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CASE REPORT

Life-Threatening Neutropenia

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ABSTRACT

We report a 57-year-old male who was admitted to the hospital with mediastinal mass which was diagnosed as a case of mediastinal abscess. Patient was started on piperacillin/tazobactam 4.5 g IV every 8 hours; plus thoracotomy and abscess drainage. On the 25th day the patient developed leucopenia, the total leukocyte count (TLC) was 1900/µl with 0% neutrophils, 87% lymphocytes and 5% eosinophils; monocyte 8%, absolute neutrophilic count (ANC) was zero, while haemoglobin and platelets remained unchanged. Suspecting antibiotic-induced neutropenia, piperacillin/tazobactam was stopped and bone marrow examination was done, which showed arrest of maturation of the granulocyte series with normal other component. Neupogen granulocyte stimulating factor (GCSF), 300 µg, subcutaneously once daily was started and the patient was transferred for reverse isolation. Neutrophils count started to rise and it reached 4200/µl on the fourth day.

Key words: piperacillin/tazobactam, neutropenia, Mediastinal Abscess

Introduction

Tazocin is an injectable antibacterial combination consisting of the semisynthetic antibiotic piperacillin sodium and the ß-lactamase inhibitor tazobactam sodium. Piperacillin exerts bactericidal activity by inhibiting septum formation and cell wall synthesis. In vitro, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. Tazobactam, in combination with piperacillin, enhances and extends the antibiotic spectrum of piperacillin to include β-lactamase producing bacteria normally resistant to piperacillin.

As a complication, bleeding manifestation or significant leukopenia following prolonged administration has occurred in some patients receiving β-lactam antibiotics, but it is rare. We report a 57-year-old male who developed leucopenia with (ANC) of zero, after prolonged treatment with tazocin.

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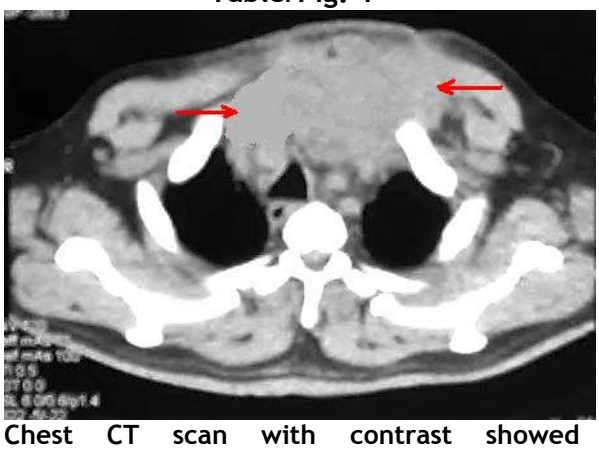
Case Report

A 57-year-old male was admitted to the hospital with a medical problem dated back to 3 months when he had fever and left-side chest pain with swelling and redness diagnosed as a case of mediastinal abscess, thoracotomy and drainage done to him.

Two weeks before admission to our hospital, the patient started to have the same problem again. Chest X-ray showed sternotomy with bilateral basal atelactetic opacities with adjacent elevation of both hemi-diaphragms. Chest CT scan with contrast showed inflammatory process in the upper mediastinum and left sternoclavicular joint and first and second sternocostal junctions with high suspicion of osteomyelitis [Table/Fig 1].

Table/Fig. 1



Chest CT scan with contrast showed inflammatory process in the upper mediastinum and left sternoclavicular joint and first and second sternocostal junctions with high suspicion of osteomyelitis.

Initial investigations showed a haemoglobin level of 11.1 g/dl; total leukocyte count (TLC) of 5600/µl with neutrophil of 61%, lymphocyte of 24%, eosinophil of 7%, monocyte of 8% and absolute neutrophil count (ANC) of 3000/µl; and platelet count of 246,000/µL. HIV serology was negative. The patient was started on piperacillin/tazobactam 4.5 g IV every 8 hours; paracetamol tablets were given on PRN bases.

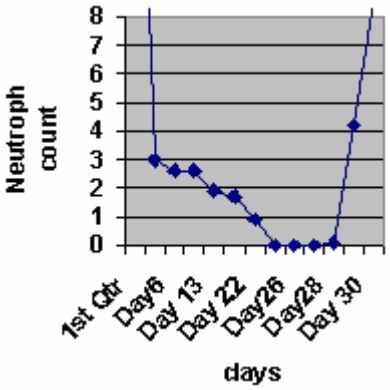
On the following day the fever subsided, chest pain decreased and he was kept on the same antibiotic while paracetamol was stopped. Twelve days later, the WBC started to decrease and his WBC was 4300 µ/l. ANC dropped to 1.7/µl; thus we order for daily CBC to monitor neutrophil.

On the 25th day the patient developed leucopenia, the TLC was 1900/µl with 0% neutrophils, 87% lymphocytes and 5% eosinophils; monocyte 8% ANC was zero [Table/Fig 2], while haemoglobin and platelets remained unchanged. The blood cell count was checked by automated blood cell counter and then rechecked manually.

Suspecting antibiotic-induced neutropenia, pipracillin/tazobactam was stopped and bone marrow examination was done, which showed arrest of maturation of the granulocyte series with normal other component.

Neupogen granulocyte stimulating factor (G-CSF), 300 µg, was subcutaneously OD started and the patient was transferred for reverse

Table/Fig. 2



Absolute Neutrophil Count during hospitalisation.

isolation with reverse isolation diet. Neutrophil count started to rise and it reached 4200/µl on the fourth day, but the patient restarted to have fever again with swelling and redness in the same site and started to reaccumulate again, subjected to surgery, which revealed a large mediastinal abscess 6–7 cm in dimension. Culture of drained materials grew *Staphylococcus aureus*. Histopathology showed just necrotic material with acute inflammatory cells, no granuloma or malignant cells were seen.

Discussion

Piperacillin/tazobactam is a β-lactam/β-lactamase inhibitor combination with a broad spectrum of antibacterial activity against most gram-positive and gram-negative aerobic and anaerobic bacteria. Piperacillin/tazobactam is effective and well tolerated in patients with lower respiratory tract infections, intra-abdominal infections, skin and soft-tissue infections and febrile neutropenia [1].

Combining tazobactam, a β-lactamase inhibitor, with the ureidopenicillin, piperacillin, successfully restores the activity of piperacillin against β-lactamase-producing bacteria. Tazobactam has inhibitory activity and therefore protects piperacillin against Richmond and Sykes types II–V β-lactamases, staphylococcal penicillinase and extended-spectrum β-lactamases [2].

It is known that adverse effects include hypersensitivity reactions, neurotoxicity, hepatotoxicity, diarrhoea, electrolyte and acid–base disturbances, bleeding disorders,

neutropenia and thrombocytopenia and rarely haemolytic anaemia [3]. Leucopenia is an uncommon but serious adverse effect of piperacillin and other β-lactam antibiotics. There have been several previous reports of leucopenia and bone marrow suppression following the use of piperacillin [4],[5] and piperacillin/ tazobactam [6],[7],[8]. This bone marrow suppression is usually reversible, recovers with discontinuation of the drug and is possibly related to direct toxicity to myeloid precursors [9]. Large cumulative doses are needed and neutropenia rarely develops before 10 days of therapy [9],[10].

Our patient developed neutropenia 25 days after the start of piperacillin/tazobactam. In previous reports, neutropenia has been reported to occur 11–17 days after the therapy was begun [6],[7]. Also bone marrow suppression occurred in patients who had received a cumulative piperacillin/tazobactam dose of 4919 ± 1975 mg/kg [6], i.e. 4372 ± 1755 mg/kg, body weight of piperacillin. Our patient had received piperacillin/tazobactam in a dose of 13.5 g/day, with a cumulative piperacillin dose of 3000 mg/kg body weights, which falls within the suppressive range mentioned above.

The diagnosis of bone marrow suppression due to piperacillin/tazobactam in this patient is supported by many facts: First, the patient was not receiving any medications except piperacillin/tazobactam, when bone marrow suppression was noticed. Second, the neutrophil counts returned towards normal within few days after discontinuation of the antibiotic and initiation of Neupogen (Filgrastim). Thus, bone marrow suppression, especially neutropenia, is a serious adverse effect of piperacillin/tazobactam, which should be kept in mind while treating patients with this drug, especially in patients who received a high cumulative dose.

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