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Severe Myelosuppression Induced by Piperacillin/Tazobactam: A Case Report

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Abstract: This case report presents an elderly patient who developed severe bone marrow suppression following the administration of Piperacillin/Tazobactam. The patient exhibited a declining trend in platelet and white blood cell counts during Piperacillin/Tazobactam treatment. Subsequently, upon discontinuation of Piperacillin/Tazobactam, platelet and white blood cell counts gradually increased. Negative drug allergy test results and the absence of evidence for bone marrow suppression caused by platelet antibodies or other drugs led to the consideration of the possibility of immune-mediated bone marrow suppression induced by Piperacillin/Tazobactam. This report emphasizes the importance of close monitoring of hematological parameters to mitigate the risk of bone marrow suppression during the clinical use of Piperacillin/Tazobactam.

Keywords: Piperacillin/Tazobactam; Myelosuppression; Adverse Drug Reaction

Introduction

Piperacillin is a semi synthetic penicillin antibiotic, while tazobactam serve as a β- Lactam enzyme inhibitor. The combined use of Piperacillin/Tazobactam can cover most gram-positive and gram-negative bacteria (especially Pseudomonas aeruginosa), and Piperacillin/Tazobactam has high safety, which is the most commonly used antibacterial drug for hospital infection [1,2,3]. The most common adverse reaction of piperacillin is diarrhea [4]. Hematological abnormalities are serious adverse reactions of piperacillin and tazobactam, and symptoms such as leukopenia and thrombocytopenia have been reported in relevant case reports after the use of piperacillin [4,5,6]. Here, we report a case of severe thrombocytopenia caused by the use of piperacillin tazobactam. After the application of anti allergic therapy and discontinuation of piperacillin tazobactam, platelets and white blood cells rapidly rebounded. This report reminds us that for patients who use Piperacillin/Tazobactam, regardless of whether the skin test results are negative, hematological parameters should be closely monitored.

Case report

On December 28, 2022, a 78-year-old male patient was admitted to the Tumor Treatment Center of Traditional Chinese Medicine at our hospital. He presented with a persistent cough lasting for 14 days and worsening asthma and fatigue over the past 7 days. The patient had a medical history of hypertension and a previous appendectomy. He denied any prior history of drug allergies. Upon admission, the patient's vital signs were as follows: body temperature of 36.3 ℃, pulse rate of 76 beats per minute, blood pressure measuring 118/73 mmHg. The patient was alert and oriented, and physical examination revealed prominent breath sounds in both lung fields, with a few crackles in the lower lung regions. No other positive findings were noted during the remaining physical examination.

Additional investigations yielded the following results: A chest computed tomography (CT) scan revealed multiple inflammatory changes in both lung fields. The complete blood count indicated a white blood cell count of 5.92 × 10^9/L, with a differential count showing 82.5% neutrophils and a platelet count of 222 × 10^9/L. C-reactive protein (CRP) was elevated at 21.33 mg/L, and the partial pressure of oxygen measured 79 mmHg. Furthermore, the novel coronavirus antibody test returned a positive result.

In response to the patient's condition, a treatment regimen was initiated. Piperacillin/Tazobactam (Zhuhai United Laboratories, batch number: 28083201) was administered at a dosage of 4.5g every 8 hours to address the infection. Moreover, the patient received dexamethasone sodium phosphate (6mg) to manage inflammation and asthma symptoms. Esomeprazole was prescribed for acid suppression and gastric protection. The patient also underwent low-flow oxygen inhalation (3-5 L/min) to enhance oxygenation. In addition, the patient was administered an oral traditional Chinese medicine decoction known as Maxing Shigan Decoction. On January 5, 2023, the patient's cough and asthma symptoms improved compared to before. The blood routine examination showed that white blood cells were 7.94 * 10 ^ 9/L, neutrophil

percentage was 77.8%, platelet count was 171 * 10 ^ 9/L, and CRP results showed no abnormalities. The blood gas analysis showed oxygen partial pressure was 77mmHg, and the coagulation test showed no abnormalities. Therefore, dexamethasone and esomeprazole were discontinued, and piperacillin tazobactam was continued to be used according to the course of treatment.

On January 10, 2023, a blood routine examination revealed that the patient's white blood cell count was 3.69×10^9/L, with a neutrophil percentage of 65.9%, and a platelet count of 46×10^9/L.

The patient was suspected to be allergic to piperacillin and tazobactam, prompting an immediate cessation of the medication. Subsequently, the patient received a 25mg intramuscular injection of promethazine hydrochloride, and cetirizine hydrochloride was administered orally as an antiallergic agent. A consultation with the hematology department was sought, which strongly suspected drug-induced thrombocytopenia. However, other hematological conditions could not be definitively ruled out. Therefore, a comprehensive workup was recommended, including an enhanced evaluation of antinuclear antibodies, antiplatelet membrane glycoprotein autoantibodies, and consideration of a bone marrow puncture. The patient was prescribed 0.3g of caffeic acid tablets three times a day for oral platelet elevation treatment, following the consultation's guidance. The patient adhered to the recommendations and exhibited no abnormalities in subsequent evaluations of antinuclear antibodies and antiplatelet membrane glycoprotein autoantibodies. However, the patient declined to undergo a bone marrow puncture procedure. Throughout this period, the patient continued to take the traditional Chinese medicine decoction orally. Daily blood routine examinations showed a progressive increase in platelet counts, coinciding with the gradual resolution of the skin rash.

On January 16, 2023, a blood routine examination revealed that the patient's white blood cell count had risen to 5.08×10^9/L, and the platelet count was measured at 108×10^9/L. A chest CT examination indicated a reduction in the extent of inflammation in both lungs, with certain lesions exhibiting decreased density compared to previous scans. As a result of these positive developments, the patient's treatment with caffeic acid tablets was discontinued, and he was subsequently discharged from the hospital.

On January 25, 2023, during a follow-up appointment, the patient's blood routine revealed a platelet count of 156×10^9/L, indicating a further improvement in platelet levels after discharge.

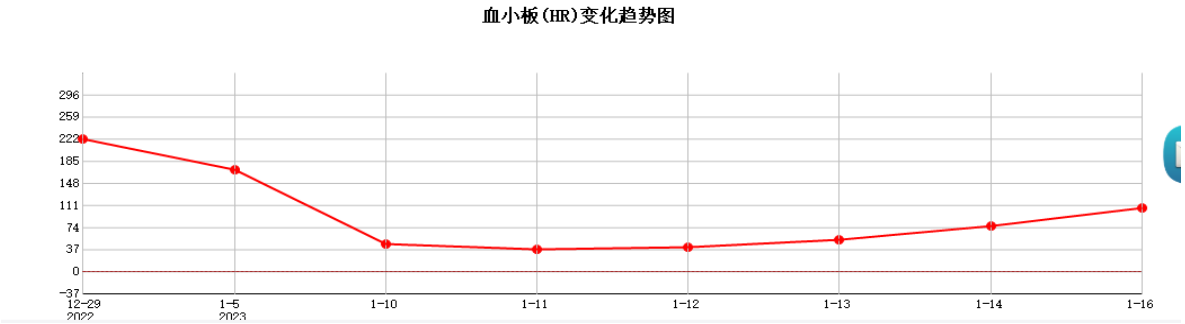

Figure 1: Platelet changes

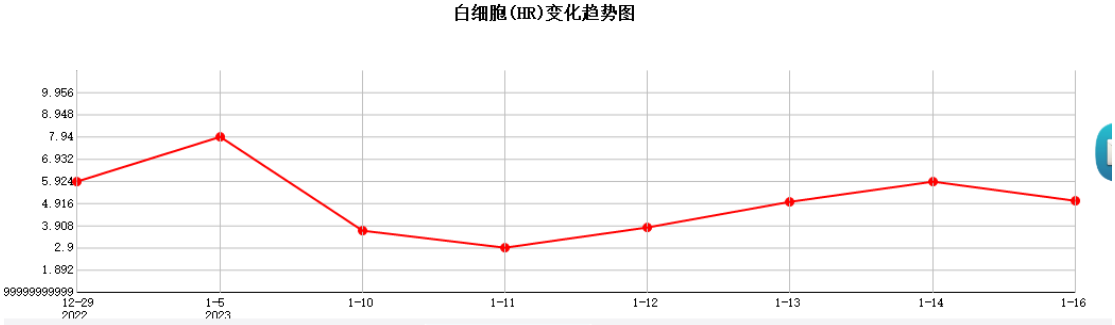

Figure 2: Changes in white blood cells

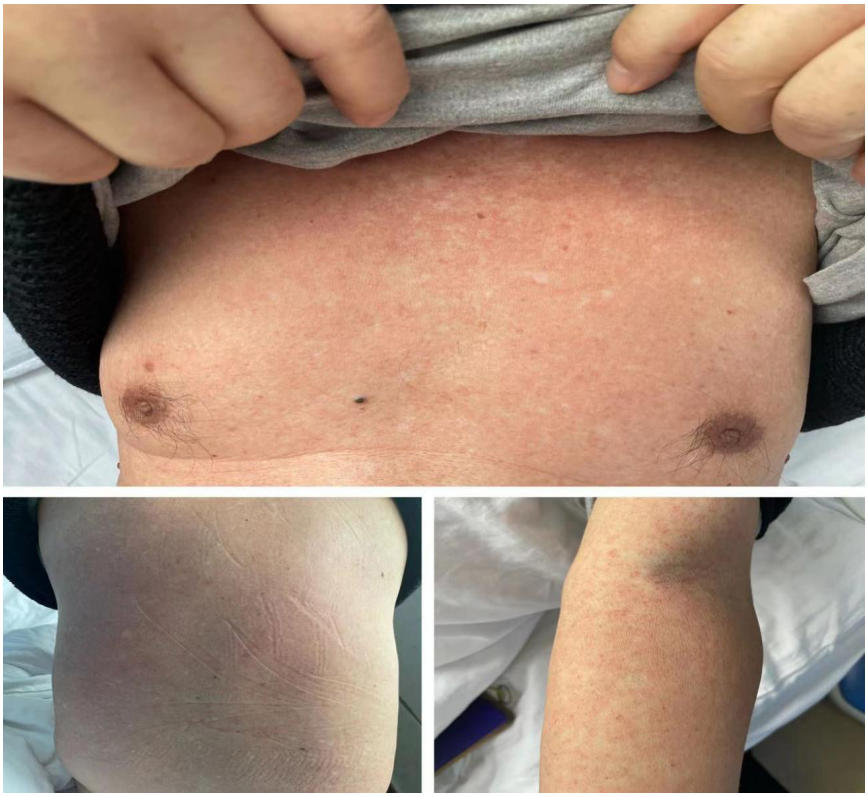

Figure 3 Rash situation of the patient

Discussion

This case report presents an elderly man who developed severe bone marrow suppression following the administration of Piperacillin/Tazobactam. The predominant manifestations included thrombocytopenia, accompanied by leukopenia and allergic skin reactions. Notably, the patient experienced severe thrombocytopenia on the 14th day of Piperacillin/Tazobactam treatment, followed by the onset of allergic skin reactions on the 15th day. Discontinuation of Piperacillin/Tazobactam and the introduction of anti-allergic medications led to significant improvements in both bone marrow suppression and skin reactions.

Throughout the treatment course, both dexamethasone and esomeprazole were administered, and it's noteworthy that neither of these medications showed any indications of adverse reactions related to bone marrow suppression in their respective instructions or within existing literature reports. Simultaneously, due to the patient's positive novel coronavirus antibody status, we advised oral intake of Maxing Shigan Decoction, a traditional and well-established Chinese herbal prescription containing ephedra, almond, gypsum, and licorice. Notably, our review of research reports on the application of Maxing Shigan Decoction did not reveal any hematological-related adverse reactions [7,8].

It's important to highlight that bone marrow suppression resulting from the use of Piperacillin/Tazobactam is a rare and severe adverse reaction, with reports indicating that such adverse events typically manifest between days 11 and 17 of treatment [4]. The most commonly observed hematological abnormality in these cases is a reduction in both neutrophils and platelets [9]. As of now, there is a paucity of research investigating the precise mechanisms underlying bone marrow suppression triggered by Piperacillin/Tazobactam. Nonetheless, some studies have proposed a positive correlation between the cumulative dose of Piperacillin/Tazobactam and bone marrow toxicity [10], with higher dosages and longer durations of treatment increasing the likelihood of hematological adverse reactions. It is pertinent to note that thrombocytopenia may arise from either bone marrow suppression or immune-mediated platelet destruction [6]. The patient received dexamethasone intervention during the early stages of treatment, resulting in a gradual decrease in platelet counts and an upward trend in white blood cell counts. Following the discontinuation of dexamethasone, platelet and white blood cell counts experienced a sudden decrease, accompanied by the onset of allergic skin reactions. These observations indirectly hint at the possibility of immune-mediated bone marrow suppression.

Therefore, in clinical application of Piperacillin/Tazobactam, especially in patients with high-dose and long-term use, it is necessary to closely monitor hematological related indicators and be vigilant for the occurrence of bone marrow suppression.

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