Documenta Haematologica -
Revista Romana de Hematologie | 2025, Vol. 3, Nr. 2

https://doi.org/10.59854/dhrrh.2025.3.2.107

– CASE REPORT –

Tacrolimus-Induced Diabetic Ketoacidosis (DKA) in Post Bone Marrow Transplant Patient

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Abstract

Introduction. *Hematopoietic stem cell transplant is an established management in various blood disorders. This contemporary management has improved patient survival; tackling immunosuppression and managing post-transplant complications is of prime importance. Post-transplant Diabetes Mellitus is one of the complications encountered in these patients, and various causes include Calcineurin inhibitors (CNIs), Cytomegalovirus (CMV) viremia, Graft versus host disease (GVHD), and Insulin resistance.*

Case Presentation. *A 20-year-old male known case of severe aplastic anaemia with matched sibling donor (MSD) allogeneic stem cell transplant day + 351 presented in drowsy condition in casualty. His blood sugar level was 584mg/dl, and arterial blood gas (ABG) showed metabolic acidosis. Urine ketones were moderately positive. The patient was diagnosed with Diabetic Ketoacidosis, was managed in the Intensive Care Unit (ICU), gradually recovered with insulin therapy and was discharged.*

Conclusion. *Regular close follow-up is required to detect post-transplant DM(PTDM) for better prognosis.*

Keywords: *post-transplant DM(PTDM), Calcineurin inhibitors, Hematopoietic stem cell transplant (HSCT)*

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Introduction

Hematopoietic stem cell transplant (HSCT) is considered the standard of care in benign and malignant haematological disorders. The current practice of myeloablation followed by stem cell transplant along with immunosuppression consists of the use of Tacrolimus or Cyclosporine along with mycophenolate mofetil and steroids. While immune suppression handles the acute rejection, it contributes to post-transplant Diabetes Mellitus(PTDM), which develops in 10-30% of patients.[1] Other adverse effects include metabolic syndrome and posterior reversible encephalopathy syndrome(PRES).[2]We are describing a case of severe aplastic anemia, post-allogeneic stem cell transplant, presenting in a drowsy condition. His blood sugar level was 584mg/dl, and arterial blood gas(ABG) showed metabolic acidosis. Urine ketones were moderately positive. The patient was diagnosed with Diabetic Ketoacidosis, was managed in the Intensive Care Unit(ICU), gradually recovered with insulin therapy and was discharged.

Case presentation

A 20-year-old male known case of severe aplastic anaemia with matched sibling donor (MSD) allogeneic stem cell transplant day + 351 presented in drowsy condition in casualty. He received Fludrabine, cyclophosphamide, and anti-thymocyte globulin (ATG) as a conditioning regimen. Allogenic stem cell transplantation was done with Graft Versus host disease (GVHD) prophylaxis with cyclosporine and methotrexate. Neutrophil engraftment occurred on day +10, and platelet engraftment occurred on day +13 of HSCT. The patient was transfused with 7 units of PRBC and 7 units of SDP during the transplant. On day +27 of the transplant, the patient had common terminology criteria for adverse events(CTCAE) grade III-IV diarrhoea managed with anti-diarrhoeal and orally locally acting steroids. Upper gastrointestinal endoscopy(UGIE) and Sigmoidoscopy were normal. On resolution of diarrhoea, Steroid was stopped, and further treatment was continued with intravenous antibiotics. His Day +28, XY chimerism was 98%. The patient on day +34 had generalized tonic-clonic seizure (GTCS) episodes. Because of uncontrolled seizures, he was started on Levetiracetam, followed by phenytoin and Clobazam due to refractory seizures. MRI was suggestive of posterior reversible encephalopathy syndrome (PRES) (Image 1). Gradually, the patient recovered because of no fresh episodes of seizures; phenytoin and Clobazam were stopped, and Levetiracetam was continued. CMV level on day +38 went up to 6114 copies/ml; hence, Inj Gancyclovir was continued till day +51, followed by Valacyclovir. Tablet Acivir was started on day +59. On day+117, the patient developed a repeat episode of seizures. Repeat imaging showed features of PRES; hence, cyclosporine was stopped, and tacrolimus was started. On day+118, the patient had oral cavity GVHD and was started on short-term prednisolone; subsequent days in the post-transplant period were uneventful.

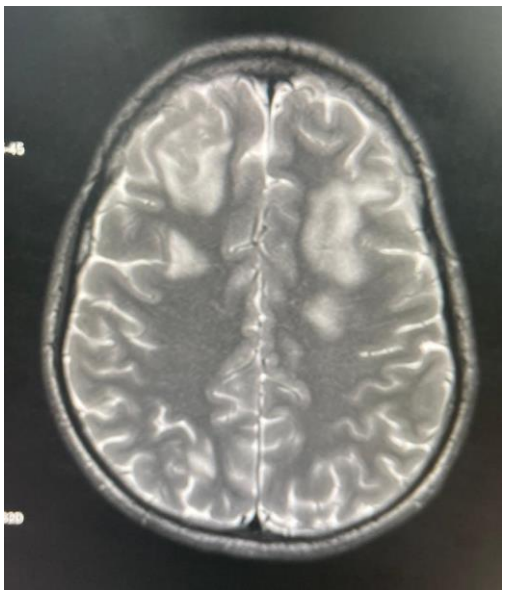

Figure 1. *Magnetic resonance imaging depicting posterior reversible encephalopathy syndrome (PRES)*

On examination, there was no pallor, icterus, cyanosis, clubbing, palpable LN or oedema. The patient's Blood pressure (BP) was 70/50 mmHg, PR=122/min, RR-28/min, Spo2-70% at room air, not responding to verbal commands. The patient was immediately intubated and shifted to the intensive care unit(ICU). Arterial blood gas (ABG) showed, pH-6.90, PCo2- 22.1mmHg, PO2-68mmHg, HCO3- 6.1mmol/l, SO2- 68.7%, RBS-584mg/dl, Urine Ketone –moderate positive. The patient was put on IV fluids, Inj Insulin and other supportive therapy. Serum Tacrolimus level was within the therapeutic range. CMV PCR was negative, and other investigations, including serum lipid profile, were unremarkable. The patient gradually improved with the insulin and supportive therapy and was extubated on day 2 of the current admission. Blood sugar levels attained normal physiological values in the subsequent hospital stay, and the patient was discharged.

Discussion

Diabetes in post solid organ transplant is a well-established phenomenon however, its occurrence in bone marrow transplant patients is rare. The available literature suggests Tacrolimus has a higher incidence of hyperglycemia than Cyclosporine. [3] Our patient was on Tacrolimus with normal serum levels during the episode of Diabetic ketoacidosis (DKA). Moreover, other confounding factors like Body mass index [21 kg/m2] along with the lipid profile were normal. Calcineurin inhibitors (CNI) play a role in immunosuppression and have diabetogenic potential by decreasing the uptake of glucose into adipose tissue by GLUT4 endocytosis. Moreover, CNIs cause pancreatic Beta cell apoptosis.[4]
Chronic Graft versus host disease (GVHD) leads to a high level of pro-inflammatory cytokines, leading to decreased insulin secretion. GVHD is associated with a high risk of Diabetes mellitus(DM).[5] Our patient had episodes of GVHD in the early days of the transplant however, the patient has not been on steroids recently. Hence, the possibilities of steroid-induced hyperglycemia and concurrent DKA were unlikely. Cytomegalovirus(CMV) viremia during the post-transplant period is also associated with hyperglycemia by destructing Pancreatic Beta cells. In one of the meta-analyses, the relative risk of 1.94 was found in CMV-positive patients for having post-transplant Diabetes mellitus(PTDM). [6] In our patient, CMV viremia appeared on day +51 of HSCT, treated with Gancyclovir and subsequent reports did not detect CMV. Although one of the possible mechanisms of PTDM is insulin resistance, which a patient may suffer from before transplant however negative family history with normal pre-transplant workup for hyperglycemia along with the absence of other risk factors make it very unlikely. [7]
The allogenic stem cell transplant in our patient was done with a full match with his sister, and the conditioning regime did not include total body irradiation, which could also result in PTDM.[8] The transplant period in the bone marrow unit was complicated by febrile neutropenia, and the patient had not received any parenteral nutrition, which is associated with PTDM. Moreover, the patient had received a magnesium supplement monitored with serum magnesium levels, which was treated optimally. [5,9]
Pre- and post-transplant close follow-up is required for early detection and treatment of PTDM, as it is associated with increased morbidity and mortality.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all participants in this study.

Conflict of interest:

No known conflict of interest correlated with this publication.

Availability of data and materials

The data used and/ or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interest

The authors declared that they have no competing interests.

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