CASE REPORT

AML transformation after autologous stem cell transplant for multiple myeloma

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SUMMARY

A 59-year-old male patient was diagnosed as multiple myeloma in 2005 and received chemotherapy consisting of thalidomide, cyclophosphamide, and dexamethasone. The patient subsequently received high-dose melphalan followed by autologous stem cell transplantation and maintenance therapy with thalidomide. During the follow-up, the patient developed fever and cytopenias in 2012. The work up revealed 55% blasts in the marrow with myeloid phenotype leading to a diagnosis of acute myeloma leukaemia (AML). The karyotype was normal (46,XY) on conventional cytogenetics. The therapy was initiated, however, the patient expired within 1 month of diagnosis. The treatment related factors like alkylating agents are usually taken as the responsible agents for therapy-related AML, however, recent studies have proposed a multifactorial pathogenesis of leukaemic transformation in multiple myeloma.

BACKGROUND

The clinical course of multiple myeloma is usually punctuated by multiple relapses and occasionally second malignancies. We report a case of acute myeloid leukaemia (AML) with normal cytogenetics occurring in a patient of multiple myeloma; 7 years postautologous stem cell transplant. The acute leukaemia in our case could be secondary to chemotherapy, or a second primary malignancy; however, the exact cause remains uncertain in absence of any specific molecular marker. Few recent reports have also proposed a multifactorial pathogenesis of secondary malignancies in multiple myeloma.^{1 2}

CASE PRESENTATION

A 59-year-old male patient presented at a peripheral hospital, in August 2005, with symptoms of weakness, pallor and palpitations for 2 months.

INVESTIGATIONS

He had reduced haemoglobin (Hb) 71 g/L, raised erythrocyte sedimentation rate (135 mm in first hour) with normal leucocyte count and platelets. Biochemical work-up revealed raised total proteins 90 g/L (normal range 60–84 g/L) and globulins 50 g/L (23–35 g/L) with a monoclonal protein (IgG)—34 g/L. X-ray-pelvis, skull and spine showed multiple punched out lytic lesions and osteoporotic changes in spine. Bone marrow examination revealed increased plasma cells (35%) including abnormal forms and paratrabecular foci of plasma cells in the biopsy. The patient was then referred to our centre with a diagnosis of multiple myeloma.

Serum β 2-microglobulin was 37.05 mg/L (normal <2 mg/L) and calcium 86 mg/L (85–105 mg/L). Renal function tests were normal and Bence-Jones proteins were absent in urine.

TREATMENT

The patient was started on thalidomide, cyclophosphamide, oral dexamethasone and injectable zole-dronic acid. He achieved a good partial response after five cycles of chemotherapy. The follow-on findings included reduced marrow plasma cells (2%), improved Hb (101 g/L), and reduced proteins (total-56 g/L, albumin-31 g/L, globulins-25 g/L) and β 2-microglobulin (14.67 mg/L). The patient was subsequently given high-dose melphalan (total dose 300 mg) followed by autologous stem cell transplantation (HDM-ASCT) with a total of 4.8×10^8 /kg mononuclear cells and 1.86×10^6 /kg CD34+ cells. The maintenance therapy contained thalidomide, which was continued for almost 7 years.

OUTCOME AND FOLLOW-UP

During the follow-up, the patient presented with fever, in November 2012. The peripheral smear examination revealed pancytopenia with few blasts and occasional blast with Auer rods (figure 1). A bone marrow examination was advised to rule out acute leukaemia. The bone marrow showed 55% blasts which, on flow cytometric immunophenotyping, expressed CD13, CD33, CD117, HLA-DR, CD34 and myeloperoxidase consistent with myeloid phenotype. The blasts did not express CD3, CD2, CD7, CD79a and CD19. Conventional cytogenetics showed normal karyotype (46,XY). A diagnosis of AML was made and planned for

Figure 1 Peripheral smear showing a blast with Auer rod (Giemsa $\times 1000$), myeloperoxidase stain showing Auer rod in a blast (inset) ($\times 1000$).

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induction chemotherapy. However, due to poor performance status and old age of the patient, only low-dose cytarabine (Ara-C) single agent therapy was given for 15 days. The patient developed severe chest infection with bilateral pleural effusion and expired within 1 month of AML diagnosis.

DISCUSSION

It has been known for long that extended chemotherapy with alkylating agents, like melphalan and cyclophosphamide, carries an increased risk of therapy-related acute myeloid leukaemia (t-AML). Despite this information, accurate estimates of incidence and pathogenesis of second malignancies after multiple myeloma are lacking.² Moreover, the separate contributions of pretransplantation-related and transplantation-related therapy are not well characterised. Although the underlying biological mechanisms of AML after multiple myeloma are unknown, treatment-related factors, such as alkylating agents and/or anthracyclines, are often accepted to be responsible. More recent reviews have proposed a multifactorial pathogenesis of secondary malignancies in multiple myeloma including disease-related factors like baseline complex cytogenetics³ and type of immunoglobulin secreted,⁴ host-related factors like polymorphisms in germline genes,⁵ as well as environmental and behavioural factors in addition to the treatment-related factors.^{1,2} The incidence of secondary malignancies, including AML, was found to be 5.5% in a Swedish registry database that included 8656 patients with myeloma.⁶ Another study, including 8740 patients with myeloma diagnosed in Sweden between 1986 and 2005, found almost similar rates of MDS (myelodysplastic syndrome)/AML before and after introduction of HDM-ASCT in 1995, suggesting that high-dose melphalan has not changed the risk of subsequent MDS/AML, beyond that of prolonged use of lower doses of melphalan. Thus, cumulative doses of melphalan may be more important than the duration of therapy.⁴ Our centre has 225 cases of multiple myeloma post autotransplant after high-dose melphalan who are on regular follow-up since 1995 (till December, 2013) and this case is the first to have transformed to AML. In our case also, high dose of melphalan was a possible cause of AML. However, our patient had received another alkylating agent cyclophosphamide in pretransplant period before HDM-ASCT, thus, further complicating the pathogenesis. The risk of AML with cyclophosphamide, though, is known to be lower than melphalan. Another chemotherapeutic agent used during the maintenance was thalidomide. There is no documented evidence of malignant potential of thalidomide, however some recent reports, while inconclusive, indicated more haematological malignancies in patients treated with lenalidomide as maintenance.^{7,8} The majority (>90%) of t-AML have abnormal cytogenetic findings but our case had normal cytogenetics at AML transformation. Thus, the possibility of a second primary malignancy cannot be ruled out in our case. This case also highlights the importance of keeping a high index of suspicion in the appropriate clinical setting and thorough peripheral smear screening to look for any evidence of transformation to secondary leukaemia, particularly in presence of cytopenias. It can prevent a possible delay in the diagnosis of such cases. There was an Auer rod in the peripheral blood blasts in this case. There are conflicting reports about the occurrence of Auer rods in the cases of secondary AML. Vardiman *et al*⁹ did not find Auer rods in 21 cases of secondary AML as compared to their presence in 42% (54/129) of de novo AML. On the other hand, Auer rods were reported in nearly 32% (12/37) cases of secondary AML in another series.¹⁰

Thus, it is not clear whether the presence of Auer rods could favour a second primary malignancy in this case. In terms of outcomes, such patients of secondary AML have a grim prognosis with median survivals of less than 3 months.^{1,11,12} Although the outcome of such cases of secondary AML is poor, the importance of a careful peripheral smear screening and early diagnosis cannot be overemphasised especially because it can yield satisfying results even in the resource limited settings.

In the absence of any molecular markers specific for therapy-induced cancer, the exact role and contribution of HDM-ASCT, cyclophosphamide and possibly thalidomide in the leukemic transformation of multiple myeloma needs more extensive planned studies. With improvements in myeloma therapy and the resultant improved survival, this question is bound to be more relevant in near future.

Learning points

- ▶ Alkylating agents like melphalan and cyclophosphamide are risk factors for therapy-related acute myeloid leukaemia (AML).
- ▶ Recent reviews suggest that pathogenesis of secondary malignancies, including AML, in multiple myeloma is multifactorial.
- ▶ The overall prognosis of secondary AML in multiple myeloma is poor, with a median survival of around 3 months.

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Contributors SKG reported the case and wrote the manuscript. LK was involved in clinical care of the patient and reviewed the manuscript. JC was involved in reporting of the case. SKG, JC and LK approved the manuscript before submission.

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