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Case Report

Meteoric effect of meropenem: an unrevealed case report on Jarisch Herxheimer reaction

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ABSTRACT

Jarisch Herxheimer Reaction is an immune mediated, self- limited reaction that releases endotoxins from the spirochetes. It occurs due to an acute inflammatory response when lipoproteins, owing to their entry into the patient's bloodstream, cause an increase in inflammatory cytokines during the period of exacerbation, resulting in body aches, fevers, rashes, nausea and vomiting, and flushing, along with other symptoms. These symptoms usually begin within 2 hours after the administration of the antibiotics. We represent a 76-year-old male patient who has had a known case of recurrent urinary tract infections since 2017 and was recently diagnosed with urosepsis and syphilis after being administered an injection of Meropenem, wherein he developed a Jarisch Herxheimer Reaction. The causality assessment revealed a Naranjo score of 7, indicating a probable adverse drug reaction. This patient was treated with intravenous antihistamines and corticosteroids for its management. Benzathine penicillin was avoided owing to the previous suspected Jarisch Herxheimer Reaction. None of the studies reported that Meropenem could contribute to such a reaction. All healthcare professionals should maintain a high alert of suspicion and be aware of antibiotic induced Jarisch Herxheimer Reaction symptoms and their management to avoid life threatening conditions.

Keywords: Adverse drug reaction, Jarisch Herxheimer reaction, Meropenem, Syphilis, Urosepsis

INTRODUCTION

The acronym Jarisch Herxheimer reaction is defined as the Jarisch Herxheimer reaction. It is prevalent in 70-90% of cases of secondary syphilis and 10-25% of all combined cases of syphilis, primarily treated with penicillin derivatives.[1] In Lyme disease (LD), leptospirosis, and relapsing fever (RF), a similar reaction was reported after treatments with Penicillin, Tetracyclines, and Erythromycin. Newer antimicrobials such as Cephalosporins, Meropenem, Ciprofloxacin, Levofloxacin, Clarithromycin, and Azithromycin can also provoke a Jarisch Herxheimer Reaction.[2-8] The characteristic symptoms shown are fever, chills, myalgia, headache, tachycardia, hyperventilation, and mild hypotension 1-2 hours after administration of antibiotics for spirochaetal infections.[9] A Jarisch Herxheimer Reaction produces varied complications, from chills, rising temperature, and intensification of skin rash to meningitis, pulmonary failure, liver and renal dysfunction, acute respiratory distress syndrome, alterations in consciousness, myocardial injury, premature uterine contractions in pregnant patients, and worsening cerebral function, as well as strokes and seizures.[10] The Jarisch Herxheimer Reaction is self-limited, and treatment with an anti-inflammatory agent and corticosteroids (Hydrocortisone, Dexamethasone, or Prednisone orally or IV) may stop its progression. Here, we report a case of a

76 years old male patient who was administered with Injection Meropenem wherein he had developed a Jarisch Herxheimer reaction.

CASE REPORT

A 76-year-old male patient was admitted with chief complaints of poor urine output, strain in passing urine since morning, and a history of fever with chills and rigor, body ache, and dysuria for the past 2 days. He has been a known case of systemic hypertension and type 2 diabetes mellitus for the past 10 years and is on irregular treatment with tablets of Amlodipine (5 mg PO OD) and Metformin (500 mg PO BD).

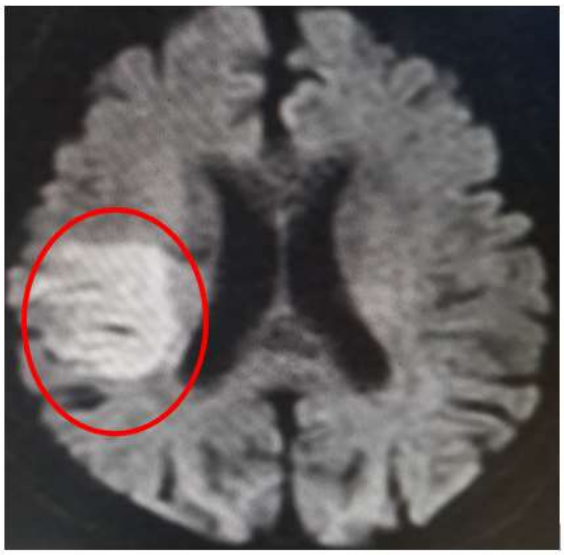

Figure 1: MRI of brain: red circled portion indicates acute infarct.

His social history revealed he had multiple sex partners and was an alcoholic. He has been admitted and treated for recurrent urinary tract infections since 2017. For acute urinary retention, the patient came to the emergency department, and on examination, he was found to have bladder distension along with respiratory distress. A 16 Foley catheter was tried on the bladder, but the attempt failed due to a stricture in the urethra. However, the patient was catheterized with a 10 French tube, and cloudy urine was drained.

Urine and blood cultures were sterile. On the day of admission, a complete blood count (CBC) was ordered, and the results revealed a decrease in platelet count of 1,34,000 cells/mm^3, and polymorphs showed a high spike of 90.6%. Liver function tests indicated hyperbilirubinemia (total bilirubin, bilirubin direct, and bilirubin indirect were respectively 2.4 mg/dl, 0.8 mg/dl, and 1.6 mg/dl). Aspartate transaminase (AST), alanine transaminase (ALT), globulin, gamma-glutamyl transferase (GGT), and Prothrombin time (PT) times were 189 mg/dl, 109 mg/dl, 3.4 g/dl, 80 U/l, and 16.5 seconds, respectively, showing elevations. Glycated hemoglobin (HbA1c) and random blood sugar (RBS) were 10.5% and 450 mg/dl. On the first day of admission (3rd March 2023), his serum potassium was 5, and on the second day (4th March 2023), it showed an elevated value of 5.5 mmol/l. Serum bicarbonate showed values of 18 and 20, which decreased from the normal range on the first and second days, respectively.

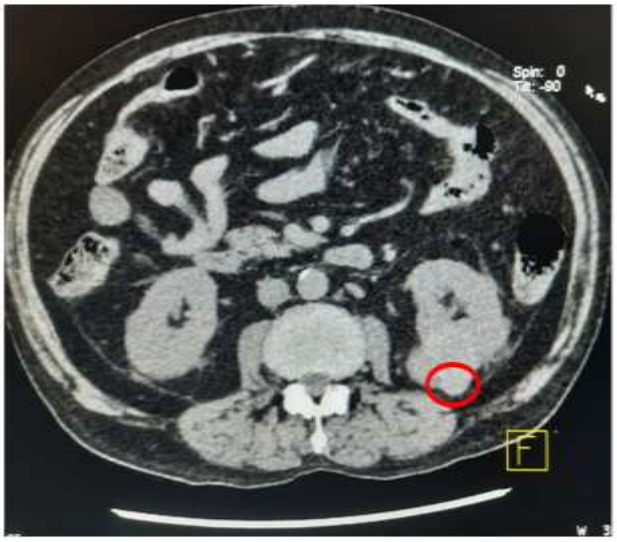

Figure 2: CT KUB- red circled portion indicates hyperdense lesion in the posterior cortex of the left kidney.

Urine analysis was undertaken, and white blood cells were found to be 10-12 high power field (hpf) along with creatinine and procalcitonin (1.8 mg/dl and 14 ng/ml, respectively), which showed high elevations and are indications of urosepsis. Since the patient was in sepsis and had low saturation with severe tachycardia, he had been shifted to the ICU, where he was on ventilator support. The patient had been shifted to a room with stable vitals. He was treated with a high dose of Meropenem injection (1g IV TID) for urosepsis, wherein he developed skin rashes with severe chills and bronchospasm. Injection Pheniramine 1 ampule IV BD, injection Hydrocortisone 100 mg IV QID, and injection Dexamethasone 4 mg IV OD were given for its treatment. Owing to his previous sexual activity, the physician suspected that he might have a sexually transmitted disease. A treponema pallidum hemagglutination assay (TPHA) was done, and the results also became positive, along with HIV I and II showing negative results. Injections of Meropenem continued along with injections of Doxycycline 100 mg IV BD. After 3 days of admission, a stroke with left hemiplegia was diagnosed as neurosyphilis by a neurophysician. An MRI of the brain revealed an acute infarct in the right frontoparietal temporal lobe involving the insula and chronic lacunar infarcts in the bilateral basal ganglia. CT kidney, ureter, and bladder (KUB) plain revealed a hyperdense lesion in the posterior cortex of the left kidney.

DISCUSSION

This patient was diagnosed with urosepsis. Urethral strictures give rise to urinary retention and later develop into a urinary tract infection leading to urosepsis. Uncontrolled diabetes is one of the major causes of urinary tract infections. These patients have a two-fold higher risk of community-acquired bacterial infections such as pneumococcal, streptococcal, and enterobacterial infections than patients without diabetes.[11] Since he had a known case of type 2 diabetes, he had been prescribed insulin Glargine and Human Insulin (each 12 units SC), tablets Sitagliptin and Metformin 50/1000 mg PO BD, and tablets Gliclazide 60mg PO BD. Liver function tests showed elevation owing to his alcoholic behavior. A nebulizer with a Formoterol and Budesonide combination dose of 0.5mg BD was given for respiratory distress.

Unprotected sex is a major risk factor for the transmission of syphilis. It is a sexually transmitted disease, a multisystem chronic infection caused by *Treponema pallidum*.[12,13] If untreated, it progresses into four stages: primary, secondary, latent, and tertiary. Chancre which is a typical painless syphilitic ulcer was observed at the inoculation region after an incubation period lasting 2-3 weeks. 25% of untreated patients develop secondary syphilis weeks or months later, followed by gastrointestinal symptoms, lymphadenopathy, and central nervous system alterations. About 25% of untreated patients develop tertiary syphilis at the end of the latent period. This is seen 1-30 years after the primary infection. Neurosyphilis is preceded slowly by the above inflammatory disease.[14,15] Meningeal invasion, endarteritis, and parenchymal invasion are seen in the tertiary stages when a patient has developed neurosyphilis. Endarteritis results in blockage of blood vessels and later progresses to stroke.

Cerebrospinal fluid (CSF), meninges, and vascular structures are involved in the early stages of neurosyphilis, while in the late stage, memory and judgment impairment, confusion, delusions, and seizures are prominent, along with cerebral tissue and spinal cord parenchyma.[16] A worsened metabolic pattern was observed in patients with neurosyphilis. Recently, an increased prevalence of type 2 diabetes has been reported among patients with neurosyphilis with elevated fasting glucose and glycated hemoglobin levels.[17] Injection Enoxaparin 0.4 cc SC BD was administered to recover the patient from a stroke. Fluconazole 100 mg IV BD was injected to prevent fungal infections. Benzathine penicillin was avoided owing to the previous suspected Jarisch Herxheimer Reaction. When Meropenem was administered for the treatment of urosepsis and syphilis, the same reaction occurred. The Naranjo scale score was 7, indicating a probable adverse drug reaction. Meropenem is a broad spectrum carbapenem antibiotic approved by the US food and drug administration (FDA) for the treatment of severe urosepsis and emphysematous pyelonephritis, severe urinary tract infections, and also complicated skin and skin-structure infections.[18,19] It is more effective against gram-negative pathogens and somewhat less active against gram-positive pathogens.[20-24] Compared to other treatment options, a reduced length of hospital stay and a shorter duration of therapy were observed with this drug. It is well tolerated and has an acceptable safety profile. The patient was discharged with a Doxycycline 100 mg OD capsule, a prescribed oral medication for syphilis.

CONCLUSION

Broad spectrum antibiotics are recommended as initial empirical therapy, followed by streamlining to more specific therapy after culture results are known, to minimize the development of antibiotic resistance. Research is focused on the optimization of Meropenem dosing strategies based on pharmacodynamic concepts, local rates of pathogen prevalence, and antibiotic resistance profiles. Our patient had been administered a Meropenem injection and developed a Jarisch Herxheimer Reaction. None of the studies reported that Meropenem could contribute to a Jarisch Herxheimer Reaction. Our case report aims to reveal a drug that causes the Jarisch Herxheimer Reaction.

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