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MEROPENEM INDUCED THROMBOCYTOSIS - A RARE ADVERSE DRUG REACTION

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ABSTRACT: Thrombocytosis is defined as platelet count greater than 400, 000/mm^3. Thrombocytosis can be either primary or secondary. Meropenem is a parenteral carbapenem antibiotic that has great bactericidal activity against almost all significant aerobes and anaerobes. Common adverse effects such as pain at the injection site, skin rash, transitory metabolic disorders such as increased liver enzyme levels, increased creatinine blood levels, or increased urea levels, or hematological disorders (thrombocytosis, eosinophilia) may be observed. Thrombocytosis due to Meropenem is relatively rare and here we report one such case of Meropenem induced thrombocytosis in a 26-year-old patient post cesarean delivery. A 26-year-old primigravida with 38 weeks gestation presented in labour for four hours. Her investigations revealed hemoglobin of 10.3, deranged LFT and thrombocytopenia. A provisional diagnosis of primigravida with 38 weeks gestation with Fetal Growth Restrictionwith jaundice, thrombocytopenia (TTP) in latent phase of labour was made. Later, the patient was taken up for emergency caesarean in view of fetal distress. Postoperatively the patient was given injectable ceftriaxone and metronidazole. Patient developed high grade fever (101 -103 F) on day 4 for which sepsis screen was done. Vaginal swab culture showed growth of *Klebsiella pneumoniae* which was sensitive to meropenem. Meropenem was started. A repeat complete blood count on postop day 5 revealed moderate anemia with thrombocytosis. It was observed that the patient's general condition improved and fever resolved after 4 days of antibiotics but the platelet count peaked to 1400×1000/mm3 by POD9. In view of improved general condition of patient a possibility of reactionary drug induced thrombocytosis was considered and the decision to stop meropenem was made. As soon as meropenem was stopped the platelet count gradually dropped to 1000×1000/cumm by post op day 13.On her next visit her platelet count showed reducing trend and became normal within few weeks.

INTRODUCTION: Thrombocytosis is defined as platelet count greater than 400, 000/mm^3 [1]. Thrombocytosis can be either primary or secondary.

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Many drugs have been implicated in causing secondary thrombocytosis like low molecular weight heparin, all-trans-retinoic acid, antibiotics, clozapine, epinephrine, gemcitabine, and vinca alkaloids [2].

Carbapenems are parenteral bactericidal β-lactam antibiotics that have an extremely broad spectrum anti-microbial coverage. Carbapenems (imipenem, meropenem, doripenem and etrapenem) are an important class of antibiotics for infections due to community-acquired or nosocomial aerobic and

anaerobic organisms, especially the extended-spectrum beta-lactamase producing Entero-bacteriaceae [3]. Meropenem is a parenteral carbapenem antibiotic that has great bactericidal activity against almost all significant aerobes and anaerobes. Its high activity is explained by the ease of entry into bacteria combined with a good affinity for essential penicillin-binding proteins, including those associated with cell lysis. Meropenem is less active against gram-positive cocci and is more active against gram-negative bacilli [4]. Amongst common human pathogens, only methicillin-resistant staphylococci and *Enterococcus faecium* are uniformly resistant to meropenem. Common adverse effects such as pain at the injection site, skin rash, GI side effects (nausea, vomiting, diarrhoea), or even transitory metabolic disorders such as increased liver enzyme levels, increased creatinine blood levels, or increased urea levels, or hematological disorders (thrombocytosis, eosinophilia) may be observed [3]. All the above side effects usually disappear by discontinuation of the drug. Meropenem may also cause a mild increase in alanine aminotransferase (ALT), aspartate transaminase (AST), and alkaline phosphatise [5]. Rarely, it can cause haematological changes leading to thrombocytosis, eosinophilia, and neutropenia [6]. Thrombocytosis due to Meropenem is relatively rare and here we report one such case of Meropenem induced thrombocytosis in a 26-year-old patient post cesarean delivery.

Case Summary: A 26-year-old primigravida with 38 weeks period of gestation presented to OPD in labour for four hours. The past medical or surgical history was insignificant. Her vitals were normal and general physical examination revealed pallor, icterus and facial puffiness. On Per abdomen examination uterus was 34 weeks, presentation was cephalic, mild contractions were present and fetal heart rate was 144 bpm. On per vaginal examination she was in latent phase of labour. Her investigations revealed hemoglobin of10.3, deranged LFT (serum bilirubin -2.36mg/dl, SGOT -112, SGPT-125, ALP-410) and thrombocytopenia (81000). The tests for viral hepatitis markers were negative. A provisional diagnosis of 26-year-old primigravida with 38 weeks gestation with Fetal Growth Restriction, with jaundice (most likely IHCP), thrombocytopenia (TTP), in latent phase of labour was made. Patient was planned for spontaneous progression of labour with continuous fetal monitoring. The patient was taken up for emergency caesarean section in view of abnormal CTG and a live male baby of 1.755 kg was delivered with APGAR of 7 and 9. Immediate postoperative period was uneventful. Postoperatively the patient was given injectable ceftriaxone 1gm 12 hrly and metronidazole 8 hourly. On post-operative day 3 she developed abdominal distension with gross ascites. Ultrasonography abdomen and pelvis showed mild liver parenchymal changes with free fluid +++ and postpartum uterus. Ascitic fluid analysis revealed low SAAG, negative for tubercular bacilli and any other growth which ruled out infective pathology. Repeat investigations on postoperative day 3, showed moderate anemia (Hb =9.3g%) and improving LFT (serum bilirubin -1.56, SGOT -59, SGPT -40, ALP -263). The ascites reduced to mild on USG on day 5. Patient started developing high grade fever (101 -103 F) on day 4 for which sepsis screen was done. Widal test, blood culture, high vaginal swab and wound culture were sent. Vaginal swab culture showed growth of *Klebsiella pneumoniae* which was sensitive to meropenem. Meropenem 500mg in 100ml infusion 8 hourly was started. A repeat complete blood count on postop day 5 revealed moderate anemia with thrombocytosis (platelet count - 460 ×1000/cumm).

It was observed that the patient's general condition improved, and fever resolved after 4 days of antibiotics, but the platelet count peaked to 1400×1000/mm3 by POD9. In view of improved general condition of patient, a possibility of reactionary drug induced thrombocytosis was considered and the decision to stop meropenem was made. Stitch removal was done on POD 10. Suture line showed gaping however there was no discharge. As soon as meropenem was stopped the platelet count gradually dropped to 1000×1000/cumm by post op day 13. The patient was discharged and advised for regular outpatient follow-up. On her next visit her platelet count showed reducing trend and became normal within few weeks.

DISCUSSION: Thrombocytosis can be primary or secondary (reactive). Essential thrombocythemia (ET), a chronic myeloproliferative disorder is characterized by clonal proliferation of

megakaryocytes, which is caused by a defect of the early pluripotent or a committed stem cell. These patients may present with both thrombotic and hemorrhagic diathesis [7]. The most frequent causes of secondary thrombocytosis were tissue damage (42%), infection (24%), malignancy (13%) and chronic inflammation (10%) [8]. Most common causes of reactive thrombocytosis are infection, surgery, blood loss, anaemia, asplenia or ruptured spleen and drug reaction. Although reactionary thrombocytopenia is a benign and self-limiting condition in most individuals, extreme thrombocytosis may sometimes lead to late thrombotic complications [9]. Secondary thrombocytosis is caused by stimulated megakaryo-poiesis. Imipenem, Carbepenam, Meropenem are known to cause megakaryopoiesis. The mechanism underlying the rise in platelet counts in patients with reactive thrombocytosis is probably mediated through the release of IL-6 and IL11. Interleukin 6 causes thrombocytosis by elevating thrombopoietin [10].

In the existing literature there were no such cases reported except for few cases of Itrapenam and Carbepenam induced thrombocytosis. In a review article by Quyen T Vo *et al* drug induced thrombocytosis was referred as a relatively rare drug adverse reaction and only 43 cases of various drug induced thrombocytosis were reported till 2019 [11]. The safety of Meropenem has been evaluated in a clinical trial program of 3187 adults and children in a range of bacterial infections including pneumonia, complicated urinary tract, intraabdominal and skin/skin structure infections, gynecological infections and meningitis [12].

A subsequent safety review by an expanded clinical trial database of 4872 patients treated intravenously or intramuscularly with Meropenem (5026 treatment exposures) was consistent with earlier findings [13]. They have stated that thrombocytosis accounts for ≥1% of adverse reactions caused by meropenem [4]. Huadongchen *et al* reported one such case of imipenem induced thrombocytosis in a 51-year-old female patient [6]. Study conducted by HL Hsu in 2001 on 53 patients and 21% patients experienced adverse events.7.5% had elevated hepatic enzymes, 3.8% had increased alkaline phosphatase and 3.8% had thrombocytosis [14]. Norrby *et al* evaluated 5000 patients on Meropenem therapy and Meropenem-related adverse events most frequently reported were diarrhoea (2.3%), rash (1.4%), nausea/vomiting (1.4%) and injection site inflammation (1.1%). On contrary thrombocytosis (1.6%) was reported to be a relatively common haematological adverse effect with Meropenem [15]. Drug induced thrombocytosis is difficult to identify and is rarely reported. Although it being a rare adverse reaction with Meropenem but should be kept in mind while evaluating one such case. Thrombocytosis can be diagnosed on clinical evidence however; the type of thrombocytosis and the cause of secondary thrombocytosis are always difficult to determine. Patients with thrombocytosis always had multiple factors contributing to their condition. In the current case, platelet count was independent of infection progression and recovery. Hence, we suggest that meropenam should be considered as a possible cause in patients with thrombocytosis.

TABLE 1: NARANJO SCORE QUESTIONNAIRE FOR A PATIENT WITH THROMBOCYTOSIS

Question	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	+1
Did the adverse events appear after the suspected drug was given?	+2	-1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	+1
Did the adverse reaction appear when the drug was read ministered?	+2	-1	0	0
Are there alternative causes (other than the drug) that could have caused the reaction?	-1	+2	0	+2
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1

Current literature regarding drug-induced thrombocytosis covers a wide variety of drugs and no pattern is evident as of yet. Some antibiotics have been implicated in the development of thrombocytosis and this was one such rare case in which it was concluded that thrombocytosis was probably induced by meropenem.

It has been reported that patients with secondary thrombocytosis did not need specific anti-platelet or platelet-lowering therapy. Unless there are additional risk factors, secondary thrombocytosis of various aetiologies, including post-splenectomy thrombocytosis, seemed not to be associated with a significant risk for haemostatic complications. Identifying the cause of secondary thrombocytosis and then treating the underlying disease is more important.

CONCLUSION: Meropenem is a broad-spectrum antibiotic with potential adverse effects. Well versed adverse effects include nausea, vomiting, rash, diarrhoea and fever. The drug can also cause reactionary thrombocytosis which is reversible on discontinuation. It is a form of thrombocytosis which cannot be easily differentiated from more common forms of thrombocytosis. Hence before arriving at a diagnosis of drug induced thrombocytosis other infective and non infective causes should be ruled out. Drug induced thrombocytosis often regresses on discontinuation of antibiotic or the offending drug which confirms the diagnosis. We suggest that clinicians need to be vigilant concerning the impact of Meropenem on the platelet count in patients with thrombocytosis. Replacement with other class antibiotics and evaluation of risk of thromboembolism should be kept in mind while treating drug induced thrombocytosis. Any patient with thrombocytosis should be assessed with a careful and detailed history of presenting illness, comorbid conditions, medications, other hematologic parameters, and past platelet counts.

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