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BIOMEDICAL SCIENCE IN BRIEF

Leukocytosis induced by tigecycline in two patients with severe acute pancreatitis

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Tigecycline is the first member in the glycylcycline class of antibacterial agents which was approved by the U.S. Food and Drug Administration in 2005. The 9-t-butylglycylamido derivative of minocycline is used for the treatment of complicated skin and skin-structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia [1]. Tigecycline is the most sensitive drug used against extensively drug-resistant bacteria [2]. Currently, tigecycline associated adverse drug reactions are increasing, the most common being nausea, vomiting, diarrhoea and liver dysfunction [3], with a lower incidence of acute pancreatitis and hypofibrinogenemia [4–7]. Several cases have reported that minocycline may induce leukocytosis, but none have indicated a link between tetracycline antibiotics and leukocytosis [8–10]. Here, we describe two cases in which leukocytosis developed within a week of initiating tigecycline in infected pancreatic necrosis.

Case 1

A 27-year-old male patient was admitted to the Department of Pancreatic and Biliary Surgery complaining of ongoing abdominal pain for 24 hours. The serum amylase was 1598 U/L (reference range 30–110) triglyceride was 2.31 mmol/L (1.7), and there was a neutrophil leukocytosis, hypoalbuminaemia, grossly increased CRP and procalcitonin, and abnormal renal function (Table 1). The abdomen computed tomography (CT) scan confirmed acute pancreatitis with pancreatic enlargement and extensive peripancreatic oedema (Figure 1(a)). The patient was diagnosed with hypertrigyceridemia-induced acute pancreatitis. The dyspnoea and tachycardia (respiratory rate of 40/min, cardiac rate of 148/min) occurred after his admission and then the patient was transferred to intensive care unit (ICU)

In ICU, mechanical ventilation, abdominal puncture catheter drainage, and thoracocentesis were implemented. Broad-spectrum antibiotic therapy, sulperazone cefoperazone and culbactam sodium were given for the first five days, and as *Enterococcus faecalis* was demonstrated, linezolid was prescribed. On day 15, the clinical status and biochemical parameters of patient were improved and he was transferred back to a medical ward.

On day 21, all enteral feeds could be tolerated. The white blood count was 9.7×10^9/L, C-reactive protein 23 mg/L, procalcitonin 0.04 ng/mL, and all intravenous drugs were stopped. On day 30, the patient had a sudden chill and fever (40°C). The serum C-reactive protein increased to 130 mg/L and white cell count to 30×10^9/L. The CT scan revealed gas bubbles within the necrotic pancreatic tissue and the patient was diagnosed with infected pancreatic necrosis (Figure 1(b)). Imipenem/cilastatin was given intravenously (1 g, every 8 hours) and open necrosectomy was performed on day 40. The patient still had fever six days after open necrosectomy and the abscess culture demonstrated carbapenem-resistant K. pneumoniae. The antibiotic therapy was adjusted to 50 mg tigecycline q12h (loading dose was 100 mg). The tigecycline was well tolerated without complaints of nausea and vomiting. However, serial blood over the following week showed a neutrophil leukocytosis, thrombocytosis, raised CRP and increased liver function tests. As the leukocytosis was not explained by primary infection or other cause, a tigecycline-induced leukocytosis was suspected as the only received agent at that time. After the multi-disciplinary team discussion (haematology, surgery, microbiology, pharmacy, and ICU), the tigecycline

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Table 1. Serial laboratory data.

		Case-1						Case-2					
		Days after tigecycline						Days after tigecycline					
Analyte (unit)	Reference ranges	AD	Day1	Day3	Day5	Day7	Day11	AD	Day1	Day6	Day8	Day11	Day16
White blood cell count ($\times10^9$/L)	3.7–9.2	16.1	20.0	11.8	47.5	16.0	7.0	38.2	18.3	27.5	46.3	29.8	11.9
Neutrophil count ($\times10^9$/L)	2.00–7.00	13.2	18.6	9.5	44.4	14.0	4.9	35.2	14.8	23.0	39.4	26.3	9.6
Red blood cell count ($\times10^{12}$/L)	4.1–5.7	4.8	3.2	3.7	4.7	/	3.6	3.1	3.1	3.2	3.3	2.9	2.8
Haemoglobin (g/L)	113–151	144	95	110	141	112	107	93	88	92	97	84	82
Platelet count ($\times10^9$/L)	98–300	167	497	327	393	/	416	309	420	415	401	342	408
Serum albumin(g/L)	30–50	20	26	28	32	28	31	23	36	34	33	32	29
Glucose (mmol/L)	3.9–6.1	6.3	6.6	5.4	4.0	4.4	6.8	13.8	/	/	8.9	10.6	8.0
C-reactive protein (mg/L)	<8	266	144	65	84	/	/	228	118	134	145	43	26
Procalcitonin (ng/mL)	<0.05	4.6	1.6	0.2	0.5	0.3	0.2	9.2	22.1	2.8	2.1	1.5	0.3
Alanine aminotransferase (U/L)	5–35	26	15	78	37	25	51	14	3	13	30	41	28
Aspartate transferase (U/L)	8–40	37	22	55	25	25	44	20	9	14	42	52	23
Total bilirubin (μmol/L)	3–21	14	16	10	14	15	10	9	21	17	24	16	13
γ-Glutamyltransferase (U/L)	10–60	21	64	64	111	81	60	25	49	59	54	114	121
Blood urea nitrogen (mmol/L)	2.9–8.2	6.6	2.4	4.9	7.8	5.3	2.7	10.6	17.4	14.4	11.9	3.8	1.5
Serum creatinine (μmol/L)	35–80	101	44	44	59	76	67	193	137	89	88	78	43

AD: Admission day.

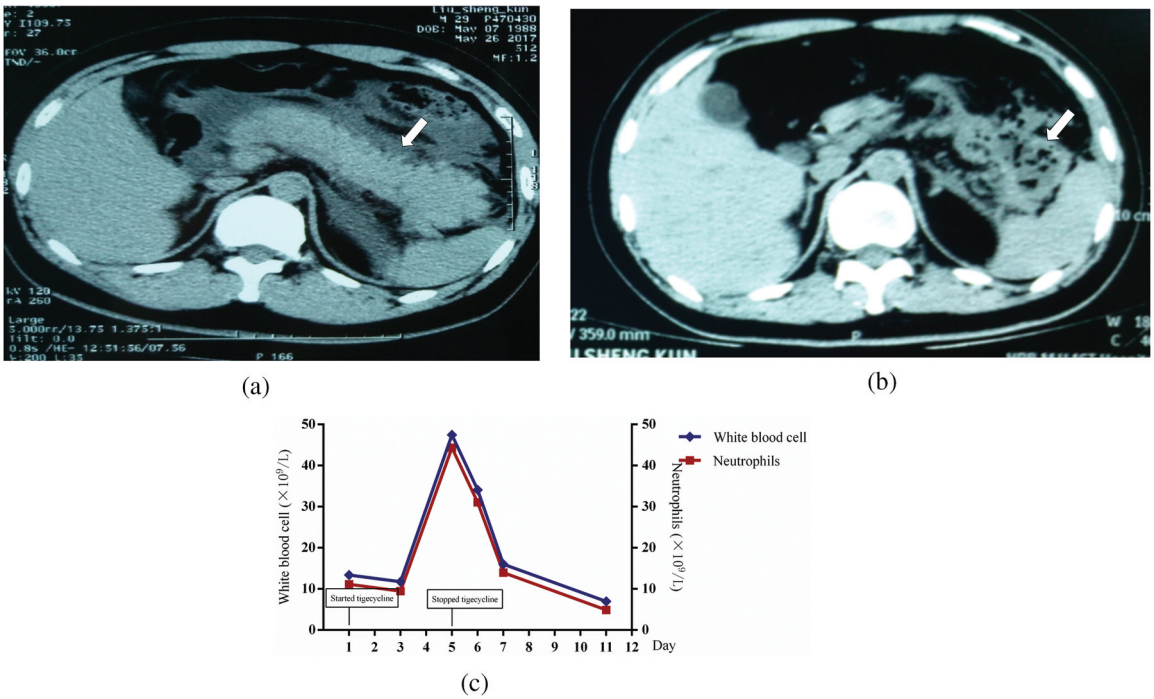

Figure 1. The CT image of pancreas and leukocyte changes in case 1. (a) The pancreatic CT scan showed acute pancreatitis with extensive peri-pancreatic edema and fluid collection; (b) The pancreatic CT scan revealed infected pancreatic necrosis with gas bubbles within peri-pancreatic fluid collection; (c) Continuous change of the number of white blood cell and percent of neutrophils following the initiation and withdrawal of tigecycline in case 1.

was stopped on day 5. The white blood cell count, neutrophil count and (mostly) liver function tests began to fall the following day and returned to normal by day 11 (Figure 1(c)). On day 61, the patient was discharged. There was no clinical symptom and abnormal laboratory investigation after 6 months follow-up.

Case 2

A 28-year-old female was transferred from a local hospital with severe acute pancreatitis. There was a medical history of type II diabetes, low haemoglobin and hypertriglyceridaemia, but no history of renal disease. Physical examination revealed a temperature of 38°C, blood pressure of 174/87 mmHg, cardiac rate of 144/min. The respiratory rate was 30/min and oxygen saturation was 93% on air. The serum amylase was 83 U/L, and there was a neutrophil leukocytosis, hypoalbuminaemia, hyperglycaemia, raised CRP and procalcitonin. Renal function was abnormal indicating acute kidney injury, a common complication of acute pancreatitis (Table 1). The abdomen CT scan showed

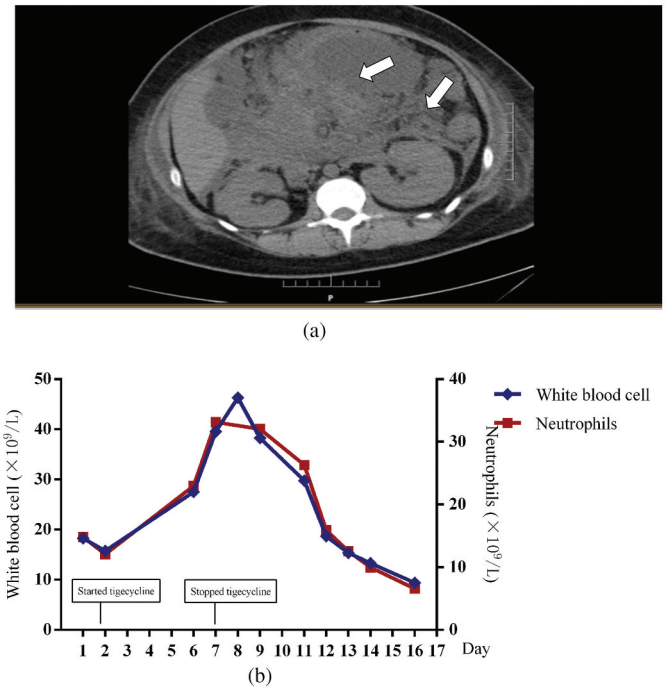

Figure 2. The CT image of pancreas and leukocyte changes in case 2. (a) The pancreatic CT scan confirmed infected pancreatic necrosis with pre-pancreatic fluid collection and walled-off necrosis; (b) Continuous change of the number of white blood cell and percent of neutrophils following the initiation and withdrawal of tigecycline in case 2.

Table 2. Naranjo adverse drug reaction probability scale of the two cases.

	Yes	No	Unknown	Case1 Score	Case2 Score
1. Are there previous conclusive reports on this reaction?	1	0	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	2	−1	0	2	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	0	1	1
4. Did the adverse reaction reappear when the drug was re-administered?	2	−1	0	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	2	0	2	2
6. Did the reaction reappear when a placebo was given?	−1	1	0	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	0	0
10. Was the adverse event confirmed by any objective evidence?	1	0	0	1	1
Total Score				6	6

pancreatic enlargement and extensive peri-pancreatic oedema (Figure 2(a)). The patient was diagnosed with hypertrigyceridemia-induced acute pancreatitis.

The patient's clinical parameters improved following homoeostasis maintenance, adequate renal perfusion, abdominal decompression, puncture catheter PCD and continuous renal replacement therapy. The antibiotic therapy was adjusted to imipenem/cilastatin (1 g every 8 hours) and fluconazole (0.4 g every 12 hours) was added. She gradually recovered consciousness and her status improved. The *Acinetobacter baumannii* bacterium was detected (pus from peritoneal drainage) on day 8 of her admission. The patient's infection was exacerbated with a higher temperature (38.3°C) and tigecycline (loading dose 100 mg the 50 mg iv every 12 hours) was given. Serial changes in laboratory indices are shown in Table 1, with a further neutrophil leukocytosis, thrombocytosis, raised CRP and calcitonin. The white blood cell count slowly declined in the following 8 days (Figure 2(b)).

Discussion

We report the two cases of tigecycline-induced leukocytosis in patients with severe acute pancreatitis. It is probable that these two cases of leukocytosis were caused by tigecycline, an adverse drug reaction, in accord with the Naranjo Adverse Drug Reaction Probability Scale [8]. The adverse drug reactions are assigned to a probability category from the total score as follows: definite if the overall score is 9 or greater, probable for a score of 5–8, possible for 1–4 and doubtful if the score is 0. Points were allocated for the appearance of leukocytosis after tigecycline was administered (2 points), improvement of leukocytosis when tigecycline was removed (1 point), leukocytosis cannot

be explained neither by primary infection nor alternative causes after careful physical examination and laboratory investigation (2 points), and leukocytosis was confirmed by objective evidence (1 point). The total score was 6 points, which categorized the adverse drug reaction as probable (Table 2).

Despite tigecycline-induced acute pancreatitis being a rare phenomenon, the manufacturer of tigecycline (Wyeth) updated the product label by adding acute pancreatitis as one of the post-marketing adverse events in 2006 [9]. Although a high-volume centre of acute pancreatitis (more than 300 patients per year), these are the first cases of tigecycline-induced pancreatitis or exacerbation of acute pancreatitis we have encountered. In these two patients, complicated intra-abdominal infections were diagnosed with clinical symptoms, imaging features, auxiliary examination, and bacterial culture results. Based on the bacterial culture results and antimicrobial susceptibility test, tigecycline was the most suitable option. Meanwhile, the abdominal pain, amylase and lipase concentrations were screened during the treatment of this disease.

The two cases have some similar features. Both were diagnosed with hypertrigyceridemia-induced acute pancreatitis, and share the same age-band, aetiology, disease presentation and progression and pathological process. The leukocytosis is occurred within a week of receiving tigecycline, and cannot be explained by primary infection or other drugs. The main mechanism which may induce leukocytosis is unclear and the three possible explanations. Firstly, minocycline can induce neutrophil movement from bone marrow into the circulation and causes leukocytosis [7,10]. Since tigecycline and minocycline are both tetracycline derivatives, they share similar structural formula. They may induce similar hypersensitivities. The possible mechanism is that neutrophils in the peripheral pool are rapidly mobilized through the accelerated blood flow after the stimulation of tigecycline. The granulocytes are released from the bone marrow storage pool, which increase the number of neutrophils entering the blood from the storage pool and reduce the outflow of neutrophils from the circulation pool. Secondly, the effective myelogenous granulocytosis is activated by tigecycline. The leucocyte exudation in the small blood vessels is decreased and the life span of granulocytes is prolonged. Finally, the underlying mechanism remains to be further elucidated with emphasis on the potential role of genetic susceptibility.

In summary, our cases point to tigecycline as a cause of otherwise unexplained leukocytosis, and recommend the white blood cell and neutrophil counts be closely monitored in patients treated with tigecycline.

Disclosure statement

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