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Case Report- Daptomycin Induced Pancytopenia and Review of Literature

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ABSTARCT

Pancytopenia is defined as a decrease in all three peripheral blood cell lines. A myriad of medications can cause pancytopenia. Daptomycin is a bactericidal antibiotic commonly used against gram-positive bacteria and has been increasingly used in treating Methicillin Staph aureus (MRSA). We present a case report of a 61-year-old male who was started on Daptomycin due to a soft tissue infection and subsequently developed pancytopenia. Pancytopenia did not initially improve by stopping the antibiotic or with colony-stimulating agents. However, blood counts did respond to trial of steroids, indicating a possible immune-mediated mechanism. This case report explores a rare, and possibly, novel adverse reaction to a commonly used antibiotic. Isolated reports of neutropenia and thrombocytopenia have been reported, but to our knowledge, this is the first case of Daptomycin-induced pancytopenia in the literature.

Key Words: Daptomycin, Pancytopenia, Adverse Drug Reaction, Skin and Soft-Tissue Infections- SSTIs

INTRODUCTION

Daptomycin is a bactericidal lipopeptide antimicrobial with activity against methicillin and vancomycin-resistant strains. [1] It is 90-93% protein bound and is primarily excreted unchanged in urine, about 78%. The half-life of Daptomycin is 8-9 hours in patients with normal renal function. Daptomycin has known side effects of rash, pruritis, headache, Clostridioides difficile diarrhea, elevated transaminases, eosinophilic pneumonia, nephritis, myopathy, rhabdomyolysis, and neuropathy. Daptomycin causes rare side effects, such as a decrease in blood counts. [2]Our case highlights an example where Daptomycin caused Pancytopenia in a patient treated for a soft tissue infection. The pancytopenia developed within a week of drug initiation and responded to steroids.

CASE PRESENTATION

Sixty-one years old male with a past medical history of dementia, hypertension, diabetes, peripheral arterial disease, tonsil cancer with dysphagia post-PEG tube placement [finished chemoradiation 7 months before admission], right below knee amputation nine years ago for midfoot osteomyelitis, left trans-metatarsal amputation, alcohol abuse came to the emergency room with left foot pain. The patient had concerns for left foot drainage. On exam, the patient had full-thickness ulceration of the plantar aspect of the prior trans metatarsal amputation stump measuring 1 x 1 cm x 7 cm on probing. Peri wound skin was atrophic. Thickened necrotic and purulent drainage was noted with significant associated malodor. The patient was evaluated by infectious disease and podiatry, bedside incision and debridement was done, and broad-spectrum antibiotics were started. Labs were significant for C-reactive protein of 221.3 mg/dl, Erythrocyte sedimentation rate of 57 mm/hr, and white blood cells of 13 k/µl. Podiatry recommended wound care and dressing changes for the foot. Bone biopsy cultures showed Methicillin-resistant Staphylococcus aureus (MRSA) light growth, and the patient was switched to Daptomycin. On this admission, the patient was also noted to have black stools and anemia, and hemoglobin was down to 5.1gm/dl. Gastroenterology was consulted, the patient was transfused, and esophagogastroduodenoscopy with push enteroscopy was done. The patient was found to have duodenal erosions and jejunal erosions; hemo-clips were applied, and pantoprazole was started. ID recommended discharge on Daptomycin at dose of 6mg/kg/day for four weeks and weekly complete blood count to monitor labs. At discharge, the patient had hemoglobin of 7.9 gm/dl, white count of 6.3 k/µl, and platelet count of 108 k/µl. During this hospitalization patient received total of 4 days of daptomycin in hospital.

Eight days later, the patient was sent back from an extended care facility due to fever and abnormal labs. The patient had a fever of 101.7 F. At this time, he was noted to have Hemoglobin of 3.5 gm/dl, WBC 2 k/µl, creatinine 1.5, and platelet count of 16 k/µl. Differentials included sepsis induced bone marrow suppression, drug induced pancytopenia. Gastrointestinal bleed with Hemoglobin drop was also considered given recent bleed but patient had no evidence of active bleeding. Stool occult blood was negative. Patient's repeat blood cultures were negative. The patient refused a bone marrow biopsy.

The patient's antibiotic was switched to Ceftaroline on Day 9. The patient had a response to antibiotics, and the fever resolved within 24-48 hours; however, blood counts failed to respond despite improving infection. The patient was then switched to Doxycycline on day 12. With oncology approval, the patient was started on Granulocyte-Colony stimulating factors to increase the blood counts on Day 10. 2 doses of Granulocyte stimulating factors failed to increase the WBC and ANC. The patient was then started on methylprednisolone on Day 13 due to thoughts of the agranulocytosis being immune-mediated secondary to Daptomycin. Within three days of the steroid use, the patient's WBC, platelets, and ANC started responding **(Table-1)**. The patient had a significant response to steroids, indicating possible immune-mediated pancytopenia **(Figure 1, 2, 3)**. As per the Naranjo algorithm, the patient had a score of 7, indicating a probable adverse drug reaction by Daptomycin. The patient was discharged on 1 month course of Doxycycline and advised to follow up in the clinic.

DATE	HEMOGLOBIN (gm/dl)	PLATELETS (k/µl)	WHITE CELL COUNT (k/µl)	TEMPERATURE (F)
DAY 1	7.9	108	6.3	98.9
DAY 9	3.5	16	0.4	101.6
DAY 10	6	17	0.2	100.4
DAY 12	7.9	11	0.4	99.5
DAY 13	6.8	4	0.4	99.3
DAY 15	7.1	15	0.5	99.8
DAY 17	6.5	11	0.5	99.7
DAY 19	7.4	17	1	98.9
DAY 21	8.1	38	2.1	98.6
DAY 23	8.1	74	2.8	98.4
DAY 25	8.2	122	2.7	98.6

DATE HEMOGLOBIN

Table 1- Trends of blood cell counts with Daptomycin use. Day 1 represents initial blood counts when patient was discharged on Daptomycin. Day 9 represents readmission in the hospital with pancytopenia. Day 10 represents the initiation of Neupogen. Day 13 represents the initiation of methylprednisolone.

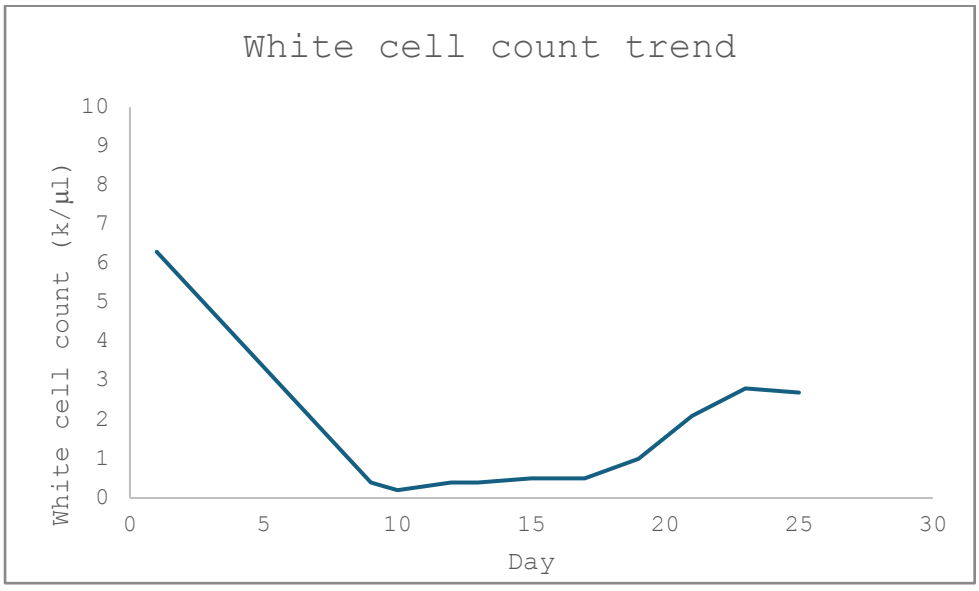

Figure 1 Graph showing White cell count trend

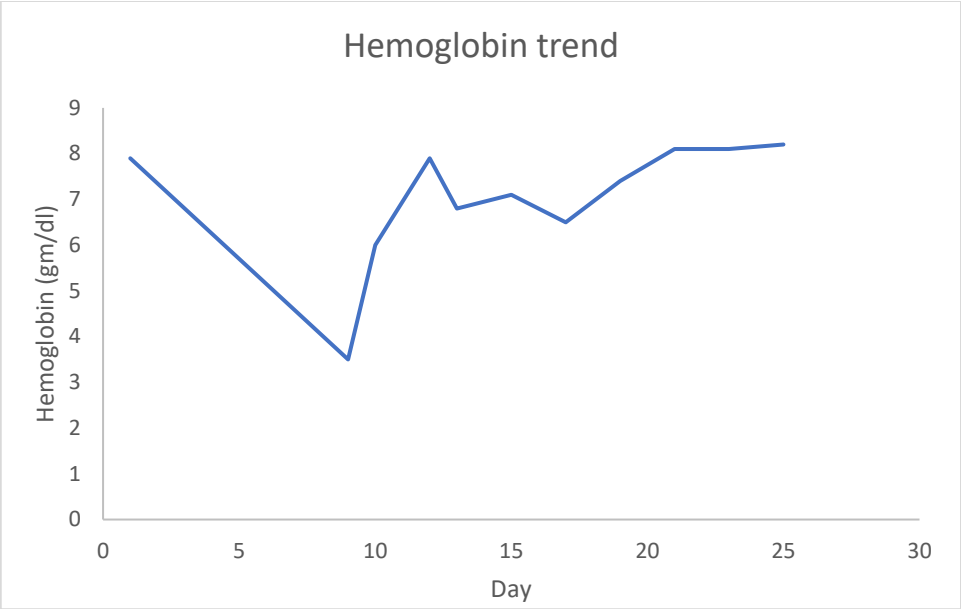

Figure 2 Graph showing Hemoglobin trend

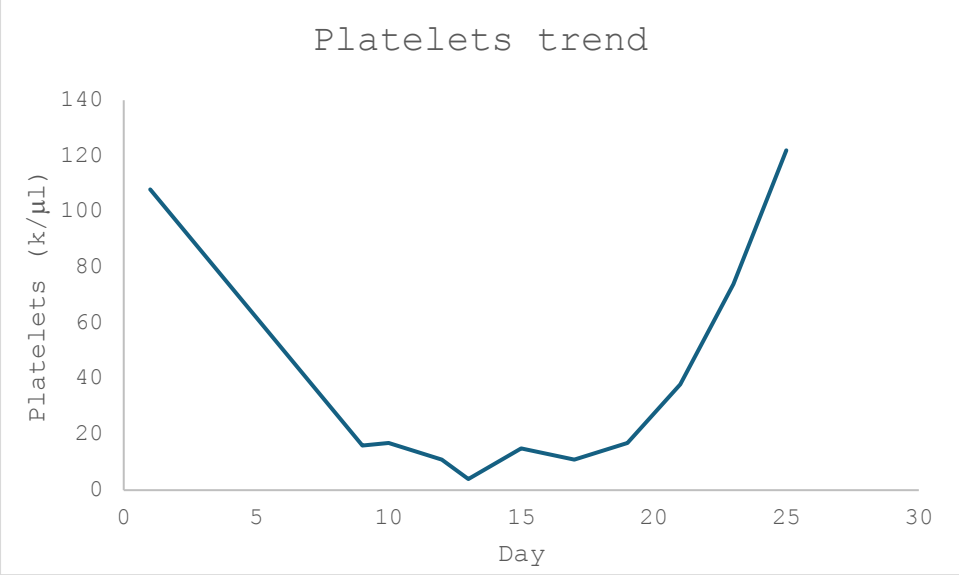

Figure 3 Graph showing Platelet trend

DISCUSSION

Daptomycin is a lipopeptide antibiotic with rapid bactericidal activity against gram- positive bacteria including Staphylococcus, enterococci and streptococci. Daptomycin shows marked in vitro cidality against Methicillin-Resistant Staph Aureus when compared to linezolid and Vancomycin [2]. Daptomycin approval for the treatment of complicated skin and soft-tissue infections (SSTIs) caused by Gram-positive bacteria was gained in 2003, with European approval in January 2006.

Daptomycin affects bacteria by affecting permeabilization and depolarization of the bacterial cell membrane, which can account for Daptomycin's bactericidal effect, correlating with the level of phosphatidylglycerol (PG)

in the membrane. Some studies suggest that Daptomycin might interfere with cell wall synthesis or cell division [3].

FDA-approved clinical use in skin and soft tissue infections, right-sided infective endocarditis, and Staph aureus bacteremia in adult and pediatric patients 1 to 17 years. Daptomycin causes side effects such as diarrhea, stomach pain, injection site pain and redness, dizziness, headache, hives. It is also associated with an increased incidence of myopathy and rhabdomyolysis [4]. Eosinophilic pneumonia (EP) has been noted in association with Daptomycin use [5,6] .

So far, no case of Daptomycin-induced Pancytopenia has been reported in the literature. We reviewed cases in Pumed and Medline and came across isolated studies of thrombocytopenia and neutropenia caused by Daptomycin. We found one case report of Daptomycin induced thrombocytopenia and neutropenia in patient treated for endocarditis by Leyra et al. developing around 5-6 weeks with high dose Daptomycin of 10mg/kg/day [7]. From a case report from Knoll et al. prolonged use of Daptomycin caused isolated neutropenia in a female with B cell non-Hodgkin lymphoma with MRSA bacteremia complicated by MRSA septic arthritis of the sternoclavicular joint during her chemotherapy. She was treated with Daptomycin with dose of 6mg/kg/day and neutropenia was noted in 10 weeks. Neutropenia resolved 1 week after discontinuation of Daptomycin [8]. Another article on Thrombocytopenia, INR prolongation and fall in fibrinogen levels was reported in 2013 by Hartmann et al. where Daptomycin was given for polymicrobial abdominal abscess at dose 6mg/kg/day and rapid development of thrombocytopenia was noted within 1 week [9]. A study by Lancaster et al. showed rapidly developing neutropenia with Daptomycin. Patient received Daptomycin at dose of 6mg/kg iv for enterococcus faecium, patient experienced profound neutropenia in under 2 weeks reaching 1.63k/mul [10]. Grégoire et al. showed Daptomycin induced immune thrombocytopenia where serum antibodies were found to be bound to platelets in the presence of Daptomycin on flow cytometry [11].

Our case report is unique as the patient had a drop in all three cell lines with Daptomycin exposure. The patient developed the reaction at a low dose of Daptomycin of 6mg/kg/day and developed the reaction within a week of drug exposure. Our patient with a score of 7 on the Naranjo algorithm suggested a Probable Adverse Drug reaction [12]. The total score comes from 1 point each from previous conclusive reports on this reaction, adverse drug reaction occurring after the drug exposure, and improvement after the drug discontinuation and steroid use. All the alternative causes were ruled out, which could cause a similar response, giving an extra 2 points towards the total score. The alternative causes included worsening infection since blood cultures were negative; gastrointestinal bleeding since occult blood was negative. Compared to the data in the literature, our case had a rapidly developing reaction developing within seven to eight days of drug exposure. Our case was also unique as the patient did respond to corticosteroids, which were not attempted in the past.

CONCLUSION

Our case report adds to the scarce literature of Daptomycin- induced cytopenias and highlights the need to increase research in the field. The mechanism of pancytopenia is currently unknown based on low research data in this field; however, response to steroids indicates possible immune mediated reaction due to the drug. Periodic hematological testing is advised to monitor for this adverse drug reaction.

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