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Acute Haematologic Reaction: Drug or Bug?

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ABSTRACT

β-lactams are known to cause haematologic reactions. Cefoperazone is one such β-lactam that is commonly combined with a β-lactamase inhibitor, sulbactam. A review of the available literature suggests that cefoperazone can cause or precipitate haematologic reactions, including anaemia, leucopenia, thrombocytopenia and hypoprothrombinemia. Similarly, Escherichia coli (E. coli) is a commonly encountered organism associated with urinary tract infections and urosepsis, which can also present in a similar. This case report is a description of an elderly patient who harboured E. coli, and was also given cefoperazone-sulbactam, and later developed haematologic reactions.

Keywords: Sepsis; E. coli; Cephalosporins; Cefoperazone; Adverse effect; Naranjo

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INTRODUCTION

β-lactams are one of the earliest discovered antibiotics, which are still widely used in the clinical setup. They are also among the safest antibiotics available today. However, no drug is entirely safe. β-lactams, which chiefly include the penicillins and cephalosporins (in addition to other groups), are not devoid of adverse reactions. These reactions include hypersensitivity, gastrointestinal symptoms, haematologic reactions and renal reactions, to list a few [1].

The most common haematologic adverse event noted with β-lactams is bleeding, either due to hypoprothrombinemia or thrombocytopenia, mostly seen with drugs that have a methylthiotetrazole ring (e.g., cefoperazone) [2]. Similarly, leucopenia has also been attributed to the use of β-lactams, and has been postulated to be dose and duration-dependent [3]. Also, haemolysis and anaemia have been reported with the use of cefaperazone [1].

The authors report a case of pancytopenia that could either be due to therapy with cefoperazone-sulbactam or due to E. coli sepsis.

CASE REPORT

A 75-year-old male patient with no premorbidities presented to the medicine outpatient department with history of high grade intermittent fever with associated chills for the past two days. He also complained of one episode of vomiting, with no blood or bile in the vomitus. On further history-taking, it was found that he had had another episode of fever two weeks ago, for which he had consulted a private practitioner, and was diagnosed to be a case of dengue fever (as the platelet count was found to be low, i.e., 62,000 cells/cu.mm.) and was treated for the same, following which he recovered.

During this admission, the patient's heart rate was 110 bpm, blood pressure was 90/60 mm Hg, and all systems were normal. The patient was started on intravenous fluids and inotropes (intravenous noradrenaline). His haemoglobin level on admission was 12.7 g%. His total leucocyte count was found to be 7,700 cells/cu.mm. (neutrophils – 87.4%), and platelet count was "low" on day 1 of admission. Urine examination revealed presence of protein (2+), blood (3+), leucocytes (2+) and bacteria. Blood urea was slightly elevated (48 mg/dL), and so was the serum creatinine (1.8 mg/dL). All serum electrolytes were within normal limits. All routine investigations for fever of unknown origin were performed, and turned out to be negative. Urine and blood culture reports showed growth of E. coli. Drug sensitivity testing (DST) showed susceptibility to cefoperazone-sulbactam, following which the drug combination was initiated intravenously at a dose of 3g twice daily on day 2.

Following start of therapy with cefoperazone-sulbactam, the total leucocyte count started dropping as follows (all values in cells/cu.mm.): 6,400 on day 2; 2,500 on day 4; 1,800 on day 5 and 2,100 on day 6. Also, the haemoglobin levels started dropping (all values in g%): 9 on day 2; 8.5 on day 4 and 8.6 on day 5. Platelet count (all values in cells/cu.mm.) was 1,10,000 on day 2; 1,03,000 on day 3; 92,000 on day 5 and 82,000 on day 6. Following these investigations, it was suspected that the reduction in counts could have been caused by the antibiotic in question. Hence, cefoperazone-sulbactam was withdrawn, and intravenous meropenem (as the DST showed susceptibility) was started instead at a dose of 1g twice a day, from day 6 post-admission.

After the drug combination was stopped, there was an improvement in the patient's blood counts: total leucocyte count was 4,200 cells/cu.mm., haemoglobin was 10.9 g% and platelet count was 1,29,000 cells/cu.mm. (all on day 10 post-admission).

Improvement in counts could suggests that the reaction was probably drug-induced. Causality assessment using Naranjo's scale returned a score of 6 (showing that the reaction was "probably" due to the drug). However, the bone marrow aspirate showed infective changes, with normal M:E ratio. This probably suggests that the reaction was organism-induced. So, the question remains: drug or bug?

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DISCUSSION

Cephalosporins are one of the most commonly used classes of antibiotics in clinical practice. However, there are instances where they have led to hematological adverse effects ranging from thrombocytopenia to the more dangerous pancytopenia. There are reports of pancytopenia due to cefroxadine use, a second generation cephalosporin. The mechanism of this reaction is not clearly known [4]. Studies done on dogs have shown the cause for cytopenia as immune mediated destruction of blood cells. Cefazedone was the cephalosporin used in this canine study [5]. We were unable to find an article where pancytopenia was induced by cefoperazone-sulbactam. However, there are reports of isolated thrombocytopenia induced by cefoperazone sulbactam [2].

In addition, even sepsis can cause bone marrow depression and pancytopenia. Animal studies have implicated sepsis as a possible primary cause of pancytopenia. Septicaemia can damage the bone marrow in multiple ways. It can cause endotoxin-mediated destruction of marrow cells or inflammation-mediated bone marrow damage. In addition, there are other contributory factors like blood loss, rapid migration of white blood cells to infected site and also sequestration of platelets and neutrophils [6].

In order to rule out these causes, tests like Coomb's test and bone marrow aspiration have to be performed. We went ahead and performed bone marrow aspiration in this patient. The bone marrow aspirate showed infective changes. Based on this report, we came to a conclusion that it is the bug and not the drug that caused pancytopenia in this case.

To conclude, we are sad that a painful procedure of bone marrow aspiration had to be performed on the patient, but at the same time, glad that we could conclude that it was pancytopenia due to infective origin, and not drug-induced.

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