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

Name of candidate (print and sign):
Hospital and Unit: Specialty:
Name of supervisor (print and sign):
Date(s) and place (hospital) of patient encounter: 23 October 2018
Date of report submission:10/9/2021

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: Neurosyphilis

Case history:

A 66-year-old Chinese man was transferred from psychiatric ward of Kwai Chung Hospital to medical ward of Princess Margaret Hospital on 23 October 2018 for fever. He had a voluntary psychiatric ward admission on 21 October 2018 for unstable emotion. He enjoyed good past health. He was a non-smoker. He stopped drinking beer more than 10 years ago. He run a trading business with overseas supplier. He denied history of substance abuse or high-risk sexual behavior. He was noticed by his family, his wife and 2 daughters to develop personality change, progressive memory impairment, work performance decline for eight months. He became more irritable and was brought to emergency department due to violent behavior towards his wife. The preliminary psychiatric diagnosis was frontotemporal lobe dementia.

He was sent to medical ward 2 days later due to fever. He had no localizing symptoms of infection. He denied neurological or psychiatric symptoms. His temperature was 38.1^{0}C. Glasgow Coma scale was 14 (E4V4M6). Apart from confused speech, neurological and systemic examination were unremarkable. Chest X-ray was clear. Complete blood count revealed

neutrophil predominant leukocytosis (white cell count 10x109/L and neutrophil count $12.8x10^9$/L). The liver, kidney function, electrolytes were normal. C-reactive protein was mildly elevated (27 mg/L). He was given empirical antibiotic, Amoxicillin with clavulanic acid (Augmentin) for possible urinary tract infection with acute delirium on background dementia. Urine and blood culture were later shown negative. His fever subsided.

Baseline total score of Montreal Cognitive Assessment Hong Kong Version 5-Minute Protocol was 14/30 (below 2nd percentile). Urine toxicology result was negative. Computed tomography of brain (CTB plain) was unremarkable. Blood test showed normal vitamin B12, folate and thyroid function. Serologic testing for syphilis showed positive Treponema pallidum antibody (EIA) and reactive Venereal Disease Research Laboratory (VDRL) (titre 1:256 dilution). Anti-HIV was negative. Lumbar puncture (LP) was performed and cerebrospinal fluid (CSF) showed pleocytosis (white blood cells 6/mm^3, red blood cells less than 2000m^3), increased protein concentration (1.24g/L) and normal glucose 4.5 mmol/L (plasma glucose 7.0mmol/L), VDRL reactive (1:8 dilution). Other CSF microbiological workup was negative.

The patient was diagnosed with neurosyphilis. He was treated with intravenous penicillin G 4 millions unit every 4 hours for 14 days. Daily oral prednisolone 40mg for 3 days was given to prevent Jarisch-Herxheimer Reaction. The first dose of steroid was given 24 hours before the start of anti-treponemal treatment. There was no febrile or systemic reaction. He had prolonged hospitalization for 5 months due to recurrent nosocomial pneumonia caused by methicillin-resistant staphylococcus aureus and klebsiella pneumoniae requiring mechanical ventilation.

After rehabilitation, he was able to walk unaided with mild assistance. The Modified Barthel index total score was 40/100. He was discharged home with constant care from his wife. However, 1 month after discharge, he was admitted to medical ward again for increasing irritability and disturbing behaviour. Total score of Montreal Cognitive Assessment was static (14/30, below 2nd percentile). CTB plain showed mild generalized atrophic changes and ill-defined hypodensities at left temporal lobe. 6-month post-treatment LP was performed and CSF showed persistent pleocytosis (white blood cells 9/mm^3, red blood cells less than 2000m^3), increased protein concentration (0.65g/L), similar CSF VDRL reactivity (1.4 dilution). Diagnosis of

unsuccessful treatment of neurosyphilis was made. The patient was given second course of IV penicillin G 4 millions unit every 4 hours for 14 days. Patient and family declined reassessment LP.

During subsequent follow up at 1 year after completion of second neurosyphilis treatment, he showed improvement in mood and behavior change. Total score of Montreal Cognitive Assessment Hong Kong Version 5-Minute Protocol was 18/30 (below 2nd percentile). He was independent in most daily activities. Modified Barthel Index total scored improved to 88/100.

Discussion and literature review

Syphilis is a sexually transmitted infection caused by Treponema pallidum. The disease has been divided into stages on the basis of clinical findings. Central nervous involvement can occur during any stage of syphilis. [1] Of the 48,045 cases of early syphilis reported to Centers for Disease Control and Prevention (CDC) between 2009 and 2015, 403 (0.8%) cases of neurosyphilis were reported. [2] Some patients can have asymptomatic neurosyphilis. Those with symptoms can present as meningitis, stroke and Tabes dorsalis. General paresis or dementia paralytica presents as progressive dementia manifested as impaired memory and judgment followed by progressive disorientation, confusion and occasional seizures. [1]

The diagnosis of neurosyphilis requires a combination of clinical presentation, serologic testing for syphilis, CSF parameters. Regarding physical findings associated with general paresis, neurological examination may be normal. Sometimes, dysarthria, facial and limb hypotonia, intentional tremors and reflex abnormalities could be found. Pupillary disturbance, Argyll Robertson pupils may or may not be observed in general paresis. Neuroimaging most commonly shows atrophy. Magnetic Resonance Imaging of brain may show unilateral or bilateral medial temporal lobe high signal on T2 and fluid-attenuated inversion recovery (FLAIR) sequences, which can be resolved after treatment in neurosyphilis. Typical CSF findings in neurosyphilis include reactive CSF VDRL, CSF pleocytosis (white blood cell >5 cells/ul) elevated CSF protein (>45mg/dL). [1]

Neurosyphilis should be treated regardless of the presence of neuropsychiatric symptoms to prevent disease progression. The CDC recommended treatment regimens for neurosyphilis are aqueous crystalline penicillin G 18-24 million units per day administrated intravenously as 3-4 million units every 4 hours or 24 million units daily as a continuous infusion for 10-14days. Alternative regimen includes procaine penicillin G 2.4 million units intramuscularly daily with probenecid 500mg orally 4 times per day for 10-14 days, Ceftriaxone 2g intramuscularly or intravenously daily for 10-14days. Doxycycline 200mg orally twice daily for 21 days was not recommended due to limited supporting data. [2,3] Some experts advocate use of systemic steroid before penicillin treatment to prevent the Jarisch-Herxheimer reaction. However, several case series show varying level of efficacy. [1]

Apart from monitoring symptoms, the CDC recommends that lumbar puncture should be repeated every 6 months after completion of therapy until abnormalities resolves. [2] Retreatment should be considered if either of the following occur. CSF white blood cell has not decreased after 6 months. CSF cell count or protein fails to normalize after 2 years. CSF VDRL does not decline fourfold (or to nonreactive if the initial titer is <1:2) 1 year after therapy. [2] Literature review on assessing treatment responses in HIV-infected patients with neurosyphilis treated with intravenous penicillin G shows serological non-response rate at 12 month post-treatment was about 27%. Treatment failure rate in patients without HIV was uncertain. [4]

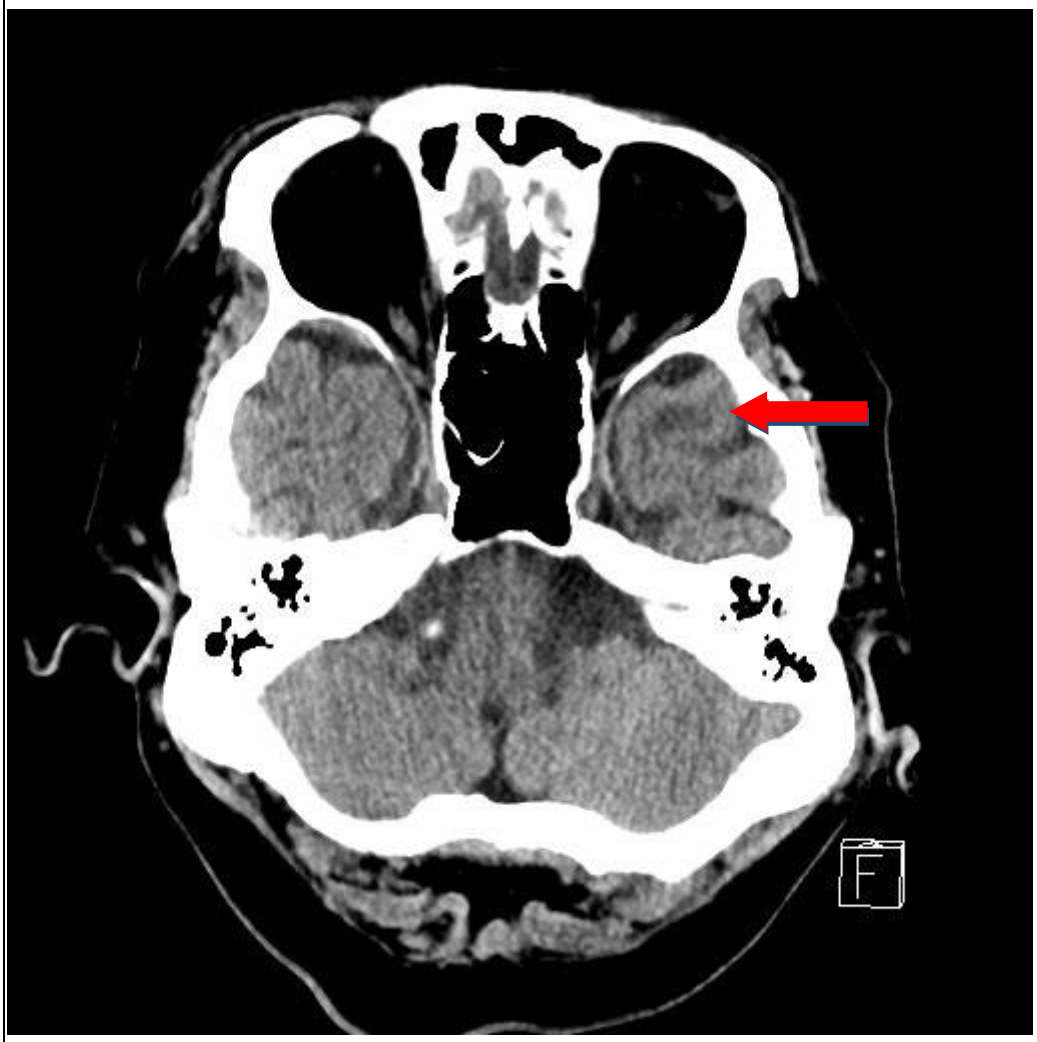
The prognosis mostly depends on the subtype of neurosyphilis and early detection of the disease. Patients with asymptomatic or meningeal neurosyphilis generally return to normal functional status if treated adequately. By contrast, patients with meningovascular disease, general paresis or tabes dorsalis may improve after completion of treatment but usually do not return to their baseline functional status. Besides, patient who are treated years after initial infection tend to have more poor neurological outcomes. [2]

In our patient, he was initially diagnosed with frontotemporal lobe dementia. Given the history of subacute onset of dementia, together with reactive serum EIA and high titer VRDL reactivity, lumbar puncture was essential to rule out neurosyphilis. Without resolution of clinical symptoms,

neurosyphilis treatment failure should be considered and lumbar puncture should be repeated.

Currently, well-controlled clinical data are lacking on the optimal dose, duration and long-term efficacy of different frontline antimicrobials for treatment of neurosyphilis. There is limited literature to predict treatment failure or neurological outcomes. More studies is also required to recommend second-line treatment of neurosyphilis.

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



CTB plain showing ill-defined hypodensities at left temporal lobe

Reference (not more than 10)

1. Gonzalez, H., et al. (2019). "Neurosyphilis." Semin Neurol **39**(4): 448-455.
2. Workowski, K. A., et al. (2021). "Sexually Transmitted Infections Treatment Guidelines, 2021." MMWR Recomm Rep **70**(4): 1-187.
3. French, P., et al. (2009). "IUSTI: 2008 European Guidelines on the Management of Syphilis." Int J STD AIDS **20**(5): 300-309.
4. Ghanem, K. G. (2015). "Management of Adult Syphilis: Key Questions to Inform the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines." Clin Infect Dis **61 Suppl 8**: S818-836.

No of words in Case History and Discussion (excluding references): 1260

(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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(signature of Supervisor)

* Supervisors must go over the Case Report with the Trainees, advise Trainees whether further amendments are necessary, review the Originality/Similarity Report prepared by Trainees, adherence to the required format, sign on the report and remind Trainees on issues related to copyright and plagiarism.