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TIGECYCLINE-INDUCED ACUTE PANCREATITIS POST BONE MARROW TRANSPLANT: CASE REPORT

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ABSTRACT
Pancreatitis has been associated with the tetracycline class of antibiotics and concerns about tigecycline-induced acute pancreatitis have recently been raised. We describe a 16-year-old girl who received tigecycline during autologous haematopoietic transplant. Following 3 days of tigecycline she developed abdominal pain and elevated pancreatic enzymes suggesting acute pancreatitis. According to the Naranjo adverse drug reaction probability scale, tigecycline was the probable cause of her acute pancreatitis. Clinicians should be aware of this potential adverse effect of tigecycline. We recommend that clinicians must monitor patients for signs and symptoms of pancreatitis, including abdominal pain, during treatment with tigecycline.

KEYWORDS: drug induced pancreatitis, transplant and tigecycline.

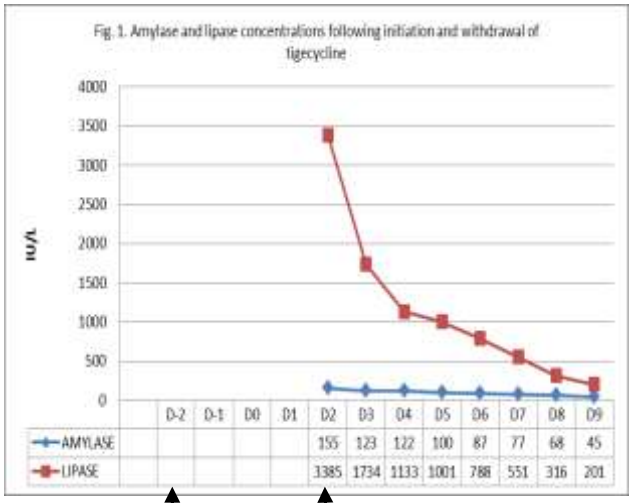
1. INTRODUCTION
Pancreatitis is a known complication post bone marrow transplant (BMT) with the reported incidence of 3-5% and is often associated with substantial morbidity and mortality in this population.[1,2] This can be related to many factors involved in the transplantation procedure, including drugs administered known to cause pancreatitis such as corticosteroids and cyclosporine, cytotoxic drugs in the conditioning therapy, graft-versus-host disease (GVHD)[3] and infections.[2,4] Drugs are responsible for less than 2% of all cases of pancreatitis and are usually associated with mild to moderately severe pancreatitis. Never the less, it is at most important that the culprit is recognised and the drug stopped in time, otherwise it may progress on to severe and occasionally fatal pancreatitis, as reported earlier with some of the cases of drug induced pancreatitis.

Tigecycline is the first member of the glycylcycline class of antimicrobials which is structurally related to minocycline and shares similar pharmacokinetic properties and side effects with the tetracyclines. The most frequent adverse effects associated with tigecycline are nausea, vomiting and diarrhoea. Pancreatitis has been associated with tetracycline but it has rarely been reported with tigecycline though concerns about tigecycline-induced acute pancreatitis have recently been raised.[5,6] We are confronted with the increasing use of tigecycline for the treatment of infections due to multidrug-resistant bacteria in BMT patients as they often get exposed to multiple antibiotics during chemotherapy.

We report a case of tigecycline-induced acute pancreatitis and highlight the importance of investigating for pancreatitis in patients who have any abdominal symptoms post BMT, particularly when they are receiving tigecycline.

2. CASE REPORT
The patient was a 16-year-old girl with primary progressive Hodgkin's lymphoma who underwent an autologous BMT. The conditioning used was LACE containing Lomustine, Ara-C, Cyclophospamide and Etoposide. She was also on Ursodeoxycholic acid (UDCA), for prophylaxis against veno-occlusive disease (VOD) of liver, acyclovir for prophylaxis against herpes simplex. On day -3 of conditioning patient had 2 episodes of loose stools for which cefeperazone sulbactum started as per her surveillance stool culture reports which grew E-Coli. Stool c/s and all lumen c/s also sent. Patient again had 4-5 episodes of watery stools on day -2 for which inj teicoplanin added. On next day patient developed fever with temp of 99.8* F and her ANC was 0.22 x 10^9 /L, and so cefeperazone sulbactum was escalated to meropenem. As patient continued to have fever spikes and loose stools inj tigecycline was added after 24 hours and teicoplanin was stopped. After three days of adding tigecycline patient started having vague abdominal pain and left infra scapular pain, malaise, nausea and had 2 episodes of vomiting. Her abdomen was tender with sluggish bowel sounds. Investigation showed WBC 0.1 X 10^9/l, with neutrophils 0.01 X 10^9/l, haemoglobin 70 g/l, hematocrit 22.0, platelets 32 X 10^9/l. All the routine biochemical

parameters including liver function tests, renal function tests, serum electrolytes, Ca, Mg, Ph, glucose, cholesterol, triglycerides and LDH were within normal range. Patient's lipase was 3385 U/L (normal range- while amylase was 154.8 U/L (normal range-). Her other medications at this time included acyclovir, Norethisterone, UDCA, Granulocyte colony stimulating factors (G-CSF), meropenam and tigecycline. A diagnosis of acute pancreatitis was made and tigecycline was stopped suspecting drug induced pancreatitis. Ultrasound of abdomen showed thickened pancreas with in-homogenous echogenecity s/o pancreatitis without any evidence of gall stones or biliary tree obstruction. Patient was treated conservatively with nil by mouth, narcotic analgesia and total parenteral nutrition. For continued Gram-positive coverage, she was restarted on teicoplanin. Two days after discontinuation of tigecycline her abdominal pain improved. Within 4 days her abdominal pain, nausea and vomiting had completely resolved and amylase and lipase decreased to 125 IU/L and 74 IU/L, respectively.



3. DISCUSSION

Pancreatitis as a complication of BMT is well known but finding the aetiology can be troublesome. These patients are at an increased risk of getting pancreatitis because of multiple factors like the intensive conditioning regimen containing many cytotoxic drugs; GVHD itself perhaps causes pancreatitis and further the drugs to prevent or treat it are known to cause pancreatitis; and even other drugs administered throughout the transplant period like various antibiotics and supportive care with total parenteral nutrition (TPN) through its lipid content, are known or suspected causes of pancreatitis. The prolonged period of immunosuppression post BMT also exposes patients to viral infections which are known to cause pancreatitis. Detection of this complication at the earliest suspicion is very important to avoid the morbidity and mortality associated with it. There is always a risk of development of a pancreatic pseudo cyst in an immunocompromised host which may require a surgical drainage.

At the time of onset of pancreatitis, our patient was receiving many drugs including granisetron, metoclopramide, acyclovir, meropenem, tigicycline, nor ethisterone, ursodeoxycholic acid. Extensive literature search did not reveal any association of pancreatitis with other drugs listed above. We excluded other possible causes of pancreatitis in our patient, which included extra hepatic biliary obstruction, hypercalcaemia and hyperlipidaemia, which were not present. There was no evidence of infections including CMV, Herpes Zoster, adenovirus, mumps, mycoplasma and viral hepatitis. Of all the above drugs, only tigecycline has been reported to be associated with pancreatitis. According to the Naranjo adverse drug reaction probability scale, +6 was the score.[7] Hence, our case can be considered as a probable association between tigecycline and pancreatitis.

There are very few published case reports of tigecycline induced pancreatitis to date. Based on unpublished data, the estimated incidence of tigecycline-induced pancreatitis is 0.1–1%.[8] Patients usually report nausea and abdominal pain following initiation of tigecycline as first symptoms, and the onset of acute pancreatitis is mostly within 7–14 days unlike tetracycline-induced pancreatitis which can occur after weeks.[9] Symptoms such as severe nausea and abdominal pain resolve within 2–5 days after withdrawal of the drug. Despite the lack of a significant number of cases of pancreatitis reported in initial phase 3 trails, the manufacturer of tigecycline has updated the product label in July 2006 to include acute pancreatitis as one of the post-marketing adverse events.[10]

4. CONCLUSION

Tigecycline-induced acute pancreatitis though a rare phenomenon and the manufacturer does not recommend routine monitoring of serum amylase and lipase. However, we recommend that clinicians monitor for symptoms of abdominal pain during treatment with tigecycline and have a low threshold to order amylase and lipase concentrations if the clinical presentation is compatible with acute pancreatitis. Knowledge of this adverse effect of tigecycline is critical to promote prompt and appropriate management of pancreatitis, including drug cessation.

5. Competing interests

The authors declare that they have no competing interests.

6. Authors' contributions

All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.

7. ACKNOWLEDGEMENTS
Consent for publication was given by the patient.

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