International Journal of
Clinical Images and Medical Reviews

Case Report

Acute pancreatitis in Thalassemia post allogeneic stem cell transplant with Cyclosporine-A as a possible etiology: a report of two cases

Mohd Rizwan Shaikh[1], Bhaarat Folbs[1], Pallavi Mehta[1], Rohan Halder[1], Reema Singh[1], Vishvdeep Khushoo[1], Rayaz Ahmed[1], Dinesh Bhurani[1], Narendra Agrawal[1*]

[1]Rajiv Gandhi Cancer Institute & Research Centre, Delhi, India.

Abstract

Cyclosporine is an important component of GVHD Prophylaxis in Hematopoietic Stem Cell Transplant (HCT). It has narrow therapeutic index and is known to cause hypertension, electrolyte imbalances, Acute Kidney Injury, etc. High suspicion of these adverse effects helps us in managing them effectively. We report here two cases of pediatric age group who presented with acute pancreatitis post matched sibling HCT for Thalassemia transplant. To our knowledge we could find only 2 case reports of Cyclosporine induced pancreatitis post HCT in literature and none reported post HCT in Thalassemia. Diagnosis of acute pancreatitis especially in pediatric age group can be challenging without high suspicion. The purpose of our report is to highlight the importance of keeping acute pancreatitis in differential of unwell child post HCT in Thalassemia and careful rechallenge of Cyclosporine may be possible with careful monitoring, thereby not compromising on GVHD prophylaxis.

Keywords: Pancreatitis; cyclosporine; thalassemia; GVHD prophylaxis.

Key Messages

This report highlights the importance of suspecting pancreatitis in a paediatric thalassemia patient post allogeneic stem cell transplant with cyclosporine - A as possible causative factor. CSA reintroduction can be attempted with careful monitoring after recovery.

Introduction

Cyclosporine (CsA) is a cyclic polypeptide immunosuppressant agent. It is produced as a metabolite by the fungus species *Beauveria nivea* [1]. CsA has been used extensively for immune suppression in allogeneic hematopoietic cell transplantation (alloHCT) as well as solid organ transplants for prevention and treatment of graft versus host disease (GVHD) and graft rejection1. CsA has a narrow therapeutic index and requires therapeutic dose monitoring. Common adverse effects of CsA include nephrotoxicity, hyperkalemia, hypertension, and hypomagnesemia [1]. Acute Pancreatitis has been reported with the use of CsA in organ transplants [2]. With an extensive literature search, we could not find any report of CsA induced acute pancreatitis after alloHCT for thalassemia or other hemoglobinopathies. Here we report two pediatric patients with thalassemia major, of CsA induced acute pancreatitis after HLA matched family donor HCT

Case History

Case 1, a 2-year-old female child with Thalassemia major, presented on day +66 of HLA matched mother donor alloHCT with a history of constipation, irritable behavior, episodes of crying, decreased oral intake and vomiting of 2 days duration. Abdominal examination was remarkable for mild diffuse tenderness and sluggish bowel sounds. X-ray abdomen was suggestive of dilated colon while an USG of abdomen was suggestive of gaseous bowel distension. Pediatric Surgery review suggested a possibility of subacute intestinal obstruction. The patient was treated conservatively by withholding oral foods and fluids (NPO) and application of bisacodyl suppositories. Constipation resolved but she continued to remain irritable with the persistence of abdominal signs. A possibility of acute pancreatitis was considered and serum amylase and lipase were sent which turned out to be 183 IU/L (normal range 22-80) and 2350 IU/L (normal range 23-300). CT Abdomen was notable for modified CT severity index for acute pancreatitis (CTSI) of 4 [3]. A careful review of her drugs and history of illness was carried out. She was not found to be suffering from viral prodrome anytime in the previous month. Her serum calcium and

***Corresponding Author:** Narendra Agrawal, Senior Consultant, Department of Hemato-Oncology, Rajiv Gandhi Cancer Institute & Research Centre, Sector 5, Rohini, Delhi, India -110085, Phone Number: 91-9868764808.
Email: narendra_ag1@rediffmail.com

Received: Nov 09, 2021 Accepted: Dec 20, 2021 Published: Dec 28, 2021

Citation: Narendra Agrawal. Acute pancreatitis in Thalassemia post allogeneic stem cell transplant with Cyclosporine-A as a possible etiology: a report of two cases. IJ Clin Img and med Rew. 2021; 1(1): 1008.

triglyceride levels were normal while PCRs for CMV and EBV were negative. She was receiving CsA along with prophylactic acyclovir, penicillin V and co-trimoxazole. Her plasma CsA trough level was 61 ng/mL on the day of her presentation. A possibility of CsA induced acute pancreatitis was considered [4]. *Naranjo* algorithm for causation score was 7 for CsA suggesting probable causation [5]. Her blood pressure and renal functions were normal. She had no other CsA toxicity. With conservative management her symptoms improved over 1 week, USG done after 1 week was suggestive of resolving pancreatitis with falling levels of serum lipase and amylase. She was shifted to Mycophenolate Mofetil (MMF) for GVHD prophylaxis. On day+100 follow up, her chimerism was maintained at 100% donor, but liver enzymes were raised. After excluding infective and drug-induced hepatitis, a possibility of liver GVHD was considered. A decision to re-challenge with CsA under close monitoring was taken. CsA was re-introduced starting at low doses with monitoring of amylase and lipase levels and close monitoring for clinical signs. She did not have a repeat episode of acute pancreatitis and is currently on tapering immunosuppression on day+260 of follow up.

Case 2, a 4-year-old female child with thalassemia major presented on day+154 of HLA matched sibling donor alloHCT with a history of abdominal pain, vomiting and poor oral intake of 2 days duration. The patient had no history of fever. On examination, the patient had tachycardia, normal blood pressure for age, abdominal distention with mild diffuse tenderness. Her USG was suggestive of the bulky pancreas, amylase, and lipase levels were 643 IU/L and 4253 IU/L. The plasma CsA trough level was 252ng/mL. Her chimerism test showed 68% of donor cells. A careful review of her clinical history, lab results, and medications couldn't find other causes of acute pancreatitis than CsA. Naranjo algorithm causation score was 7 for CsA suggesting probable causation [5]. There were no other CsA toxicities. CsA was stopped and she improved with conservative management. The patient was started on MMF for GVHD prophylaxis thereafter. She was considered for a re-challenge of CsA especially after our experience of successful re-challenge of CSA in our previous patient. She was restarted on CsA starting from low doses with amylase and lipase monitoring from day +185 onwards. Currently, she is on escalating doses of CsA on day +225 of follow up with donor chimerism improved to 76%.

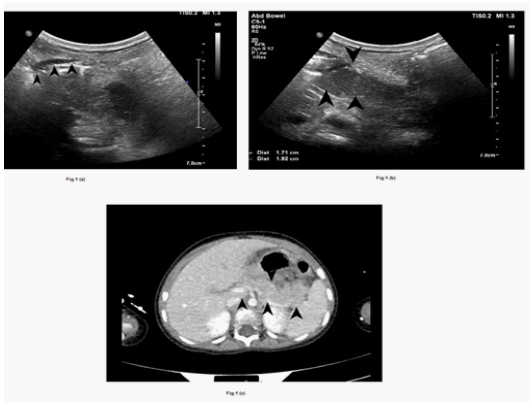

Figure 1a (Case 2): Peripancreatic fluid collection.
Figure 1b (Case 2): Bulky pancreas.
Figure 1c (Case 1): Bulky pancreas CTSI score 4 s/o moderate acute pancreatitis.

Discussion

Ito, T. et al showed that intravenous injection of CsA 10 and 20mg/kg body weight (BW) in rats increased the content of pancreatic amylase and protein and decreased the content of pancreatic DNA [6]. Histologically, intraacinar vacuolization and individual cell necrosis were observed [6]. CsA induced a significant increase in serum amylase and pancreatic wet weight in a dose-dependent manner [6]. Qi C et al reported acute pancreatitis in a 16-year-old female patient with acute leukemia on day 24 of alloHCT with CsA or Tigecycline as potential causative agents [4]. In a case report by Guo R et al from China, CsA induced acute pancreatitis was reported on day+20 of HLA matched alloHCT in a 49-year-old male with AML-M2 [7]. Whether Acute pancreatitis developing in post alloHCT patients with relatively lesser duration of exposure to CsA is idiosyncratic or dose-dependent is yet to be elucidated. Although animal experiment data points towards dose-dependent toxicity, in both our cases acute pancreatitis, developed at acceptable plasma levels, questioning this notion.

Other than that, Post-transplant diabetes mellitus (PTDM) is a complication that takes place after solid organ transplant as well as alloHCTs, with reported incidences ranging from 2 to 53%. Cyclosporine is one of the risk factors for developing PTDM probably due to direct toxic effects on beta cells of the pancreas [8].

From this experience, we conclude that studies are needed in the pathogenesis of CsA induced acute pancreatitis in post alloHCT patients. High suspicion of acute pancreatitis should be kept in post alloHCT patients with abdominal signs and symptoms especially in pediatric patients who may not be able to communicate the typical pain history. CsA re-challenge didn't precipitate pancreatitis in our patients.

Declarations

Funding: Funding information is not applicable to this study.

Conflict of Interest: All authors declare no conflict of interest to declare.

Compliance with Ethical Standards

Ethical Approval Statement: All authors stated that the study has been approved by the appropriate institutional review board and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Acknowledgements

We would like to acknowledge Dr Rayaz Ahmed, Dr Vishvdeep Khushoo and Dr Pallavi Mehta in treatment of the patients. We thank all the members, and staff of Rajiv Gandhi Cancer Institute and Research Centre, India for their contribution in the conduct of the study.

References

1. fda. NEORAL ® Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED NEORAL ® Oral Solution (cyclosporine oral solution, USP) MODIFIED.

2. Tabakovic M, Salkic NN, Bosnjic J, Alibegovic E. Acute pancreatitis after kidney transplantation. Case Rep Transplant. 2012;2012:768193

3. Mortele KJ, Wiesner W, Intriere L, Shankar S, Zou KH, Kalantari BN. et al. A modified CT severity index for evaluating acute pancreatitis: Improved correlation with patient outcome. Am. J. Roentgenol. 2004;183:1261-1265.

4. Qi C, Feng Y, Lu H, Chen L, Li J, Qiu H, et al. Acute pancreatitis developed after allogeneic hematopoietic stem cell transplantation: a case report and literature review. Int J Clin Exp Med 2019 Jan 1;12(8):10973-7.

5. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, J. et al. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther. 1981;30:239-245.

6. Ito T, Kimura T, Yamaguchi H, Kinjo M, Sumii T, Nakano I, Nawata H. Acute pancreatitis induced by cyclosporin A under stimulation of pancreas by caerulein. Pancreas. 1993 Nov 1;8(6):693-9.

7. Guo R, Weng JY, Deng CX, Wu SJ, Luo CW. Acute pancreatitis induced by cyclosporine a following allogeneic hematopoietic stem cell transplant. Zhongguo shi yan xue ye xue za zhi. 2009 Apr 1;17(2):472-5.

8. Gomes, M.B., Cobas, R.A. Post-transplant diabetes mellitus. Diabetol Metab Syndr. 2019;1:14. https://doi.org/10.1186/1758-5996-1-14.