EJCRIM
European Journal
of Case Reports
in Internal Medicine

TIGECYCLINE-INDUCED ACUTE PANCREATITIS WITH ELECTROCARDIOGRAM CHANGES IN RENAL INSUFFICIENCY ELDERLY

Hong Chin Wee[1,2], Ru Shing Ng[1,2], Loke Meng Ong[1,3]

[1] Clinical Research Centre, Hospital Pulau Pinang, Georgetown, Malaysia; Ministry of Health, Putrajaya, Malaysia
[2] Institute of Clinical Research, National Institute of Health, Shah Alam, Malaysia
[3] Internal Medicine Department, Penang Adventist Hospital, Georgetown, Malaysia

Corresponding author's e-mail: wee.hongchin@moh.gov.my

Received: 06/11/2024
Accepted: 25/11/2024
Published: 09/12/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: The patient was deceased, and exhaustive attempts were made to contact next of kin without success. This case contributes to scientific knowledge and highlights the importance of the management of the clinical practice; therefore we decided to publish this case even without consent but maintain the confidentiality of the patient. The authors declare no ethical conflict. Ethical approval was obtained for the publication of this case report (NMRR ID-24-03205-DGC).
Acknowledgments: A big thanks to Dr. Murli Naraindas Lakhwani, consultant vascular and clinical radiologist, Dr. Alex Lee Fook Seng, for their collaborative effects in managing this patient's care. The authors would like to thank the Director General of the Ministry of Health Malaysia for his permission to publish this article.
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How to cite this article: Wee HC, Ng RS, Ong LM. Tigecycline-induced acute pancreatitis with electrocardiogram changes in renal insufficiency elderly. *EJCRIM* 2024;**11**:doi:10.12890/2024_005033

ABSTRACT

Background: The prevalence of multidrug-resistant and extensively drug-resistant pathogens has led to increased reliance on broad-spectrum antimicrobials, such as tigecycline. This medicine is commonly used to treat complicated skin and intraabdominal infections as well as community-acquired pneumonia. However, the increasing use of tigecycline has been linked to serious complications, including acute pancreatitis.

Case description: We present a case of tigecycline-induced acute pancreatitis in a 78-year-old man with complex medical conditions, including type 2 diabetes mellitus, chronic renal insufficiency, and triple vessel disease. The patient was initially treated with tigecycline for bilateral dry gangrene of his toes. Six days after initiation of the tigecycline treatment, the patient developed symptoms of acute pancreatitis with electrocardiogram changes. Magnetic resonance imaging confirmed the diagnosis of acute pancreatitis. Tigecycline was stopped promptly, and supportive treatment was initiated. The patient recovered from the acute pancreatitis and was discharged home. He later passed away at home due to his underlying cardiac disease.

Conclusions: This case highlights the potential complications of tigecycline therapy, particularly in patients with significant comorbidities.

KEYWORDS

Tigecycline, acute pancreatitis, chronic renal insufficiency, adverse drug reactions

EFIM
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smc media srl

LEARNING POINTS

- Elderly patients with complex medical issues, such as diabetes mellitus type 2, chronic renal insufficiency, and cardiovascular disease, are at higher risk for adverse drug reactions. Recognizing these risk factors is important for management.
- Addressing the use of magnetic resonance imaging for diagnosing acute pancreatitis in this specific patient due to their already compromised kidneys highlights the need for a tailored approach. Most commonly, angiographic transformers or computed tomography scan are used for high-risk patients.
- The symptoms of acute pancreatitis and the presence of cardiac diseases cause problems in managing patients. Changes on the electrocardiogram may suggest cardiac overload; as a result, constant follow-up is necessary for patients suffering from underlying cardiac conditions.

INTRODUCTION

The increasing incidence of multidrug-resistant and extensively drug-resistant pathogens has led to a rise in the use of broad-spectrum antimicrobials including tigecycline. Tigecycline is widely used to treat complicated skin and skin structure infections, complicated intraabdominal infections as well as community-acquired bacterial pneumonia due to its broad-spectrum antibacterial activity. With the increasing clinical use of tigecycline, there has been a growing number of reports linking tigecycline to acute pancreatitis, a serious complication that can lead to significant morbidity. A recent study has identified renal insufficiency as an independent risk factor for tigecycline-induced pancreatitis, suggesting that patients with impaired renal function are more susceptible to acute pancreatitis[1]. While the exact mechanism of tigecycline-induced pancreatitis remains unclear, it is hypothesized that a high biliary concentration of drug[2], accumulation of an unidentified toxic metabolite[3], and hypertriglyceridemia[4] have been suggested as potential factors.

In this report, we present a case of tigecycline-induced acute pancreatitis in a patient with renal insufficiency, to provide further insight into the rare but important clinical condition/serious complication.

CASE DESCRIPTION

A 78-year-old man presented with a 5-week-old bilateral dry gangrene of his toes with pulsating pains during his routine follow-up in a nephrology clinic. He was an ex-smoker 7 years ago, type 2 diabetes mellitus, hypertension, hyperlipidemia, chronic renal disease, and triple vessel disease post coronary artery bypass grafting 7 years ago. The patient was diagnosed with dry gangrene of the toes with worsening of renal function after a series of workups. Two days after the

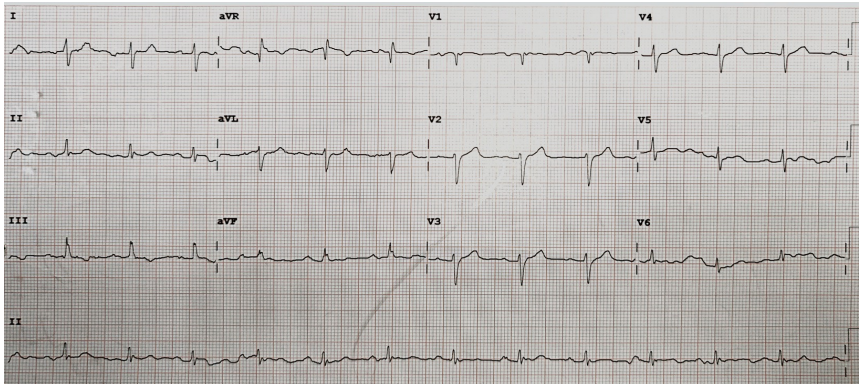


Figure 1. Baseline ECG during admission (ECG speed 25 mm/sec).

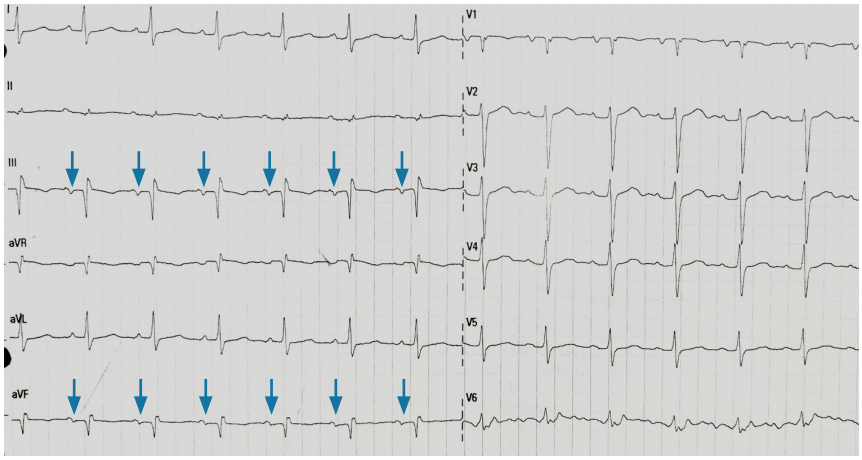


Figure 2. Q wave (blue arrow) at lead II, III and aVf during the initial workup of epigastric pain on day 6 of tigecycline therapy (ECG speed 25 mm/sec).

first visit, the man revisited the clinic to review the swab culture report. A swab culture of the toes showed growth of *Enterobacter cloacae complex* (anaerobes) and *Staphylococcus haemolyticus* (Gram positive). The drug sensitivity test showed those microorganisms were sensitive to tigecycline and ceftazidime. The patient was promptly admitted for intravenous antibiotic therapy and wound management of gangrenous toes, along with pain control. Upon admission, the patient complained of poor appetite and pain in his gangrenous toes. Physical examination revealed that he was alert and oriented to person and time, with stable vital signs. Wound inspection showed gangrene and necrotic tissue on his right big toe as well as the left big, second, and third toes. Blood investigation did not indicate significant signs of infection with a white blood cell count (WBC) of 7.9 $\times 10^9$/l (reference range 4-11 $\times 10^9$/l). Baseline serum creatinine was 454 µmol/l (estimated glomerular filtration rate eGFR 9.9 ml/min/1.73m^2) and liver enzymes were within the normal range.

Tigecycline 50 mg was administered every 12 hours combined with ceftazidime 1 g every 12 hours. Six days after intravenous antibiotics were started, the patient suddenly appeared to be lethargic and complained of epigastric pain, poor appetite and mild shortness of breath. The patient's vitals were notable for a heart rate of 112 bpm but otherwise were stable. Physical examination revealed tenderness in the epigastric region with bibasal crepitations audible on auscultation, while the remainder of the physical exam was unremarkable.

The patient was transferred to a high dependency unit for close observation, and an urgent workup for acute abdomen was initiated. A 12-lead electrocardiogram (ECG) revealed new changes in inferior limb leads, with a Q wave present in lead II, aVF and III *(Fig. 1 and 2)*. Cardiac biomarkers, especially troponin-T levels for 48 hours, and chest X-ray showed no significant abnormalities. The slight ECG changes were probably due to ischaemic strain to the heart. A computed tomography cardiac angiography (CTCA) graft study was planned by the cardiologist for further assessment. Urgent laboratory results confirmed the diagnosis of acute pancreatitis, with an elevated WBC count and a 10-fold increase in peak serum amylase level (1614.4 U/l). This further supported by magnetic resonance imaging (MRI) of the abdomen *(Fig. 3)*. Tigecycline was recognized as the most likely cause of pancreatitis and, was promptly discontinued on the 6th day following exposure. The patient was switched to meropenem 500 mg every 8 hours to cover Gram positive bacteria related to the initial medical condition. Supportive treatments, including nil by mouth, a proton pump inhibitor to reduce gastric acid secretion and intravenous hydration, were continued for approximately 4 days. The patient's epigastric pain fully resolved, and the serum amylase level returned to normal by day 4 after discontinuing tigecycline. He was discharged home after an additional week of hospitalization due to his underlying medical condition. He was readmitted and discharged well after a 2-week stay for management of heart failure and fluid overload symptoms. Unfortunately, the patient passed away at home a week after the second admission, with the cause of death related to his underlying cardiac disease.

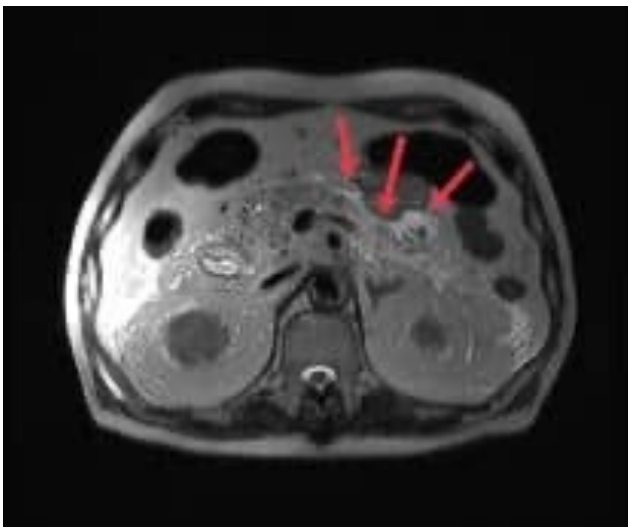


Figure 3. MRI abdomen, axial T2 images show peripancreatic fluids (red arrows) and oedematous pancreas.

DISCUSSION

The case was in concordance with the recent literature which reports an increase in the cases of acute pancreatitis due to tigecycline use. Our patient has multiple comorbidities, including diabetes mellitus type II, hypertension, chronic renal insufficiency, and cardiovascular disease with a history of coronary artery bypass grafting. This profile agrees with current evidence suggesting that elderly patients with multiple comorbidities are more likely to experience adverse reactions to medications, such as tigecycline-induced pancreatitis[5,6].

Acute nausea, abdominal pain and vomiting are the characteristic symptoms of acute pancreatitis. The onset occurs within 5-7 days of tigecycline initiation[7-9]. Our patient's medical history set the foundation for a complex case of drug-induced pancreatitis with an onset timeline of 6 days after treatment, this onset timeline is comparable and consistent with current evidence. This onset of symptoms led to a comprehensive diagnostic evaluation to verify the suspected acute pancreatitis. Acute pancreatitis diagnosis was confirmed through blood tests (elevated serum amylase) and MRI[10]. While this approach follows standard diagnostic procedures, it is noteworthy that most cases in the literature[1,11], used ultrasonography or CT scan for diagnosis. The use of MRI in this case, owing to the patient's compromised kidney function, highlights the importance of flexibility in diagnostic methods for patients with multiple comorbidities.

Following diagnosis, clinical management focused on appropriate treatment and vigilant monitoring of the patient's condition. The implicated medication was promptly discontinued, and supportive care was initiated, in accordance with current guideline for managing drug-

induced acute pancreatitis[12]. The patient's symptoms rapidly resolved, and serum amylase levels normalized within 4 days of tigecycline cessation, further supporting a causal relationship. This swift recovery is similar to other cases reported in the literature[6,13].

Naranjo's score of 7 indicated a probable relationship between tigecycline use and AP development, based on previous reports[7,8], temporal relationship, improvement upon discontinuation, absence of other causes and objective evidence[14].

During the initial diagnosis of acute pancreatitis, the patient's pre-existing heart conditions complicated the clinical picture, as indicated by notable ECG changes. These ECG alterations in acute pancreatitis are multifactorial. One contributing factor may be the release of inflammatory mediators, which can adversely affect cardiac function and conduction. Additionally, stimulation of the autonomic nervous system likely increases sympathetic activity, further complicating the patient's cardiac status. This situation highlights the challenges of managing patients with multiple health issues and emphasizes the need for a comprehensive approach to patient care. Other case reports have documented similar complexities, including those involving kidney transplant patients[6]. The intricacies encountered in this case emphasize the importance of careful monitoring in high-risk patients. The study highlights the need for close observation for adverse effects in patients receiving tigecycline, especially in vulnerable populations. Tigecycline is excreted via the kidneys, and renal insufficiency can increase the likelihood of adverse effects. This aligns with a retrospective study on the clinical characteristics and risk factors for tigecycline-induced pancreatitis[1].

The necessity for close monitoring is particularly relevant when considering the initial decision to use tigecycline, which was based on specific clinical factors. The choice to use tigecycline was informed by culture sensitivity results for the patient's gangrenous toe infection. This demonstrates the complex decision-making process in selecting appropriate antibiotics, particularly in patients with impaired kidney function. Similar considerations were noted in other case reports[9,15].

This case report aligns well with the current evidence on tigecycline-induced pancreatitis while highlighting the complexities of managing such adverse events in patients with multiple comorbidities. It emphasizes the need for careful drug selection, close monitoring, and prompt recognition and management of adverse effects in vulnerable populations.

CONCLUSIONS

In conclusion, the occurrence of tigecycline-induced acute pancreatitis is uncommon, however, it is of clinical significance, especially in elderly patients. Clinicians should exercise caution when prescribing tigecycline, especially in elderly patients or those with underlying renal or cardiac disease. Close monitoring of clinical symptoms, including abdominal pain, and laboratory markers of pancreatic injury is essential. Early recognition and prompt intervention can significantly improve patient outcomes. This case emphasizes the importance of good pharmacovigilance in identifying and mitigating the risks associated with drug-induced adverse events. By adhering to these guidelines and reporting suspected adverse drug reactions, healthcare providers can contribute to safer and more effective medication use.

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