CASE REPORT

Meropenem Induced Severe Thrombocytopenia in an Adult Patient: A Case Report

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Abstract:

Drug induced immune thrombocytopenia is a serious life-threatening clinical condition, the diagnosis of which is often very difficult, and mainly performed on clinical criteria and rarely on confirmatory laboratory tests. A 52-year-old male, post Covid-19 patient, admitted to the hospital for the management of severe vomiting and abdominal pain, developed sepsis, and started with meropenem as an empirical anti-microbial agent. After two days of therapy, the patient presented with severe oral gingival bleeding, thrombocytopenic purpura, and severe thrombocytopenia, which was also accompanied by lymphopenia in the patient. The clinical significance of this case encouraged us to report this rare complication of meropenem. The health-care professionals and caretakers should be aware of this adverse drug reaction so that it can be promptly diagnosed and managed.

Keywords: Meropenem, Thrombocytopenia, Lymphopenia, Adverse Drug Reaction

Introduction:

Meropenem is a broad-spectrum bactericidal anti-microbial agent with activity against both Gram-positive and Gram-negative organisms, including Extended-spectrum beta-lactamase-producing Gram-negative rods [1]. Meropenem is used against susceptible organisms in sepsis, bacterial meningitis, febrile neutropenia, complicated urinary tract infections, severe community-acquired pneumonia, intra-abdominal infection, etc. [2-3]. The most common adverse effects of meropenem are diarrhea, nausea, vomiting, headache, rash and thrombophlebitis [4]. Leucopenia, neutropenia and pancytopenia are the rare adverse effects associated with meropenem (<1%). Moreover, meropenem is also known to cause immune hemolytic anemia in some cases [3]. Meropenem involvement in causing thrombocytopenia and leucopenia are rarely reported.

Case Report:

A 52-year-old male, post Covid-19 pneumonia (1 month back), came to the Emergency Medicine Department (EMD) with complaints of severe vomiting, abdominal pain, and hematuria of one day's duration. He was a known case of diabetes during the previous eight years, hypertension during the previous ten years, ischemic heart disease during the previous six years, and acute kidney injury with a history of hemodialysis only once a week for the last year. Pantoprazole 40mg, ondansetron 4 mg, nor-adrenaline according to blood pressure, and rapid-acting insulin as per blood sugar levels were given in the EMD before the patient was shifted to Intensive Care Unit (ICU) for further investigations. On day 5 of ICU management, the patient developed sudden fever spikes, and a rapid antigen test for Covid-19 was performed, which came negative. Blood culture was sent to rule out sepsis, and intravenous meropenem 1g stat dose, followed by 0.5g every 8

hours was initiated empirically, as per Creatinine Clearance (CrCl: 34 ml/min). Serum inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) were significantly increased. Procalcitonin was found to be 11.14 ng/ml (normal <0.05 ng/ml), which indicated severe sepsis. On day 7, two days of meropenem therapy, the patient presented with severe gum bleeding and thrombocytopenic purpura over the bilateral elbows and left forearm; complete blood count report showed severe thrombocytopenia, with platelet counts of 22,000/µl, declined from the baseline of 135,000/µl (before meropenem initiation). On day 8, the blood culture report showed growth of Gram-negative bacteria *Providencia rettgeri*, which was sensitive to meropenem. Hence, meropenem was continued. The same day, platelet counts declined further to 16,000/µl, for which the patient managed with six units of Random Donor Platelets (RDPs) and one Packed Cell Volume (PCV).

Total Leucocyte Count (TLC) also fell abruptly to 3600/mm^3 from the baseline of 57,400/mm^3 (before meropenem administration). Differential TLCs showed an Absolute Lymphocyte Count (ALC) of 360/mm^3, but Absolute Neutrophils Count (ANC) were normal, with a value of 3132/mm^3. The patient had also developed herpes labialis infection during this phase, with lesions over the lower and left upper lip, which might be attributed to acute lymphocytopenia in this patient. Drug-Induced Immune Thrombocytopenia (DITP) due to meropenem and sepsis-induced thrombocytopenia was suspected at this point, and meropenem was immediately discontinued. As the patient was still in severe sepsis and his clinical deterioration continued, meropenem was switched to piperacillin/ tazobactam 4.5 g every 8 hours. On day 9, the platelet count increased to 66,000/µl. On ruling out other causes and stopping meropenem therapy, the platelet count showed an increasing trend and returned to normal by day 18 of the hospital stay. At that time, the patient was relatively in good health and was discharged from the hospital. The changes in platelet and TLCs during the hospital stay are shown in Figs. 1 and 2.

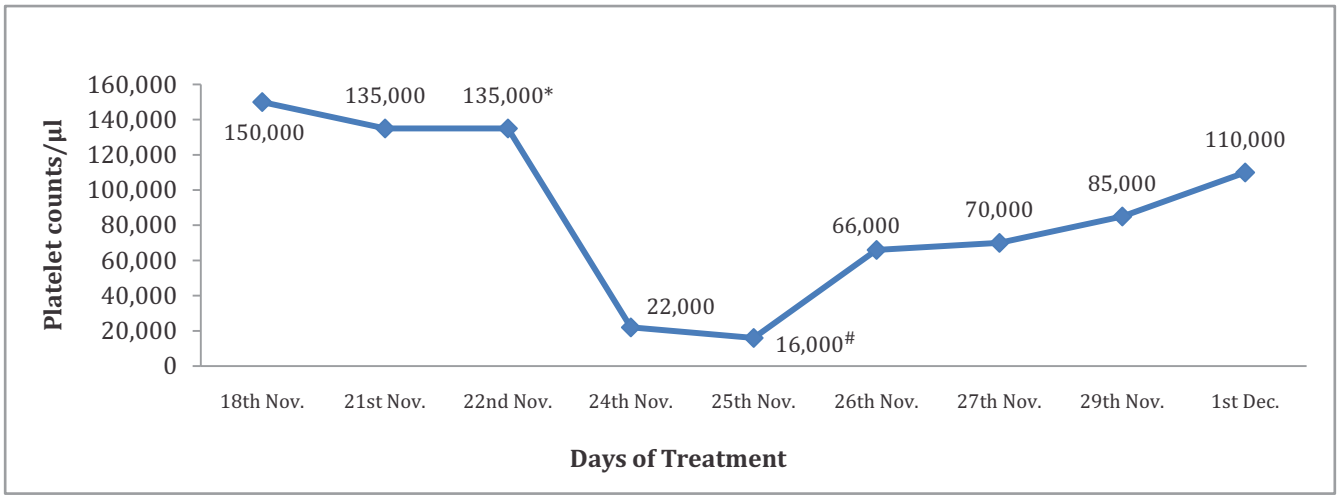

Fig. 1: Trend of Platelet Counts of the Patient during Course of Treatment

*Meropenem treatment started, #Meropenem treatment stopped

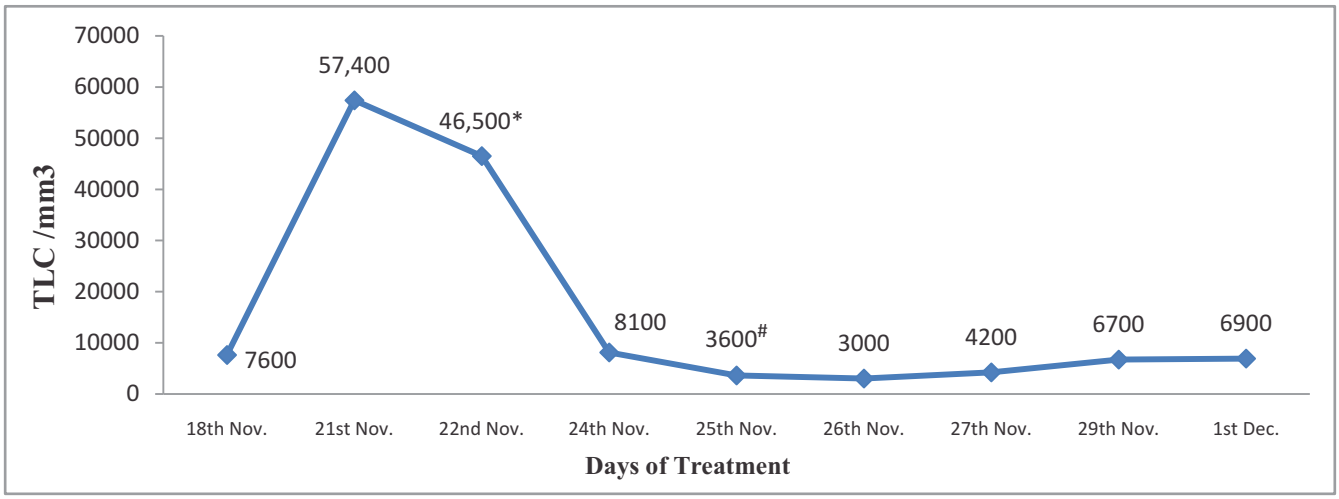

Fig. 2: Trend of TLCs of the Patient during the Course of Treatment
*Meropenem treatment started, #Meropenem treatment stopped

Discussion:

Drug-induced immune thrombocytopenia is considered in patients with decreased platelet counts within one week of drug exposure, and in some cases, within hours of exposure [5]. Platelet counts <150,000/µl is considered thrombocytopenia in adults. Leucopenia is a TLC of <4000/mm^3, and lymphocytopenia results when ALC are <1000/mm^3 in differential TLC counts [6]. Several drugs have been known to cause thrombocytopenia like heparin, Beta-lactam antibiotics (penicillin, cephalosporin), sulfonamides, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), anticonvulsants, rifampicin, etc. by DITP mechanisms [5].

Hematological adverse effects of meropenem have been reported in post-marketing surveillance [7]. Few studies have shown meropenem association in causing thrombocytopenia [3, 4, 8]. One of the studies have confirmed the association of meropenem in causing this adverse effects by identifying antiplatelet antibodies, which were present in patient serum only when meropenem was administered to the patient [4]. Leucopenia is also a known effect of meropenem [7]. Till date, to the best of our knowledge, there is no case report which has described thrombocytopenia in a patient undergoing meropenem therapy accompanying lymphopenia in an adult. In this case report, we have described a patient who suffered from nosocomial infection on day 5 of ICU management. The patient was stabilized on treatment, and no other adverse effects were seen until meropenem started. The sudden drop in TLCs within 4 days accompanying oral bleeding inclined us to suspect meropenem as a probable causative agent.

Although the severe thrombocytopenia in this patient might have been attributed to severe sepsis, his platelet counts despite being septic, showed an increasing trend when meropenem was stopped. Other drugs which were going concomitantly (pantoprazole, ondansetron, febuxostat, dexamethasone, and furosemide) might have caused this event. However, the probability of causing this

Table 1: Criteria for Evaluating Causal Relationship between Drug and Thrombocytopenia [9]

Suspected drug administration preceded thrombocytopenia. Complete and sustained resolution of thrombocytopenia after suspected drug discontinued.	✓
Platelet count remained normal after discontinuation of suspected drug, despite the resumption or continuation of other drugs.	✓
Alternative etiologies of thrombocytopenia were excluded.	✓
Re-exposure to the suspected drug was followed by thrombocytopenia.	×

event was more in support of meropenem as per literature [3, 4, 8], and Adverse Drug Reaction (ADR), only subsided after the cessation of meropenem and no other drugs. This event met 3 out of 4 criteria of drug-induced thrombocytopenia outlined by James *et al*. illustrating it as a probable cause (Table 1) [9]. Causality assessment was performed using the World Health Organization (WHO) and Naranjo ADR assessment scale [10-11]. On Naranjo's scale, this case scored 6 out of possible 13 points, where a score in between 5 to 8 is equated with a "Probable" association that his thrombocytopenia is due to an ADR. Likewise, the WHO scale also indicated the probable relationship between the suspecting agent and ADR occurred. The thrombocytopenic purpura and counter management with the RDPs and PCV characterized this reaction as a serious adverse drug event. The patient also suffered lymphocytopenia, which might be the cause of herpes labialis infection after starting meropenem therapy; all these complications collectively prolonged the hospital stay of the patient and overall cost of the treatment. The diagnosis of DITP is often made empirically, the suspecting agent is stopped, and recovery from the adverse effect is seen to confirm a DITP. In this case, no re-challenge of the drug was done. The patient was stopped on meropenem therapy on day 4 of its administration, and an alternative anti-microbial agent was started, platelet count showed an increasing trend, and TLCs also began to normalize.

Conclusion:

Drug-induced immune thrombocytopenia can be a serious clinical condition that should be considered in patients undergoing meropenem therapy. Prompt diagnosis and stopping the suspecting agent can improve the prognosis and prevent the patient from being exposed to the same drug in the future.

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