CASE REPORT

Leukemic Transformation of Severe Aplastic Anemia Following Matched Allogenic Stem Cell Transplantation, Transplanted Again in CR 1

Prabhu Manivannan · Abhishek Purohit · Venkatesan Somasundaram · Ankur Ahuja · Mukul Aggarwal · Rajiv Kumar · Pawan Kumar Singh · Hara Prasad Pati · Pravas Mishra · Tulika Seth · Manoranjan Mahapatra

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Abstract Aplastic anemia (AA) is a life-threatening bone marrow failure disorder, if untreated, is associated with very high mortality. Allogenic bone marrow transplantation (BMT) is the standard of care for severe aplastic anemia (SAA) patients those who are younger than 40 years of age. The development of secondary malignancies in post-BMT setting for AA is a rare, however, well documented phenomenon. Among the secondary malignancies, development of acute myeloid leukemia is even rarer entity. Here we report a case of acute myeloid leukemia following human leucocyte antigen (HLA) matched sibling peripheral blood stem cell transplant (PBSCT) in a case of SAA. The patient achieved complete remission (CR) following chemotherapy and in CR1, a second HLA matched PBSCT from a different donor was offered. The patient is presently in remission at day +180 post-PBSCT.

Introduction

The various modalities of treatment available for severe aplastic anemia (SAA) are immunosuppressive therapy (IST) and allogenic bone marrow transplantation (BMT). Among these modalities, BMT is often proven to be successful treatment for very severe aplastic anemia (VSAA) [1]. The major complications that can occur in the post-

BMT setting include graft failure and graft versus host disease (GVHD). Leukemic transformation in aplastic anemia (AA) is a known phenomenon, especially after IST [2]. However, occurrence of leukemia in post-BMT setting for AA is a very rare phenomenon [3, 4]. Here, we report such a case of acute myeloid leukemia (AML) following human leucocyte antigen (HLA) identical sibling matched peripheral blood stem cell transplant (PBSCT) performed for SAA.

Case details

A 15 year-old-male presented with chief complaints of weakness, easy fatigability and skin bleeds for two years duration in April 2011. There was no history of fever, jaundice, bony pains, bleeding from other sites and swelling anywhere in the body. There was no history of exposure to drugs or chemicals. He had received six units of packed red cell transfusion previously. On clinical examination, he had pallor and petechiae. There was no icterus, lymphadenopathy, organomegaly, bony tenderness, gum hypertrophy or congenital malformations. Systemic examination was within normal limits.

Baseline complete hemogram showed hemoglobin (Hb) of 57 g/L, total leucocyte count (TLC) of $2.88 \times 10^9/\text{L}$ with lymphocytic preponderance (80 %) and absolute neutrophil count (ANC) of $0.46 \times 10^9/\text{L}$ and platelet count of $90 \times 10^9/\text{L}$. Bone marrow aspiration (BMA) was paucicellular and showed predominantly lymphocytes and plasma cells. Its corresponding bone marrow biopsy (BMB) was hypocellular for age (<10 % cellularity) and there were no abnormal cells, granuloma or parasites (Fig. 1). A diagnosis of severe aplastic anemia (SAA) was made as per Camitta et al. [4] criteria and adopted by

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Presented as part at a meeting, the organisation Nil.

P. Manivannan · A. Purohit · V. Somasundaram · A. Ahuja · M. Aggarwal (✉) · R. Kumar · P. K. Singh · H. P. Pati · P. Mishra · T. Seth · M. Mahapatra
Department of Hematology, All India Institute of Medical Sciences (AIIMS), Ansari Nagar, New Delhi 110068, India
e-mail: mukulmame@gmail.com

British Committee for Standards in Hematology (BCSH) [5]. Flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH) clone and a chromosomal breakage study for Fanconi's anemia (FA) were negative.

Patient was started on IST with cyclosporine (CSA) (5 mg/kg/day) and anabolic steroid (Danazol) for initial five months with supportive care and blood products. However, no response was obtained with these drugs. He had 10/10 HLA-matched elder brother and planned for SCT. He received conditioning regimen with fludarabine, cyclophosphamide and anti-thymocyte globulin (ATG) and peripheral blood was used as a stem cell source. For GVHD prophylaxis, he had received cyclosporine and methotrexate. His initial post-transplant period was uneventful and engrafted on day +11 and later discharged in a stable condition.

On subsequent follow-up, he had cytomegalovirus (CMV) reactivation on day +59, managed with ganciclovir. Serial monitoring with polymerase chain reaction (PCR) studies showed CMV titers to be negative. On day +318, his chimerism was 95 % and further dropped to 78 % on day +645. The serial follow-up data on complete hemogram, CMV titers and chimerism were shown in Figs. 2 and 3 respectively. Because of persistent cytopenia, IST was continued for more than a year after transplant.

Patient was re-admitted on day +660 post-transplant with history of fever, weakness, easy fatigability and skin bleeds for 15 days with cough and mild respiratory distress

for 4 days. There were petechiae, pallor and oral temperature of 102 °F. Systemic examination was within normal limits. He started requiring blood products support. His electrolytes, renal and liver function tests were within normal limits. With a possible differential diagnosis of late graft rejection or relapse, bone marrow examination was done. BMA were cellular showed increase in blast (25 %) with monocytoid morphology. These cells showed positivity for non-specific esterase (NSE) and negative for myeloperoxidase (MPO). Its corresponding BMB was hypercellular and showed interstitial infiltration by immature cells (Fig. 4). Flow cytometry showed positivity for CD34, HLA-DR, CD13, CD33, and CD11c and negative for cCD3, CD19 and cMPO. Cytogenetic analysis showed complex karyotype [46XY (80 %)/45XY, del (7q), -20 (10 %)/hyperdiploidy (10 %)]. Hence, the final diagnosis of acute myeloid leukemia (AML-M4, FAB classification) in the setting of PBSCT for AA with clonal evolution was made.

Patient was treated with standard 3 + 7 induction chemotherapy with cytarabine and daunorubicin. He achieved complete remission (CR) post induction, taken up for second PBSCT and had 10/10 HLA match with his father. Conditioning was done with busulfan and cyclophosphamide; cyclosporine and methotrexate prophylaxis for GVHD. He had engraftment on day +12 and remaining post-transplant period was uneventful. Patient was discharged on day +31 and presently he was on regular follow up with stable

Fig. 1 a, b—Paucicellular bone marrow aspirate (BMA) shows predominantly mature lymphocytes (Jenner-Giemsa stain, 100× and 400× respectively). **c, d**—Hypocellular bone marrow biopsy (BMB) with less than 10 % cellularity (Hematoxylin and Eosin stain, 100× and 400× respectively)

Fig. 2 Bar diagram showing serial hemogram values **Fig. 3** Line diagram showing CMV titers and dropping chimerism levels

haematological parameters as on day +180 and 100 % Chimerism with second donor.

Discussion

Allogenic BMT is the standard of care in younger SAA patients of less than 40 years of age [1]. The development of secondary malignancies in post-BMT setting for AA is rare, however well documented phenomenon [2]. Deeg et al. [1] analyzed 700 patients with SAA in post-BMT setting for subsequent development of second malignancy.

They had documented five cases of lymphoid malignancies (two acute lymphoblastic leukemias and three lymphoproliferative disorders) and 18 cases of solid organ malignancies. However, no AML was reported in this largest series available to date.

Kojima et al. [6] analyzed the risk factors for the development of myelodysplastic syndrome (MDS)/AML in long term survivors of AA. In their study, twelve out of 113 patients (10.6 %) developed MDS at a median follow-up of 56 months with a cumulative incidence of 13.7 ± 3.9 % at eight years. In their multivariate analysis, number of days of granulocyte colony stimulating factor (G-CSF) and no

Fig. 4 **a, b**—Paucicellular BMA with 25 % blasts (Jenner-Giemsa stain, 100× and 400× respectively) and insets showing MPO negativity (1000×) and NSE positivity (arrow head, 1000×). **c, d**—BMB shows infiltration by immature cells (Hematoxylin and Eosin stain, 100× and 400× respectively)

response to IST are statistically significant risk factors for MDS. It is uncertain whether prolonged survival in these patients simply displays pre-malignant nature of the disease or whether MDS/AML secondary to therapy. In our case, IST therapy with CSA for 5 months with no response and subsequently taken for HLA matched sibling SCT.

Maciejewski et al. [7] reported an interesting finding that AA patients have constant rate of clonal evolution, with approximately 50 % of these patients show the cytogenetic changes within first 30 months of diagnosis. Trisomy 8, trisomy 6, 5q-, anomalies of chromosome 7 and 13 are the most commonly observed karyotypic abnormalities [1, 8]. The importance of these abnormalities is highlighted by their differential response to therapy. Among these abnormalities, trisomy 8 shows good hematologic response to IST. They also reported that most of the death was attributed to leukemic transformation and often associated with either complex cytogenetic aberration or chromosome 7 abnormalities or both [1, 7]. Loss of chromosome 7 is more often noted after therapy for AA and this is also commonly associated with subsequent of MDS/AML [9]. Similarly in our case, del (7q) documented during clonal evolution.

There are only six case reports highlighting that leukemic transformation may originate from donor cells after BMT for SAA [3, 10–14]. Rarely, this transformation also been reported after unrelated umbilical cord blood [15, 16].

More often, these cases are associated with monosomy 7 and morphologically AML-M4/M5 by FAB classification [3, 4]. This possibility was kept in our case; however, chimerism was dropped to 78 % at the time of clonal evolution. Possible mechanisms for such transformation include stromal defect in bone marrow microenvironment, viral oncogenic material transferred from host to donor cells, inadequate immune surveillance due to profound IST, leukemic transformation of engrafted cells and occult leukemia in the donor cells [3].

Although sparse data available regarding treatment options, best possible option would be allogeneic transplantation whenever HLA-matched donor available in first CR. This is beneficial that graft-versus-leukemia effect reduces the further risk of leukemia [17–19]. To conclude, although occurrence of AML in post-transplant setting for AA is extremely rare, such possibility should be kept along with graft rejection, if there is dropping chimerism levels or recurrence of symptoms. Whether or not, our case had donor derived leukemia is difficult to tell because of confounding effect of prolonged cyclosporine exposure as immunosuppressive therapy prior to and after transplant and also progressively falling Chimerism in the patient, suggesting the emergence of host clone, which may have clonal evolution to leukemia. Managing such cases on the lines of secondary leukemia with induction therapy followed by SCT seems most reasonable option.

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