# Acute Delirium in a Patient with Underlying Extra-nodal Diffused Large B-cell Lymphoma Post-initiation of Meropenem: A Case Report

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## *Abstract*

Carbapenems have been reported to cause neurotoxicity side effects such as hallucinations, delirium, seizures, and encephalopathy. The underlying mechanism is not widely known; however, evidence has pointed towards the antagonization of the gamma-aminobutyric acid (GABA) inhibitory neurotransmitter. Herein, we present a case of a patient with underlying extranodal diffused large B-cell lymphoma (DLBCL) Stage IV involving uterus, its adjacent structures and marrow who is currently on Day 10 ICE (Ifosfamide, Carboplatin, and Etoposide) and electively admitted for peripheral blood stem cell collection (PBSCT). This patient is a 48-year-old Chinese lady who developed neutropenic febrile episode during her admission. She was treated with an empirical intravenous Piperacillin-Tazobactam and was escalated to intravenous Meropenem due to the persistent high temperature spike. About 24 hours after the escalation, she developed delirium and altered behaviour. Subsequently, meropenem was discontinued, and her delirious condition resolved.

**Keywords:** meropenem; delirium; lymphoma; psychosis; hallucination

## Introduction

Meropenem belongs to the carbapenems antibiotics group. They are bactericidal agents which interfere with the peptidoglycan formation that make up the bacterial cell wall, hence inhibiting cell wall synthesis. Owing to its stability against beta-lactamase hydrolysis and its broad-spectrum activity, they are usually used as an empirical treatment in severe neutropenic sepsis.

Recent literatures have demonstrated its role in neurotoxicity side effects such as hallucinations, delirium, seizures, and encephalopathy. The underlying mechanism is not widely known; however, evidence has pointed towards the antagonization of the gamma-aminobutyric acid (GABA) inhibitory neurotransmitter. Direct binding of the inhibitory GABA to its receptors leads to influx of chloride ions, membrane hyperpolarization, and reduced firing of neurons, thus producing neuronal excitability, leading to altered neurological activity.

Herein, we present a case of a patient with underlying extra-nodal diffused large B-cell lymphoma (DLBCL) Stage IV who is currently on ICE (ifosfamide, carboplatin, and etoposide) therapy and electively admitted for peripheral blood stem cell collection (PBSCT).

## Case Report

A 48-year-old Chinese lady, with an underlying extra-nodal diffused large B-cell lymphoma (DLBCL) Stage IV involving uterus, its adjacent structures, and marrow was electively admitted for PBSCT. Prior to this, she had

her first line 6 cycles of R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), completed on 23/6/22 and her marrow was cleared. However, end of therapy PET-CT scan showed small volume of residual active disease in the pelvis. Hence, she was planned for second line chemotherapy as enroute for high dose consolidation chemotherapy and autologous haematopoietic stem cell rescue.

This patient is a 50-year-old South-east Asian Chinese, multiparous woman (two children), last delivery 14 years prior, both via normal vaginal delivery. She had not attained menopause; last menstrual period was a month ago (mid-June). Her BMI was 24.2kg/m2. She was a non-smoker and was a social alcohol drinker with a AUDIT-C score of 1. There was no evidence of osteoporosis from recent radio-imaging tests. These details are provided as they may influence pharmacokinetics, blood brain barriers permeability, or neuronal susceptibility to drug-induced neurotoxicity.

She had been admitted few days earlier for haematopoietic stem cell mobilisation (HSCM) with RICE protocol and receiving subcutaneous granulocyte colony-stimulating factor (GCSF) 600 mcg as outpatient (last on 30/8/22) with peripheral blood CD34 positive cells monitoring. On the day of admission (8/9/22), she developed fever (temperature, T: 38.9 degree Celsius). Her blood pressures remained within acceptable range but rather tachycardic (range 100-110). She was treated with an empirical intravenous (IV) piperacillin-tazobactam (Pip-tazo) 4.5g QID. After 48 hours, she still had multiple temperature spikes associated with tachycardia. Blood culture and at that time showed gram negative bacilli bacteraemia, pending specificity and sensitivity. Her antibiotic regime was further escalated to IV meropenem 2g stat and 1g TDS on 11/9/22 in view of the urgent need to resolve the febrile episode prior to her HSCM.

Following 24 hours after the initiation of meropenem, her fever and tachycardia completely resolved however, she developed delirium with disorganised behaviour (around 13/9/22 midnight). She called up many persons including her primary physician in eery hours and was talking incoherently, stating that she heard some music playing loudly at night (no device was turned on that time). Eventually, she went to the nurse counter and scolded the staff nurse there for being negligent of her duties. Then, she wandered around the ward and even tried entering other patient's room. After administration of IV haloperidol 5 mg stat dose, she was able to calm down and sleep for the night.

When asked on the next day (14/9/22), she was unable to recall the event. She claimed having generalized body ache and became less talkative. She appeared well, able to obey command, and give appropriate response to the staff. IV meropenem was discontinued and she was restarted back on Pip-tazo as the blood culture results shows Pseudomonas aeruginosa bacteraemia and sensitive to it. Following discontinuation of meropenem, she was regained full consciousness and was able to communicate and attend to her own needs. No neurological deficit was elicited. She remained afebrile since restarting back the Pip-tazo. Discontinuation of meropenem have led to recovery from her delirious state.

Her serial laboratory investigations are shown in Table 1. Blood culture isolated gram-negative bacilli from both central (she has central venous access device) and peripheral blood samples and no evidence of catheter related infection. After 5 days of incubation, Pseudomonas Aeruginosa was identified and sensitive to Pip-tazo.

Workup for delirium mainly entails a detailed history and physical examination. A negative meningeal sign made the diagnosis of meningoencephalitis less plausible. Furthermore, lumbar puncture and CT brain were not done during the period of delirium as we deem the patient would be unfit for the procedures and may require sedation. Regardless, an electroencephalogram (EEG) was performed on 15/9/22 (3 days after the delirious event) exhibiting normal findings with symmetrical awake basal electrical activity and posterior dominant alpha waves (9-10Hz). Also, given her rapid return to baseline and the absence of neurological deficits further investigations were not done. She was also not keen to proceed with the evaluations as suggested. A repeated blood culture showed no pathogen isolated. Her delirious condition completely resolved about 24 hours after after discontinuation of meropenem and subsequent normalization of electrolyte imbalance. She was able to complete her PBSCT session uneventfully.

The initial differential for this case includes sepsis-induced delirium, acute delirium secondary to disease progression/metastatic brain involvements, and concomitant chemotherapy drug-induced encephalopathy.

**Table 1:** Serial blood investigations

| Date | 8/9 | 9/9 | 10/9 | 11/9 | 12/9 | 13/9 | 14/9 | 15/9 | 16/9 |
|---|---|---|---|---|---|---|---|---|---|
| WBC | 0.50 | 0.24 | 0.11 | 0.88 | 1.25 | 2.39 | 3.99 | 8.03 | 14.33 |
| ANC | 0.01 | 0.01 | 0.1 | 0.26 | 0.56 | 1.31 | 2.72 | 3.46 | 3.58 |
| Hb | 9.1 | 8.1 | 8.6 | 10.4 | 10.8 | 10.3 | 10.3 | 10.0 | 10.2 |
| Plt | 41 | 15 | 33 | 26 | 15 | 15 | 10 | 11 | 41 |
| Na | 137 | | | | 138 | | 139 | 139 | 139 |
| K | 3.8 | | | | 2.6 | | 2.6 | 3.2 | 3.7 |
| Urea | 5.3 | | | | 2.9 | | 4.1 | 2.9 | 2.4 |
| Creat | 75 | | | | 79 | | 62 | 59 | |
| Ca | 2.21 | | | | 2.14 | | 2.13 | | |
| PO4 | 1.31 | | | | 0.67 | | 0.62 | | |
| Mg | | | | | 0.80 | | | | |
| Alb | 45 | | | | 41 | | | | |

*Legends: WBC: White blood cell count; ANC: Absolute neutrophil count; Hb: Haemoglobin; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Haemoglobin; MCHC: Mean Corpuscular Haemoglobin Concentration; HCT: Haematocrit; Plt: Platelet; Na: Sodium; K: Potassium; Create: Creatinine: Ca: Calcium; PO4: Phosphate; TP: Total Protein; Alb: Albumin; Glo: Globulin; AST: Aspartate Transaminase; ALP: Alkaline Phosphatase; and ALT: Alanine Transaminase.*

**Table 2:** Naranjo Scale of Causality.

| Question | Yes | No | Do not know or not done | Score |
|---|---|---|---|---|
| Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | +1 |
| Did the adverse event 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 readministered? | +2 | -1 | 0 | 0 (not done) |
| Are there alternative causes that could have caused the reaction? | -1 | +2 | 0 | +2 |
| Did the reaction reappear when a placebo was given? | -1 | +1 | 0 | +1 |
| Was the drug detected in any body fluid in toxic concentrations? | +1 | 0 | 0 | 0 (not done) |
| Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | +1 | 0 | 0 | 0 (not done) |

| | | | | |
|---|---|---|---|---|
| Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | 0 |
| Total score 5-8: probable drug reaction | | | | 7 |

*The scale is as follows: >9 definite, 5–8 probable, 1–4 possible, <0 doubtful.*

## Discussion

Carbapenems induced neurotoxicity are often presented with hallucinations, agitations, delirium, seizure, and myoclonus jerks.[1-3] Carbapenems are beta-lactam antibiotics frequently associated with proconvulsive and epileptogenic properties. Among all carbapenems, imipenem is reported to have the highest frequency of epileptogenic properties.[4] This is probably due to the difference in its C-2 side chain basicity strength, amino acid steric hindrance and distance from carboxyl group that indirectly enhance affinity of imipenem towards GABA receptors compared to other carbapenems.[5,6] Also, carbapenems are highly lipophilic and has a high blood-brain barrier penetration,[7] which may potentiate central nervous system (CNS) adverse effects under certain physiological conditions.

In our patient, the temporal relationship between meropenem administration and the onset of delirium, followed by rapid clinical improvement upon drug withdrawal, strongly suggested medication-induced neurotoxicity. According to the Naranjo Adverse Drug Reaction Probability Scale[8] (Table 2), the calculated score was 7, indicating a probable meropenem-related adverse reaction. Although ifosfamide-induced encephalopathy was initially considered, this was deemed unlikely as ifosfamide had been administered approximately one week earlier. Moreover, ifosfamide encephalopathy is typically acute, rarely associated with prolonged psychopathological sequelae sequeulae,[9] and is often accompanied by characteristic electroencephalographic (EEG) findings such as generalized periodic discharges or dominant delta activity with or without triphasic waveforms,[10] none of which were observed in this case.

Given her recent chemotherapy and profound neutropenia (absolute neutrophil count $0.01 \times 10^9$/L), sepsis-associated delirium (SAD) was initially considered. SAD is frequently observed in immunocompromised or neutropenic patients, affecting up to 70–100% during the neutropenic phase following intensive chemotherapy.[11,12] However, in our case, delirium developed after the resolution of the febrile episode, and sepsis-related encephalopathy was unlikely based on both clinical timing and investigations.

Neuroimaging and EEG further excluded central nervous system involvement from her diffuse large B-cell lymphoma (DLBCL). A subsequent PET-CT scan confirmed no intracranial or meningeal disease spread. The constellation of findings thus supports a diagnosis of meropenem-induced delirium.

While meropenem is generally well tolerated, similar neuropsychiatric reactions have been reported in other population,[13] emphasizing that ethnicity, age, hormonal milieu, and host-specific factors may contribute to CNS vulnerability. Our case adds to this growing body of evidence, representing a rare presentation in a South-East Asian female patient.

The pathophysiological mechanism of carbapenem-induced delirium remains incompletely understood. We postulate that alterations in BBB integrity, particularly under inflammatory or metabolic stress, may allow increased CNS penetration of the drug.[14] The transient nocturnal disorientation noted in this patient may represent a prodromal sleep-wake disturbance or obstructive sleep apnea preceding full-blown delirium. Such observations are consistent with emerging theories linking drug-induced sleep dysregulation with early CNS excitability. Additionally, meropenem belongs to the zinc-dependent class B metallo-carbapenems[15]; excessive zinc accumulation has been implicated in neuronal hyperexcitability and neurotoxicity.[16] Together, these factors may explain the paradoxical occurrence of neurotoxicity despite appropriate dosing and absence of renal dysfunction.

## Conclusion

In short, this report shed lights on the recognition of meropenem induced delirium. Concerns regarding carbapenem-induced neurotoxicity should be taken into consideration while administering among high-risk patients. Routine neurological monitoring should be considered, especially in older or postmenopausal women, immunocompromised patients, or those receiving concomitant neuroactive drugs. While meropenem remains a highly effective and essential therapeutic agent, individualized dosing, and vigilance for early neuropsychiatric symptoms may help prevent similar adverse events. Our findings highlight the need for continued pharmacovigilance and further research into host-drug interactions influencing carbapenem neurotoxicity.

## Disclosure

The authors declared no conflicts of interest. Written consent was obtained from the patient/kin of the patient.

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