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Secondary B-cell acute lymphoblastic leukaemia in a patient with multiple myeloma

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SUMMARY

Although patients with multiple myeloma (MM) have improved survival with current therapies, there remains a long-term risk of treatment-associated second primary malignancies. We present a case of a patient with IgG kappa MM undergoing treatment for relapsed disease who was noted to have progressive pancytopenia. For his MM, he had previously undergone autologous stem cell transplant with high-dose melphalan and had received immunomodulatory (IMiD) agents in induction, maintenance and relapse regimens. A peripheral blood smear showed abnormal lymphoid cells, and a bone marrow biopsy revealed B-cell acute lymphoblastic leukaemia (B-ALL). He underwent intensive induction chemotherapy with plans for possible allogeneic stem cell transplant. Secondary B-ALL is a rare occurrence in patients with MM, with exposure to alkylating and IMiD agents being potential risk factors.

BACKGROUND

Contemporary therapies have dramatically improved survival for patients with multiple myeloma (MM), with relative 5-year survival rates over 60% for patients younger than 65 years old.[1] Given this improved survival, there is heightened awareness and concern for the development of second primary malignancies (SPMs). Lenalidomide, commonly used in MM for induction, later-line regimens and long-term maintenance after autologous stem cell transplant (ASCT), has been associated with an increased risk of haematological SPMs including acute myelogenous leukaemia (AML) and myelodysplastic syndrome (MDS).[2] The occurrence of B-cell acute lymphoblastic leukaemia (B-ALL) as an SPM in patients with MM is much rarer. Assessing cytopenias in patients with MM is a routine clinical scenario with a broad differential diagnosis; the development of a haematological SPM, however, should promptly be considered. We report a case of a patient with IgG kappa MM who developed pancytopenia while on treatment for relapsed disease, found to have B-ALL.

CASE PRESENTATION

A man in his early 60s with a history of diabetes mellitus and hypertension was initially diagnosed with IgG kappa MM in the setting of renal insufficiency, lytic bone lesions in the humerus, monoclonal gammopathy with 3.41 g/dL M-protein, and 50% monotypic plasma cells by bone marrow biopsy. Fluorescent in situ hybridisation studies showed trisomy 5 and gain of 11q22, and cytogenetics revealed complex hyperdiploidy in chromosomes 3, 5, 9, 11, 15, 19 and 21. He was initiated on treatment and received 11 cycles of bortezomib, lenalidomide and dexamethasone with overall minimal response. He completed three additional cycles of carfilzomib, pomalidomide and dexamethasone to achieve a partial response prior to undergoing an ASCT with high-dose melphalan conditioning approximately a year after diagnosis. He achieved a very good partial response and subsequently began lenalidomide maintenance therapy at 10 mg/day. Lenalidomide was temporarily discontinued after a hospitalisation for influenza A pneumonia complicated by acute pancytopenia. Lenalidomide was resumed 2 months later and subsequently increased to 25 mg/day with dexamethasone approximately 2 years after ASCT, given a rise in the M-protein. For disease progression 4 months later, he was started on daratumumab and dexamethasone, with the addition of pomalidomide 3 months later. He continued this regimen for 10 cycles until treatment was interrupted due to pancytopenia.

At that time, his complete blood count showed a white blood cell count of 3.37×10^9 cells/L, haemoglobin of 113 g/L and a platelet count of 45×10^9 cells/L. Kappa light chains had decreased to 12.7 mg/L with a kappa:lambda ratio of 2.89, and the M-protein continued to decrease since initiation of treatment to a level of 0.31 g/dL. The patient's only notable symptom at the time was profound fatigue. The cytopenias did not improve despite the pause in therapy, prompting review of a peripheral blood smear and bone marrow biopsy.

INVESTIGATIONS

A peripheral blood smear showed abnormal lymphoid cells with multilobulated nuclei, clefted nuclei, binucleate forms, plasmacytoid forms, deeply basophilic cytoplasm and variable cytoplasmic granules/inclusions (figure 1). The findings were concerning for possible circulating plasma cells or a distinct lymphoproliferative disease. Peripheral blood flow cytometry identified a 1% CD19+/CD34+ population, an increased proportion of T-large granular lymphocyte population, no monotypical mature B-cell population and virtually no plasma cells.

A bone marrow core biopsy showed a hypercellular marrow (95%) nearly entirely replaced by sheets of immature appearing cells with irregular nuclear contours and inconspicuous nuclei consistent with blasts (75% on the aspirate smear, figure 2). Virtually no plasma cells were detected morphologically or by flow cytometry. Flow cytometry, however, identified a blast population

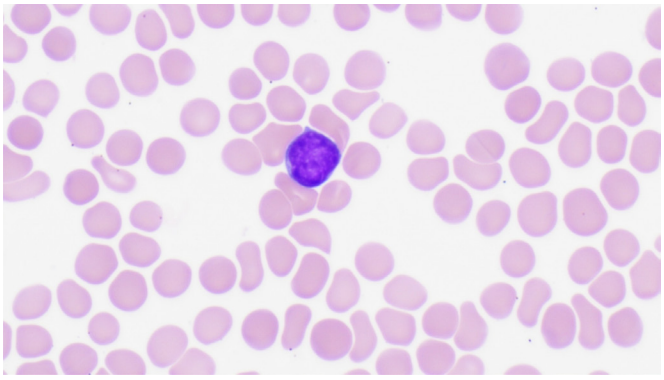

Figure 1 Peripheral blood smear.

comprising 68% of total that was CD10+, CD19+, CD20+, CD22+, CD34+, CD79a+, TdT+ and MPO-, with negative myeloid markers consistent with B-ALL.

Chromosome analysis was significant for a complex near-triploid karyotype with multiple numerical and structural aberrations observed in 11 out of 20 metaphases. The numerical abnormalities included the gain of chromosomes X, 1, 6, 10, 11, 12, 18 and 21 and relative loss of chromosomes 2, 3, 4, 5, 7, 8, 9, 13, 15, 15, 17, 19 and 20. The structural abnormalities included unbalanced rearrangements of 8 p and 18 p with unknown partners leading to losses at both loci. Fluorescence in situ hybridisation revealed 85% of nuclei with trisomy/tetrasomy 10, three copies of PBX1, four copies of MYC, ETV6 and RUNX1, and three to four copies of MLL, IGH and TCF3; in addition, 18% of nuclei had a homozygous CDKN2A deletion. No deletion of IKZF1 or ERG was observed. Cytogenetics were negative for BCR-ABL1 gene fusion, and there were no MYC, MLL or IGH rearrangements. Next-generation sequencing (NGS) was not able to be sent from the bone marrow biopsy samples. An single nucleotide polymorphism chromosomal microarray revealed evidence for a doubled low hypodiploid clone characterised by two copies of chromosomes 3, 4, 5, 7, 13, 15, 16, 17 and 20, and each of these chromosomes displayed evidence of mosaic copy neutral loss of heterozygosity.

TREATMENT

The patient was diagnosed with B-ALL and admitted to the hospital for initiation of induction therapy with modified hyperfractionated cyclophosphamide, vincristine, adriamycin and dexamethasone (hyperCVAD) plus rituximab. Diagnostic lumbar puncture was performed with cytology and flow cytometry negative for malignant lymphoblasts. The patient received two doses of prophylactic intrathecal cytarabine and one dose of intrathecal methotrexate during induction. Bone marrow biopsy after the first cycle showed a hypocellular regenerating marrow (5%–10%) with scattered cells that expressed CD34 and TdT (3%–5%). Flow cytometry did not identify an increase in CD34+ blasts. Measurable residual disease (MRD) flow cytometry detected an abnormal immature B-cell population comprising 0.72% of nucleated cells by MRD flow cytometry. Karyotype was normal (46, XY). NGS showed a PPM1D variant of unknown significance at allele frequency of 49.4%. He subsequently underwent cycle 2 of induction with hyper-CVAD part B (high-dose methotrexate and cytarabine), with postinduction bone marrow biopsy showing a normocellular marrow for age (30%) with trilineage haematopoiesis. There was no morphological evidence of residual leukaemia or increase in plasma cells by morphology or immunohistochemistry. However, MRD flow cytometry detected an abnormal immature B-cell population comprising 0.12% of total nucleated cells, consistent with residual disease. Karyotype remained normal.

Given MRD-positive disease, he started blinatumomab, for which his first cycle was complicated by grade 1 cytokine release syndrome and grade 3 immune effector cell-associated neurotoxicity syndrome requiring drug interruption and dexamethasone use. The patient's symptoms resolved and he was discharged to home on blinatumomab infusion through a continuous ambulatory delivery device pump.

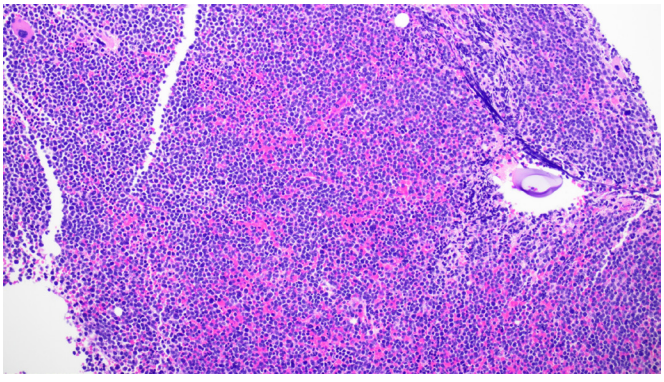

Figure 2 Bone marrow core biopsy.

OUTCOME AND FOLLOW-UP

The patient continued blinatumomab therapy with periodic intrathecal chemotherapy for central nervous system prophylaxis. He is now enrolled in a clinical trial of blinatumomab with donor lymphocyte infusions. He will be considered for allogeneic stem cell transplantation if he achieves MRD negativity.

DISCUSSION

Despite its rarity, clinicians should consider evaluating for haematological SPMs in patients with MM who develop pancytopenia of unknown cause. In the present case, the patient's peripheral blood smear with abnormal lymphoid cells was the first sign that a second haematological malignancy could be present, prompting a diagnostic bone marrow biopsy.

Patients with MM are at an increased risk of developing second haematological malignancies, particularly AML and MDS.[3] Myeloma-directed therapies play a significant role in the development of second haematological malignancies in patients with MM. The use of alkylating agents, such as oral melphalan and high-dose melphalan prior to ASCT, has been thought to significantly contribute to the development of myeloid malignancies in patients with MM.[4] An analysis of the California Cancer Registry of patients with MM showed a higher 10-year cumulative incidence of haematological SPMs in ASCT recipients at 2.1% as compared with 0.8% in matched patients who did not undergo ASCT.[5] Maintenance therapy with lenalidomide has also been independently associated with an increased risk of SPMs. A meta-analysis of three randomised controlled trials showed that lenalidomide maintenance compared with 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 haematological malignancies.[2] The risk of developing haematological SPMs has also been shown in the setting of lenalidomide-based first-line therapy, where this risk was increased when lenalidomide was used in combination with oral melphalan.[6] Despite the increased

risk of SPMs, the International Myeloma Working Group recommends use of lenalidomide in the maintenance setting, given its survival benefit.[7] Of note, the patient in the present case had also received pomalidomide and carfilzomib in addition to lenalidomide, bortezomib and dexamethasone prior to ASCT. Although this improved his MM burden prior to ASCT, it also increased his exposure to immunomodulatory (IMiD) therapies and potentially increased his risk of SPMs. There is a noted paucity of data on the risk of SPMs from pomalidomide treatment. Further attention to the risk of haematological SPMs in patients with MM who have received multiple IMiDs among multiple lines of therapy is warranted.

B-ALL is a rare SPM 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 only one patient on lenalidomide and none in the placebo group after a median follow-up of 34 months.[8] In an updated analysis after a median follow-up of 91 months, 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.[9] In our case series, the patient was found to have B-ALL at 39 months after ASCT, having received a cumulative exposure of approximately 39 months of IMiD-containing therapy throughout his MM course.

Prior case series have described similar cases of B-ALL in the setting of prior ASCT and lenalidomide maintenance therapy.[10–14] Within these series, patients often presented with asymptomatic pancytopenia after two or more years on maintenance therapy. No common cytogenetic or molecular characteristics have been identified between these cases. In the present case, the patient's ALL had a complex, near-triploid karyotype with evidence of a doubled low hypodiploid clone. These cytogenetic features have been previously described to be pathogenic in B-ALL and lead to more aggressive clinical entities with poorer prognoses.[15–17] Given the rarity of secondary B-ALL in patients with MM, similar treatment strategies for patients with de novo B-ALL have been applied. There are very limited case reports of successful allogeneic stem cell transplantation in this clinical scenario.[13 18]

Unfortunately, the prognosis for haematological SPMs in patients with MM is poor. A single-centre study of 47 patients with MM with therapy-related myeloid neoplasms showed a median overall survival of only 6.3 months.[19] A larger cohort study of patients with MM in Sweden showed an even worse median survival of 2.4 months among those patients who developed AML/MDS.[20] These patients were found to have a 1.7-fold increased risk of death compared with matched with de novo AML/MDS, similar to secondary patients with AML/MDS without MM. Given the rarity of secondary B-ALL in patients with MM, the relative prognosis compared with de novo B-ALL is unknown.

Learning points

- B-cell acute lymphoblastic leukaemia is a rare second primary malignancy (SPM) in patients with multiple myeloma (MM).
- The risk of haematological SPMs in patients with MM is significantly increased with use of long-term immunomodulatory agents.
- The presence of a haematological SPM should be considered and promptly evaluated in patients with MM who have unexplained pancytopenia.

Further investigation in secondary B-ALL in patients with MM will help define specific disease characteristics, prognosis and successful treatment strategies. Moreover, the potential role and mechanism of IMiD therapy contributing to the development of secondary haematological malignancies, including B-ALL, may further elucidate their underlying pathophysiology. As therapies for MM continue to improve survival, there should be heightened clinical awareness for secondary haematological malignancies.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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