ACUTE THROMBOCYTOSIS IN A PATIENT TREATED WITH ERTAPENEM

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ABSTRACT

Ertapenem, a carbapenem-type beta-lactam antibiotic, demonstrates broad-spectrum efficacy against a wide range of Gram-positive and Gram-negative bacteria, including aerobes and anaerobes. Importantly, it demonstrates resistance to virtually all beta-lactamases, including the extended spectrum beta-lactamases (ESBLs). Haematologic complications such as thrombocytosis, haemolysis, anaemia, and neutropenia are infrequent side effects associated with this drug. In this report, we present a rare case of ertapenem-induced thrombocytosis in a 62-year-old female patient who was admitted for a complicated urinary tract infection caused by *Escherichia coli*.

KEYWORDS

Ertapenem, thrombocytosis

LEARNING POINTS

- Ertapenem was identified as the most likely cause of thrombocytosis.
- Discontinuing ertapenem normalised the platelet count.
- It is crucial for physicians to identify and address causes of thrombocytosis, particularly when related to medications, to avoid inadvertent complications and to ensure effective patient care.

INTRODUCTION

Ertapenem is a beta-lactam antibiotic, a class that inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins, resulting in cell death. As a parenteral, broad-spectrum antibiotic, it is most often used as an alternative agent for certain complicated infections, especially those with resistance to other antibiotics. Ertapenem has pharmacokinetic superiority over the other carbapenems such as imipenem, panipenem and doripenem, due to its long half-life[1]. Ertapenem is used for the treatment of intra-abdominal infections, skin infections, pneumonia, urinary tract infections and pelvic inflammatory infections. The most common side effects from ertapenem use include diarrhoea, infusion-vein reaction, nausea and transient elevations in alanine aminotransferase levels[1]. Haematologic adverse events such as thrombocytosis, haemolysis, anaemia, and neutropenia are rare. Our focus in this report is on ertapenem-induced thrombocytosis, which is defined as a

platelet count of greater than 450,000/µl[2]; a preliminary literature search yielded only one such reported case[3].

CASE DESCRIPTION

We present the case of a 62-year-old female with a medical history of hypertension, type 2 diabetes mellitus, hyperthyroidism secondary to Graves' disease and endometrial cancer treated with a hysterectomy. The patient presented with dysuria, scant blood on wiping, fatigue, chills, fever, and general malaise. The patient denied urinary urgency, frequency, flank pain, diarrhoea, abdominal pain, nausea, and vomiting. She had a prior urinary tract infection one year prior, which was identified as extended spectrum beta-lactamase *Klebsiella pneumoniae* (ESBL-KP). When the patient's symptoms started, she took ampicillin of unconfirmed dosage for 3 days at home before presenting to the emergency room. Her family and social history are non-contributory. On physical examination, the patient's initial vitals were temperature 38.3 °F, blood pressure 102/50 mmHg, heart rate 99 beats per minute and respiratory rate 19 breaths per minute. The patient appeared in moderate distress and was mildly tachycardic, but the physical examination was otherwise benign.

In the emergency department, a urinalysis (UA) was obtained which showed cloudy urine with a large amount of leukocyte esterase, 1,200 white blood cells/high power field, 300+ proteins, random glucose of 500 mg/dl and numerous bacteria. The UA was negative for ketones, and there was no clinical concern for diabetic ketoacidosis.

The patient was admitted to the Medicine Unit for further management of dysuria and complicated urinary tract infection. Urine and blood cultures were collected. A computerised tomography scan of the abdomen and pelvis was negative for hydronephrosis or obstruction. The initial blood workup showed that the patient had a haemoglobin (Hgb) of 12.9 g/dl, white blood cell (WBC) count of 16,440/µl, platelet count (PLT) of 251,000/µl and an acute kidney injury. The patient was then started on ceftriaxone 1 g IV daily. The
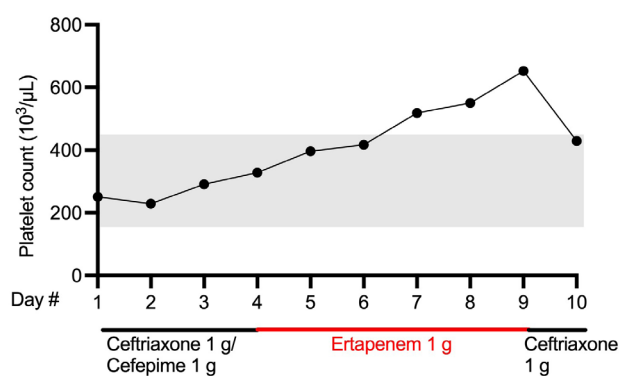

Figure 1. The antibiotic regimen and platelet count measured daily during the hospital stay. Ceftriaxone 1 g IV daily (days 1–2), ceftriaxone 1 g plus cefepime 1 g daily (day 3), ertapenem 1 g IV daily (days 4–8), ceftriaxone 1 g daily (days 9–10). There is a rapid decrease in platelet count from 652,000/µl on day 9 to 429,000/µl on day 10 following the transition from ertapenem to ceftriaxone.

patient's WBC count continued to uptrend to 21,000/µl with intermittent fevers. Coupled with the patient's prior ESBL-KP history, the patient was started on cefepime for better Gram-negative coverage while waiting for the diagnostic cultures. On day 4 of admission, blood and urine cultures had grown Gram-negative rods, which speciated to *Escherichia coli*, both sensitive to carbapenems. The patient was then started on ertapenem 1 g IV daily for a 7-day course. The patient tolerated ertapenem well, with no adverse events such as fever, nausea, or vomiting. Her temperature and WBC count started trending down, with no further fevers. Other laboratory markers began improving as well (*Table 1*). However, the patient's platelets continued to increase substantially, meeting the criteria for thrombocytosis. This finding was initially thought to be an acute phase reactant and was expected to eventually self-resolve, but the continuous uptrend and the timing that coincided with the administration of ertapenem suggested that this thrombocytosis was triggered by ertapenem. As the patient

	Baseline (previous primary care provider visit)	Day of hospitalisation									
		1	2	3	4	5	6	7	8	9	10
WBC (103/µl)	6.08	16.4	17.8	21.0	18.5	14.2	12.4	13.6	11.5	11.5	9.4
Hgb (g/dl)	13.6	12.9	11.7	11.1	11.1	10.8	10.8	11.1	10.8	11.3	11.3
PLT (103/µl)	283	251	229	291	328	396	417	518	550	652	429
Creatinine (mg/dl)	0.79	2.31	3.11	2.36	2.06	1.66	1.2	1.15	1.1	1	0.92
BUN (mg/dl)	12	35	39	42	42	35	25	20	16	13	14
Temperature oC/(oF)		38.3 (101)	37.1 (98.7)	38.4 (101.2)	36.9 (98.5)	37.1 (98.7)	37.0 (98.6)	36.6 (97.9)	36.9 (98.4)	37.1 (98.7)	36.8 (98.3)

Table 1. Patient's white blood cell (WBC), haemoglobin (Hgb), platelet count (PLT), Creatinine (Cr), blood urea nitrogen (BUN) and temperature during the hospital stay

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could have caused the reaction on their own?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	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
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
	Total Score:			5

Table 2. Naranjo adverse drug reaction (ADR) probability scale calculator[4]

was afebrile and the leukocytosis had almost resolved, and to avoid complications of thrombocytosis, ertapenem was discontinued and ceftriaxone was reinitiated for the final 2 days. Notably, the patient's platelets returned to normal (429,000/µl) 36 hours after discontinuing ertapenem (Fig. 1). The patient's symptoms resolved, and she was discharged home with stable vital signs, stable Hgb and normalised WBC, PLT and kidney function (Table 1).

DISCUSSION

Thrombocytosis is broadly categorised into primary and secondary types, where primary thrombocytosis is associated with myeloproliferative disorders, and secondary thrombocytosis results from reactive processes[3]. Distinguishing between these two types can be challenging, but it is important for effective management. Reactive or secondary thrombocytosis is relatively more common than primary causes, although the pathophysiology is not well elucidated. Reactive processes are mostly driven by increased endogenous levels of thrombopoietin, cytokines such as interleukin-6, occult cancers, acute and chronic inflammation, and certain drugs[3]. Examples of some drugs associated with thrombocytosis are beta-lactams such as

ceftazidime, ceftriaxone and moxalactam, vincristine and all-trans retinoic acid[3].

We applied the Naranjo adverse drug reaction probability scale, a model used to assess the probability of a causal relationship between a drug and an adverse reaction. Factors such as drug exposure, re-exposure, sequence, concentration, clinical confirmation and dosage adjustments are considered when using this scale[4]. A calculated score of 5 makes the causal relationship between ertapenem and thrombocytosis 'probable' according to this scale (Tables 2 and 3). Generally, drug-induced thrombocytosis self-resolves when the triggering agent is discontinued and in our patient's case, the platelet count returned to normal 36 hours after discontinuing ertapenem. The probable causality according to the Naranjo scale, as well as the clear platelet trend with ertapenem initiation and discontinuation, makes ertapenem the strongest explanation for thrombocytosis in this patient.

Naranjo Score	Interpretation
≥9	Definite
5–8	Probable
1–4	Possible
<0	Doubtful

Table 3. Interpretation of ADR score from Naranjo Probability Scale Calculator

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