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Case Report

The Outcome of a Patient with Mixed Phenotype Acute Leukemia and Diabetes Mellitus after Allogeneic Hematopoietic Stem Cell Transplantation: A Case Report and Literature Review

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Abstract

Mixed Phenotype Acute Leukemia (MPAL) is a rare type of leukemia in which lymphoid and myeloid markers are co-expressed. This type of acute leukemia is usually treated with Acute Lymphoblastic Leukemia (ALL) regimens of chemotherapy followed by allogeneic Hematopoietic Stem Cell Transplantation (HSCT).

We present a young patient with pre-existing type 2 Diabetes Mellitus (DM) who was diagnosed to have MPAL at King Fahad Specialist Hospital (KFSH) in Dammam, Saudi Arabia in early June 2019. After achieving first complete remission with Hyper-CVAD regimen of chemotherapy which caused further elevation of his Blood Glucose Level (BGL) that was treated with insulin therapy, the patient received an allogeneic HSCT from a matched sibling donor in late October 2019. After engraftment of his neutrophils following HSCT, his BGLs started to decrease gradually to the extent that no more insulin treatment was required after day+33 post-HSCT. Subsequently, the patient remained insulin independent till day 389 post-HSCT when he was found to have positive Measurable Residual Disease (MRD). At this time, BGLs became elevated again and the patient required therapy with oral hypoglycemic agents. Despite controlling the MRD of his leukemia with azacitidine therapy, the patient remained on low-dose oral hypoglycemic agents for his DM.

In Conclusion: MRD positivity in patients with MPAL following allogeneic HSCT can be abolished by azacitidine therapy. Allogeneic HSCT can control DM and cause insulin independence for prolonged period of time provided the patient remains in complete remission without MRD positivity.

Keywords: Mixed phenotype acute leukemia; Diabetes mellitus; Hematopoietic stem cell transplantation; Blood glucose level; Insulin independence

Introduction

MPAL is a subtype of acute leukemia in which the myeloid and lymphoid markers are co-expressed and blast population shows mixed features of myeloid, T-lymphoid, and/or B-lymphoid differentiation [1-3]. MPAL comprises a heterogenous group of leukemias that are genetically, immunophenotypically and clinically diverse. Additionally, given the rarity of the disease, the diagnosis and treatment of MPAL are extremely challenging [4]. For example: Early T-cell Precursor (ETP)-ALL and T-lymphoid/myeloid (T/M)-MPAL are closely related entities as they possess overlapping characteristics. Although they represent a therapeutic challenge, it has been shown that cytarabine, aclarubicin, and granulocyte colony-stimulating factor (CAG)-like regimens improve their clinical outcomes [5]. Conventionally, the diagnosis of MPAL requires either a single blast population with a lineage defining phenotypic expression of multiple lineages (myeloid, B-cell and/or T-cell) (biphenotypic) or two

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distinct blast populations that each independently satisfies criteria for designation as Acute Myeloid Leukemia (AML), B-ALL, and/or T-ALL (bilineage) [1].

There are no prospective controlled clinical trials to guide therapy of MPAL [6]. However, the majority of retrospective studies recommend the use of ALL directed regimens as induction therapy [4,6-8]. After achieving first complete remission, it is recommended to subject patients with MPAL to allogeneic HSCT as a consolidation therapy since allogeneic HSCT has been shown to be associated with improved long-term outcome and overall survival [1,4,6,9,10]. Additionally, incorporation of targeted therapies; such as the addition of a tyrosine kinase inhibitor in patients with translocation 9,22; based on the genetics and immunophenotype profiles of MPAL patients is recommended [4,6].

In adults, MPAL is characterized by relative therapeutic resistance that may be attributed in part to the high proportion of patients with adverse cytogenetic abnormalities [6]. Solid knowledge regarding the genetic features of MPAL is lacking due to its rarity and heterogeneity. However, integrative genomic and transcriptomic profiling may facilitate more precise diagnosis and develop better treatment options for MPAL [2]. The single-cell transcriptomic landscape of pediatric MPAL has demonstrated that B/My and T/My MPAL have distinct single-cell RNA sequencing profiles from each other, AML, and ALL and that differences in transcriptomic profiles were seen based on response to therapy [11]. KMT2A-rearrangement is rare and usually seen in B-lymphoid/myeloid type of MPAL [3]. The prognosis of adults and children with MPAL is variable. However, modulating the intensity of therapy, including the use of allogeneic HSCT as a consolidation strategy improves the outcome [1,4]. It has been shown that the combination of demethylating drugs and CD7-targeted chimeric antigen receptor (CAR)-T cell therapy is safe, effective, and feasible in treating MPAL patients with relapse after transplantation [12].

Case Presentation

A 35 years old Saudi male was transferred to KFSH in Dammam in early June 2019 as a case of acute leukemia. The patient presented with 2 months history of (H/O): anorexia, low-grade fever, night sweats, and loss of 26 kilograms (kgs) of his body weight. He has H/O type 2 DM for 5 years, and despite being on: metformin 100 mg twice daily (BID) and glibenclamide 10 mg (BID), his DM was poorly controlled mainly due to poor compliance with treatment. His physical examination on admission revealed: pallor, enlargement of few cervical lymph nodes, but no ecchymoses, petechiae, jaundice or leg edema. His chest was clear, the spleen and liver were impalpable, and examination of cardiovascular and neurological systems did not reveal any abnormality. Complete Blood Count (CBC) showed: White Blood Cell (WBC): 72 x 10^9/litre (L), Hemoglobin (Hb): 7.7 gram (g)/decilitre (dL), platelets (PLTs): 23x10^9/L. Peripheral Blood Review (PBR) showed 80% blast cells. Bone Marrow Examination (BME) showed cellular marrow with heavy infiltration by blast cells. Immunophenotyping showed positive: MPO, CD2, cyCD3, CD7, CD13, CD34, and CD117; partially positive: CD33, CD 45, TdT, and HLA-DR; and negative: CD4, CD10, and CD19. Cytogenetic analysis revealed: hyperdiploidy, positive TCR (Beta and Gamma), and negative leukemia translocations including: t9,22. Renal, liver, and bone profiles were all within normal limits. Negative serology for cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, brucella, and viral hepatitis. Random BGL: 18 mmole/L. lactic dehydrogenase: 3500 unit (U)/L. Meanwhile, cytoreductive therapy in the form of hydroxyurea: 2000 mg BID was administered in addition to allopurinol and Intravenous (IV) fluids for hydration. Chest X-ray, ECG, and echocardiography did not show any abnormality. After establishing the diagnosis of T-cell lymphoid/Myeloid MPAL, the patient was commenced on block-A of hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen of chemotherapy. Due to the high BGL that was exaggerated by dexamethasone, the patient was commenced on sliding scale of insulin and his daily insulin requirements ranged between 100 to 150 units of insulin. During the period of neutropenia following chemotherapy, the patient developed an oral lesion over the hard palate near the left molar teeth. Bacterial cultures were negative. Tissue biopsy showed evidence of mucormycosis with angioinvasion. The oral mucormycosis was treated with liposomal amphotericin-B and posaconazole. The patient received 3 doses of Intrathecal (IT) methotrexate and repeated Cerebrospinal Fluid (CSF) analyses showed no blasts in the CSF. BME following block-A of chemotherapy showed evidence of Complete Hematological Remission (CHR). Thereafter, the patient received block-B of the first cycle of hyper-CVAD which was composed of high- dose methotrexate and cytarabine. He was continued on prophylactic dose of posaconazole. Following this treatment, no complications were encountered. Disease evaluation after finishing blocks A and B of the first cycle of chemotherapy showed evidence of CHR but with positive MRD of 0.08% by flowcytometry. Later on, the patient received one more cycle of hyper-CVAD chemotherapy and re-evaluation after block-B of the second cycle of hyper-CVAD showed evidence of CHR without detectable MRD. However, BGL remained elevated and insulin requirements remained between 100-150 units per day.

After achieving CHR without MRD and finding an HLA-matching sibling donor, it was decided in the HSCT board meeting to offer the patient an allogeneic HSCT. On 24/10/2019, and after receiving a pre-transplant myeloablative conditioning therapy that consisted of cyclophosphamide and total body irradiation, the patient received his peripheral blood allograft. The $CD34^+$ stem cell dose was 4.6 x 10^6/kg. The patient received cyclosporine-A and methotrexate as Graft Versus Host Disease (GVHD) prophylaxis and he remained on prophylactic antimicrobials including posaconazole. Post-HSCT, the patient developed grade III mucositis that required morphine analgesia and total parenteral nutrition for 1 week. The patient engrafted his neutrophils and platelets on days 16 and 23 post-HSCT respectively. Following engraftment, BGL started decreasing gradually and this required decrease and daily adjustment of his insulin doses. On day 33 post-HSCT, the insulin requirements dropped to zero as BGL normalised. On day 36 post-HSCT, the patient was discharged on cyclosporine-A, in addition to prophylactic acyclovir for at least 1 year and posaconazole for 2 months. However, no insulin or oral hypoglycemic agents were prescribed as BGL remained normal. Thereafter, the patient had regular follow-up at the HSCT clinic. Two months post-HSCT, he developed GVHD of the skin covering less than 50% of surface area and it responded to local therapy. Disease evaluation on day 60 post-HSCT showed evidence of CHR without MRD and chimerism was 100% donor for both lymphoid and myeloid cells. As the patient had high-risk leukemia without encountering significant GVHD to counteract disease relapse, immunosuppression was tapered gradually and discontinued just before day 100 post-HSCT. Disease evaluation by on day 100 post-HSCT showed evidence of CHR without MRD and complete donor chimerism. As no GVHD was encountered later on, the patient received a total

of 6 escalated doses of donor lymphocyte infusions to induce GVHD, but these attempts failed to produce GVHD. Repeated primary disease re-evaluations by BMEs on days 200 and 365 post-HSCT showed evidence of CHR without MRD and complete donor chimerism. Additionally, monthly BGL evaluations, both fasting and random, showed results within normal limits and hence no insulin or oral hypoglycemic drugs were prescribed.

On 16/11/2020 (day 389 post-HSCT), the patient had no new complaints and his physical examination revealed no new abnormality. CBC showed normal blood indices and PBR did not reveal any circulating blast cells. New BME showed: evidence of continued CHR, the chimerism decreased to 92% and 98% donor myeloid and lymphoid cells respectively, and the MRD became positive (0.45% myeloid element). Fasting BGL was 8.3 mmol/L and random BGL was 11.9 mmol/L. Regarding the reappearance of MRD and after discussion in the HSCT board meeting, it was decided to start the patient on azacitidine to eradicate the MRD and to prevent the evolution of disease relapse. The first cycle of azacitidine was given in early December 2020. Regarding the elevated BGLs, the patient was referred to endocrine team again and they recommended commencing him on: metformin 500 mg BID and linagliptin 5 mg daily. Thereafter, the patient continued regular and close follow-up at both the HSCT and endocrine clinics and no complication was encountered.

Four weeks after receiving the 4th cycle of azacitidine, re-evaluation of both his leukemia and DM was undertaken. BME revealed CHR with negative MRD by flowcytometry, and chimerism showed 100% donor lymphoid and myeloid cells. So, the patient was continued on monthly cycles of azacitidine. Fasting BGL went down to 6.5 mmol/L and random BGL decrease to 10.0 mmol/L, so linagliptin was stopped and metformin was continued. Disease re-evaluation after the 12^{th} and 20^{th} cycles of azacitidine showed evidence of CHR without MRD by flowcytometry and chimerism showed 100% donor myeloid and lymphoid cells. However, the patient became non-compliant with his metformin therapy and as both fasting and random BGLs became elevated (10 and 14 mmol/L respectively, his HbA1C (glycosylated Hb) reached 11%, the patient was requested to be reviewed by his local endocrinologist to have optimal control of his DM.

Later on, the patient continued regular follow-up at HSCT clinic with monthly azacitidine administered at outpatient treatment area and he remained stable clinically with normal blood indices, renal and liver profiles. He was last seen at the HSCT clinic in late April 2024. He had no new complaints and his physical examination revealed no new abnormality. His CBC showed: WBC of 7.26 x 10^9/L with neutrophils of 2.9 x 10^9/L; Hb: 15 g/dL; PLTs: 179 x 10^9/L. His renal and hepatic profiles were within normal limits. He was given regular new follow- up appointment at HSCT clinic and a new cycle of azacitidine was scheduled. He was requested to have regular follow-up with his local endocrinologist to control his elevated BGLs.

Discussion

DM is a common and chronic metabolic disease which is associated with high morbidity and mortality [13-15]. It is a highly prevalent disease characterized by hyperglycaemia that damages the vascular system, leading to microvascular, and macrovascular complications [16]. The worldwide increase in the prevalence of DM has raised the demand for new therapeutic strategies targeting the symptoms and chronic complications of DM [17]. Pancreatic islet transplantation, which is one of the safest and least invasive transplantation procedure, holds great promise in the treatment of selected patients with type 1 DM [18-20]. Multiple islet infusions are often required to achieve and maintain insulin independence but many challenges remain in clinical islet transplantation, including substantial islet cell loss [19]. Additionally, the difficulty in regulating post-transplantation immune reactions to avoid both allogeneic and autoimmune graft rejection represents a bottleneck in the field of islet transplantation [18]. Recently, several strategies have been employed to overcome graft loss including exploration of alternative transplantation sites, stem cell-derived insulin producing cell therapies, co-transplantation with Mesenchymal Stem Cells (MSCs) or exploration of novel immune protective agents [19]. The remarkable progress that has been achieved occurred in the technical aspects of islet cell processing has translated into improved outcome of clinical islet transplantation in the treatment of selected patients with type 1 DM [20].

Stem cell-based therapies have become a promising tool targeting the symptoms of DM and its chronic complications [16]. Both autologous and allogeneic forms of stem cell therapies are relatively safe and effective method for selected patients with DM [15]. Not only short-term but also long-term insulin independence and even cure of type 1 DM have been reported by autologous and allogeneic forms of HSCT [21-24]. The combination of BM-HSCs and MSCs in the treatment of type 1 DM has shown that 26.5% of patients can experience insulin-free period lasting from 1 to 80 months, and 68% experience reduction in total daily dose of insulin after the SCT, while transplantation of both MSCs and BM-mononuclear cells (MNCs) have shown favorable therapeutic effects in type 2 DM [13,15,25]. In patients with type 1 and type 2 DM, transplantation of MSCs; particularly adipose tissue (AT) derived MSCs (AT-MSCs) and their derivatives such as exosomes or conditioned media; has beneficial effects such as reduction of the levels of HbA1C without obvious adverse reactions [14,17,26]. Animal models of DM as well as human clinical trials have shown that AT-MSCs can effectively facilitate endogenous β cell regeneration, reduce islet graft rejection, preserve residual β cell mass, regulate the immune system, and ameliorate insulin resistance in peripheral tissues [17].

The young patient presented with MPAL and he had pre-existing type 2 DM which was poorly controlled. Receiving Hyper-CVAD chemotherapy that included dexamethasone further elevated his BGLs and subjected him to infection with mucormycosis after induction therapy. Also, high doses of insulin (100 - 150 units of insulin/day) were required to control his hyperglycemia during Hyper- CVAD chemotherapy and during the admission for allogeneic HSCT. After engraftment of his neutrophils, his insulin requirements started to decrease significantly till no insulin injections were needed after engraftments of his 3 blood indices. Interestingly, his BGL remained normal and no treatment was needed for his DM till he started to have positive MRD on day 389 post-HSCT. Thereafter both his fasting and random BGLs remained elevated and he required treatment with oral hypoglycemic agents. After receiving the fourth cycle of azacitidine and achieving negative MRD of his MPAL, his BGLs decreased and this allowed reduction of his oral anti-diabetic therapy. Continuing azacitidine therapy for more than 20 cycles kept his leukemia in CHR with negative MRD and complete donor chimerism, but never normalized his BGLs again.

Conclusions

In patients with MPAL, the use of ALL-based regimens of chemotherapy to induce disease remission followed by alloge-

neic HSCT improve the outcome and prolong survival. In case of early disease relapse or encountering positive MRD following allogeneic HSCT, the use of hypomethylating agents is recommended to abolish MRD positivity. Allogeneic HSCT can control DM and cause insulin independence for prolonged period of time provided the disease remains in CHR without relapse or MRD positivity.

Author Statements

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Conflict of Interest

The authors declare that they have no conflict of interest and that they all participated in taking care of the patient presented and in preparing and writing the manuscript.

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