Hong Kong College of Physicians

Case report for Interim Assessment

Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

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Date(s) and place (hospital) of patient encounter: sth March 2023 UCH
Date of report submission: 14th Sept 2023

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: Just Dementia? A case of central nervous system lymphoma.

Case history:

A 55 year old gentleman with good past health presented with memory loss for two weeks. He was otherwise asymptomatic. Physical examination was unremarkable. Glasgow Coma Scale (GCS) was full and
there was no focal neurologic deficit. Hong Kong Montreal Cognitive Assessment (HK-MOCA) score was 19/30.

Endocrine and metabolic workup including vitamin B12, folate, HIV and syphilis serology were unremarkable. Plain computer tomography of brain (CTB) however revealed an alarming space occupying lesion in the central brain adjacent to the occipital horn of left ventricle with surrounding edema. He was transferred to the

neurosurgical unit for further management.

Magnetic resonance imaging (MRI) of brain with contrast revealed a 6.2cm x 3.9cm x 2.9cm irregular midline mass centered at the splenium of corpus callosum with Tl W hypointense(Figure A), T2W isointense signals (Figure B) and avid contrast enhancement. From the radiologist's report, features were suggestive of central nervous system (CNS)

lymphoma. Positron Emission Tomography/ Computed Tomography (PET- CT) whole body revealed no suspicious extracranial lesions. Closed biopsy of the brain via burr hole confirmed diffuse large B cell lymphoma.
Dexamethasone was given in view of perilesional edema with mass effect and was subsequently tapered off successfully.

Baseline complete blood counts, liver{LFT), renal function(RFT) and LOH were within normal limits. Eastern Cooperative Oncology Group (ECOG) Performance status at baseline was 1 meaning patient is only restricted in physically strenuous activity.

He was referred to the haematologist and started on induction regimen MT-R: high dose methotrexate (8g/m2), rituximab (37Smg/m2), ^ Temozolamide (150mg/m2). Urine alkalinization and leucovorin was given with each cycle of high dose methotrexate.

Cycle 1 MT-R was however complicated by acute kidney injury with creatinine rising from 80umol/L to 178umol/L and deranged L 百 with alanine aminotransferase (ALT) up to 441IU/L. Methotrexate clearance was prolonged. Serum methotrexate at day 4 was 0.76umol/L (reference range < 0.1 umol/L). Liver and renal functions gradually improved with vigorous intravenous fluid and extended course of leucovorin. He was continued on subsequent cycles at same dose with aggressive hydration (500ml fluid every 4hours) and extended courses of leucovorin. No further episodes of methotrexate toxicity or delayed drug clearance were noted.

He has received 2 cycles of induction chemotherapy so far and a reassessment plain

CT brain showed satisfactory partial response with significant tumor size shrinkage.

Discussion and literature review

Primary central nervous system lymphoma (PCNSL) is an uncommon subtype of extranodal non-Hodgkin lymphoma, accounting for only 4-6% of all non-Hodgkin lymphoma and 4% of all primary CNS tumours.[1] In Hong Kong, a local study found the incidence rate of PCNSL to be 1.03 per million per year.[2] Despite the rarity of PCNSL, it is associated with a distinct prognosis and treatment compared to other types of non- Hodgkin's Lymphoma or primary CNS malignancies. Therefore, accurate and timely diagnosis is imperative to ensure optimal treatment outcomes.

Diagnosis

Patients usually present with acute or subacute neurological symptoms such as focal neurologic deficits, gait instability, altered mental status or cognition. A minority of patients also present with ocular involvement, complaining of floaters and blurred vision.[3] This may be mistaken initially for benign pathologies such as uveitis and treated with steroids, which may mask the presentation of underlying malignancy for months or even years. Thus, a high index of suspicion is required especially in at risk groups (elderly, immunocompromised/HIV patients) and a comprehensive eye assessment (with visualization of vitreous by slit lamp examination) is a standard part of the initial staging assessment for all new cases of PCNSL.[3]

Radiologically, PCNSL is most commonly located in the deep cortical white matter/periventricular regions. Lesions may either be solitary or multifocal, with a slight predilection towards solitary lesions - in one study, 34 patients had focal lesions versus 26 with multifocal lesions.[4] In contrast, secondary brain metastases, a common radiological differential diagnosis, usually present as multiple lesions located at grey-white matter junctions.[4] MRI of the brain is the most common imaging modality used to diagnose and assess extent of disease. Lesions are usually hypointense on Tl-weighted images and hyperintense on T2-weighted images and demonstrate homogeneous contrast enhancement.5 Our patient's MRI brain demonstrated these features and was very characteristic of CNS lymphoma. On the other hand, in secondary brain metastases or high grade glioma,

features such as necrosis, bleeding and heterogenous contrast/ring enhancement are common.[5] Conversely, the presence of these features in a patient proven to have PCNSL should raise the suspicion of underlying immunocompromised state or HIV.

PCNSL lesions are associated with cerebral edema. Steroids are commonly prescribed for acute symptom control. However, as lymphomas are exquisitely sensitive to steroids, their use prior to biopsy has been reported to mask the diagnosis in up to 50% of cases.[6] Thus, for a patient where PCNSL is suspected, steroids should be avoided whenever possible to maximize diagnostic yield. Yet, our patient experienced significant mass effect symptoms with headache and nausea, rendering earlier steroid use.

As the mainstay of treatment for PCNSL is chemotherapy, neurosurgical intervention is mainly limited to obtaining tissue biopsy and in rare cases, emergent debulking of extensive tumor with significant mass effect.
After histological diagnosis, staging would include extracranial imaging with PET-CT, ophthalmic assessment to exclude ocular involvement, bone marrow examination and baseline blood tests for marrow, liver, renal function and HIV status.[3]

For those without significant mass effect or hydrocephalus, lumbar puncture for cytology is also advised to exclude leptomeningeal involvement.[3] In males, testicular examination is helpful to exclude primary testicular lymphoma, which commonly presents with secondary CNS metastases.[3]

Treatment

Regarding treatment, the first step is induction chemotherapy.[3] Currently no single standard induction chemotherapy regimen exists. More common regimens in use include MATRIX (methotrexate,
cytarabine, thiotepa, rituximab) and MT-R (Methotrexate, Temozolamide, Rituximab),[7] as was used in our case. Significant tumor regression is expected in most cases. For initial induction treatment responders, this is usually followed by consolidation therapy - autologous stem cell transplantation (ASCT) for eligible patients or whole brain irradiation for the less fit.[7]

Despite initial disease response, subsequent relapse is common, particularly for those with poor risk factors such as advanced age and unfavorable tumor location. Overall median survival rates from population-based studies remains at around 2 years.[7]

Selected patients who can tolerate aggressive treatment may achieve long term disease remission. For instance, in a UK multi-institution retrospective analysis of PCNSL cases treated with high dose chemotherapy and ASCT, 5-year overall survival rates of up to 78% were reported.7 This is relatively high compared to other malignant CNS tumors. For instance, 5-year overall survival rates Glioblastoma is only around 5 %.[8]

Our case illustrates the excellent treatment response that can be achieved with high dose methotrexate based chemotherapy; on the other hand, it also illustrates the complex management strategies required to minimize treatment related toxicity.

High doses of methotrexate are required to ensure adequate CNS penetration of the drug, however its narrow therapeutic index and severe toxicity profile including hepatotoxicity, nephrotoxicity and encephalopathy should be taken note of.[9]

Our patient, despite having no underlying comorbidities, developed significant nephrotoxicity and hepatotoxicity after cycle 1 and his case is illustrative of the complex monitoring and treatment required for those receiving high dose methotrexate.

In order to successfully manage methotrexate toxicity and minimize treatment related morbidity, one must have a sound understanding of methotrexate pharmacology.

Methotrexate induces cell death by interfering folate metabolism and the production of DNA precursors such as thymidine monophosphate (dTMP). Two enzymes are essential in the production of dTMP within the cell.
Dihydrofolate reductase (DHFR), which converts dihydrofolate to tetrahydrofolate and subsequently 5-methylenetetrahydofolate; and thymidylate synthetase (TS), which in

turn uses 5- methylenetetrahydofolate to convert deoxyuridylate monophosphate (dUMP) into thymidine monophosphate (dTMP). By inhibiting these two crucial enzymes, methotrexate blocks the dTMP production dTMP and leads to cell cycle arrest.[9] Such a mechanism however has little selectivity between neoplastic and normal cells, explaining methotrexat e's significant toxicity profile and narrow therapeutic index. The pharmacokinetics of methotrexate also play a role in its toxicity profile. Up to 90% of methotrexate is renal excreted so its drug level would be sensitive to any alterations in renal function.9 Furthermore, methotrexate itself associates with direct renal tubules insults by crystal precipitation in the tubules.[9]

In order to minimize treatment related toxicity, the following measures may be considered when managing a patient receiving high dose IV methotrexate.

First, just like the regime prescribed to our patient, a folate analog - leucovorin should be administered after high dose methotrexate. The "leucovorin rescue" strategy serves the purpose to counteract the fo!ate
metabolism block induced by methotrexate in normal cells. Since leucovorin can only "rescue" cells which have not yet undergone lethal DNA damage, it should be administered within 24 to 36 hours after starting the high dose methotrexate.[10]

Second, precipitation of methotrexate in the renal tubules is promoted by acidic urine pH and volume depletion. Thus, ensuring high urine flow with aggressive pretreatment hydration and urinary alkalinization with sodium bicarbonate significantly reduces the risk of methotrexate nephrotoxicity.[10] In our patient, his urine output and urine pH were closely monitored with a target urine output of 150-200ml/hour and urine pH at or above 7.0.

Third, since the clearance of methotrexate is variable and hepatic/renal toxicity is relatively common, close monitoring of liver/renal functions as well as serial serum methotrexate levels are necessary. In our case, protocol driven blood taking at regular hours were performed after each chemotherapy cycle.

In the event of renal failure and/or delayed clearance of methotrexate, standard measures, as was administered in our case, include aggressive hydration/urinary

alkalinization and administration of additional doses of IV leucovorin until reaching the target serum methotrexate level of less than 0.05 umol/L.[9] For severe or refractory cases of nephrotoxicity with delayed drug clearance, Glucarpidase, a reversal agent for methotrexate induced dysfunction, has been approved by the Food and Drugs Administration (FDA) in the US.[10] However, this drug has not yet been registered in Hong Kong.

Fourth, methotrexate is well known to be associated with multiple drug interactions which may delay drug clearance and enhance its toxicity, including co trimoxazole, ciprofloxacin, NSAIDS, amiodarone, and proton pump inhibitors.[9] Switching to alternative drugs should be considered to avoid co administration and if this is not possible, close monitoring of methotrexate drug levels should be ensured.

CNS lymphoma is a treatable cause of cognitive decline. Early diagnosis and proper approach to chemotherapy related toxicity are the key to successful treatment outcomes.

Tables and figures (where applicable) (no more than two figures)

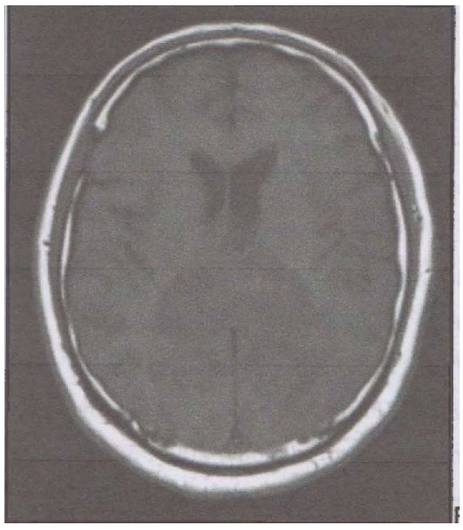
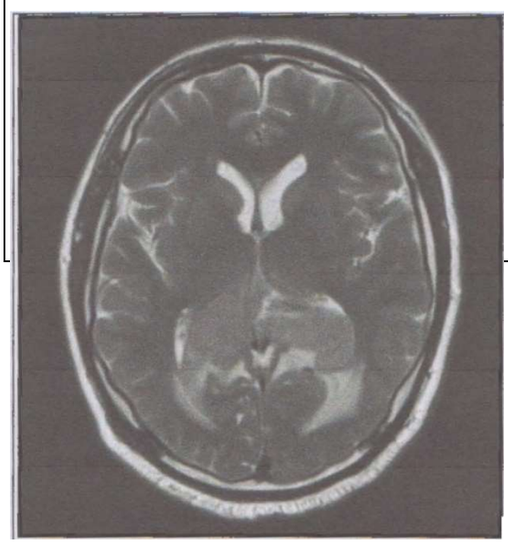


Figure A. TI W MRI brain with contrast



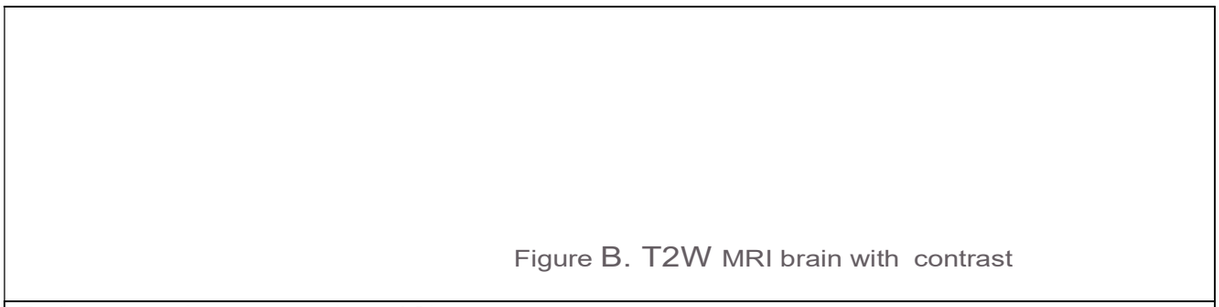


Figure B. T2W MRI brain with contrast

Reference (not more than 10)

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No of words in Case History and Discussion (excluding references): 1708 (should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee) Endorsed by

Supervisor *

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