 6.3 months [10]. Given the rarity of secondary B-ALL in patients with MM, the relative prognosis compared with de novo B-ALL is largely unknown.

Further research in secondary B-ALL in patients with MM will guide us in defining specific disease characteristics, prognosis and successful treatment strategies. Further research explaining the potential role and mechanism of IMiD therapy contributing to the development of secondary haematological malignancies is the need of the hour.

Conclusion

B-cell acute lymphoblastic leukaemia is a very rare second primary malignancy (SPM) occurring in patients with multiple myeloma (MM). Long-term use of immunomodulatory agents in MM predisposes to development of a haematological SPM. Any patient of MM presenting with unexplained bicytopenia or pancytopenia should be promptly evaluated for any underlying hematological SPM. Such patients generally have a poorer outcome and should be enrolled in a clinical trial whenever available.

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