Tigecycline-induced Hypofibrinogenaemia in a Patient with End-stage Renal Diseases

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ABSTRACT

Tigecycline is a broad-spectrum antibiotic agent used to treat severe or multidrug-resistant (MDR) bacterial infections. Bacterial infection is a common and severe complication or co-morbidity associated with end-stage renal disease (ESRD). However, few cases have been reported regarding the adverse drug reaction of tigecycline in patients with ESRD. Here, we detail the case of a 19-year-old female with ESRD, who received tigecycline to treat sepsis due to a MDR *Staphylococcus aureus*. Following seven days of tigecycline, the patient developed coagulopathy with hypofibrinogenaemia, although there was no subsequent haemorrhage. The hypofibrinogenaemia resolved within 14 days after discontinuation of tigecycline. Therefore, we recommend that clinicians strictly monitor coagulation parameters in patients with ESRD during tigecycline treatment.

Keyword: End-stage renal disease, hypofibrinogenaemia, tigecyceline

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INTRODUCTION

Tigecycline presents excellent activity against a broad spectrum of bacteria including multidrug-resistant (MDR) Gram-negative bacteria (1). Bacterial infection is a common and severe complication of end-stage renal disease (ESRD), for whom the choice of antibiotics is difficult due to drug metabolism and renal insufficiency. Tigecycline represents an effective alternative, but concerns remain regarding the safety of tigecycline in patients with ESRD. Here we report a case of an ESRD patient infected by *Staphylococcus aureus* who experienced hypofibrinogenaemia with the use of tigecycline.

CASE REPORT

A 19-year-old Tibetan girl presented with recurrent facial oedema and fatigue. She was diagnosed with chronic renal disease in Tibetan clinics and treated with traditional Tibetan medicine for one year. Two months before admission, her oedema exacerbated, with cough, expectoration, dyspnoea, coma, recurrent high fever, dyskinesia in the right upper limb and epilepsy. Laboratory tests indicated that she was suffering from hypertension, severe anaemia, significant increase of serum creatinine (685 μmol/L) and white blood cell (WBC) count (19.3 × 10^9/L), pulmonary infections, a left cerebral infarction and encephalatrophy. She had been administered antibiotics (amoxicillin-sulbactam, imipenem and moxifloxacin), regular haemodialysis, invasive mechanical ventilation, and other supportive treatments to the patient, but her symptoms did not resolve.

Upon admission, the patient was conscious and her vital signs were acceptable.

Laboratory tests revealed the following: WBC 15.48 × 10 ^9/L, haemoglobin 84 g/L, serum creatinine 286.0 μmol/L, albumin 25.3 g/L. Sputum culture showed Gram-positive streptococcus. Blood from peripheral vein and venous catheter in addition to urine were collected and sent for Gram stain microbiological culture.

This patient urgently needed a powerful antibiotic agent and broad-spectrum antibiotic coverage. Because the patient had prior exposure to several antibiotics, tigecycline was selected as the antibiotic medicine. Tigecycline monotherapy (50 mg q12 h iv) was initiated, and its efficacy was later confirmed by the isolation of tigecycline-sensitive *Staphylococcus aureus* from blood culture and a sensitive *Escherichia coli* from urine culture. New catheters were replaced, and regular haemodialysis and other supportive treatments were administered.

After the start of tigecycline therapy, symptoms of fever, cough and expectoration gradually resolved and no spasm occurred. White blood cell count (Fig. 1) and other inflammatory parameters [*eg*, procalcitonin (PCT) and C-reactive protein (CRP)] were strictly monitored and improved dramatically.

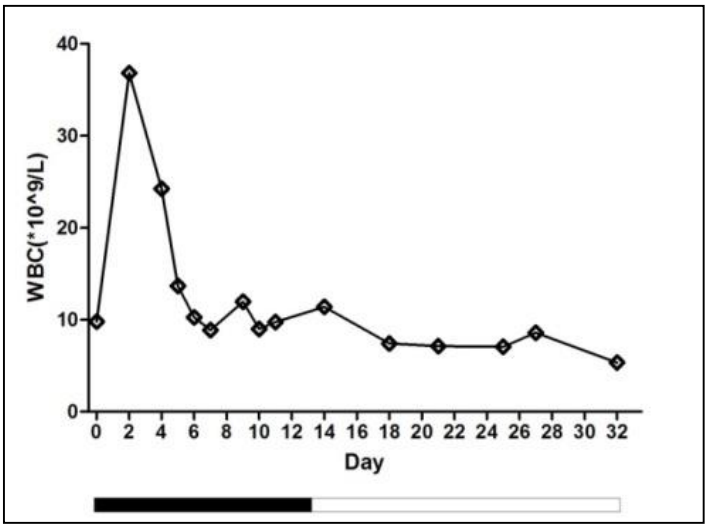

Fig: 1. Trend in white blood cell level. A gradual decrease in white blood cell count with tigecycline administration (black bar) and other antibiotics though with withdrawal of tigecycline (white bar).

However, we observed hypofibrinogenaemia (1.73 g/L), and worsening of prothrombin

time (PT) and activated partial thromboplastin time (APTT) on Day seven of tigecycline treatment (Fig. 2). As no signs of haemorrhage or disseminated intravascular coagulation (DIC) were observed, we did not change the treatment strategy. On Day 11, fibrinogen decreased sharply to an intolerable 0.86 g/L, with a slight declination in PT and fluctuation of APTT (Fig. 2B).

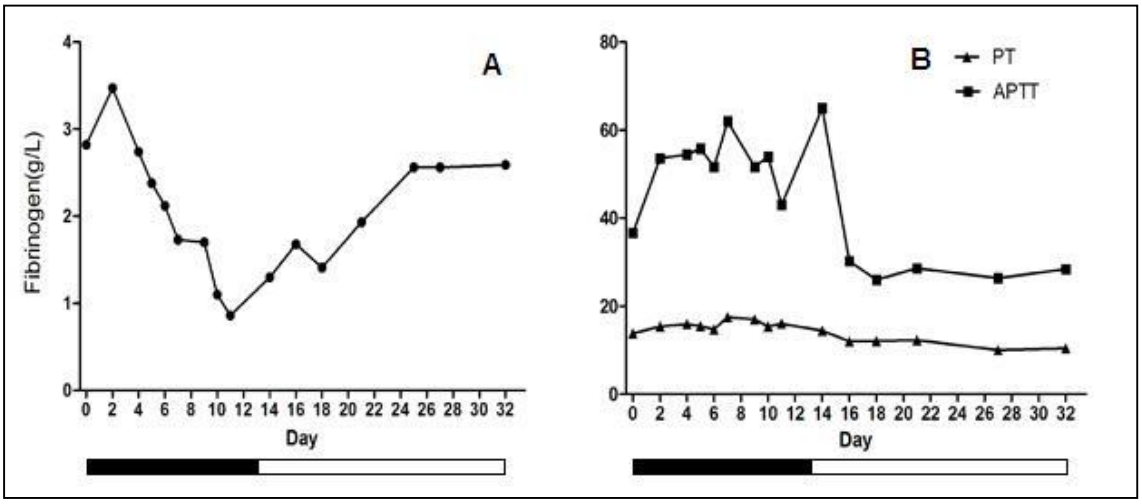

Fig: 2. Trends in fibrinogen level and PT/APTT with (black bar) or without (white bar) use of tigecycline.
A: A remarkable decrease in fibrinogen on day 7–11 of tigecycline administration, resolved gradually by its withdrawal.
B: Fluctuation of PT and APTT with the use of tigecycline, and improved by its withdrawal.

At this point, tigecycline was discontinued, as it was suspected to be responsible for this coagulation disorder. Moxifloxacin and vancomycin were selected as antibiotics after tigecycline withdrawal according to drug sensitivity tests. Meanwhile, we administered fresh-frozen plasma transfusions to protect the patient from bleeding.

From that day onward, fibrinogen climbed slowly and steadily to reach the lower limit of normal, and PT and APTT stayed within the normal range. Fourteen days after discontinuation of tigecycline, fibrinogen improved and remained within the normal level without the administration of fresh-frozen plasma transfusions (Fig. 2A). Repeated blood, urine,

and sputum cultures found no evidence of bacterial growth. The patient recovered and remained stable without any recurrence of fever, cough, epilepsy, or coagulation disorder. The patient is now waiting for a kidney transplant.

DISCUSSION

Tigecycline is a relatively novel antibiotic agent with powerful antibiotic activity against a wide spectrum of bacterial organisms. Tigecycline is mainly metabolised by the liver and it requires no dosage adjustment in patients with renal impairment (2), making it a good alternative for infections in patients of chronic renal disease or ESRD. In our case, an ESRD patient presented with sepsis, severe and complicated bacterial infection, and high risk of persisting infections, as well as resistance to several antibiotics. Tigecycline resolved her symptoms and improved her parameters of infections. Hypofibrinogenaemia occurred after seven days of tigecycline treatment, and was relieved after tigecycline was discontinued, with no changes in other therapies. Sepsis or severe infection was the most likely cause of hypofibrinogenaemia; however, systemic inflammation and the general condition of the patient were improving at the time of onset. Other causes of hypofibrinogenaemia included congenital hypofibrinogenaemia, DIC, leukaemia, malignant tumour, severe liver diseases and hemophagocytic syndrome; nevertheless, the patient displayed no evidence of these diseases. Thus, we hypothesised that hypofibrinogenaemia was a side effect of tigecycline.

It is estimated tigecycline causes nausea, vomiting, pancreatitis, hepatic injury or failure and hypoglycaemia with a relatively high frequency (3). However, few cases of

hypofibrinogenaemia have been reported as an adverse drug reaction of tigecycline. Rossitto presented a case of tigecycline-induced coagulopathy and hypofibrinogenaemia in a patient with advanced liver cirrhosis (4). Pieringer reported a case in which the use of tigecycline was associated with hypofibrinogenemia in an ESRD patient undergoing continuous ambulatory peritoneal dialysis (5). In addition to this case, our study further indicates that tigecycline is a probable cause of hypofibrinogenaemia in patients with ESRD.

Hypofibrinogenaemia is rarely found in ESRD patients. In contrast, these patients have increased levels of fibrinogen, which directly contributes to a hypercoagulable state (6, 7), thus increasing the risk of venous thromboembolism (8, 9). However, coagulation disorders, which increase the risk of bleeding, are the common complications in ESRD patients; the most prominent abnormality is prolongation of skin bleeding time (10), while APTT or PT are usually in the normal range. In our study, the fibrinogen level in the patient was initially normal, but it dropped with the use of tigecycline and recovered after discontinuation of this drug. Therefore, we believe that tigecycline caused hypofibrinogenaemia in this ESRD patient.

Due to the increasing use of tigecycline for treating complicated infections, more attention should be paid to adverse drug reactions associated with this drug. In conclusion, we strongly recommend strict monitoring of fibrinogen and other coagulation parameters in patients who are receiving tigecycline as an antibiotic agent.

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