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): Wong Edmund Ka Ming
Hospital and Unit: PWH M&T Specialty: AIM and Rheumatology
Name of supervisor (print and sign): Dr. Chan Ka Pang
Date(s) and place (hospital) of patient encounter: 3/6/2023 PWH
Date of report submission:

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: A Case of Debilitating Paradoxical Reaction in Tuberculosis

Case history:

A 61-year-old gentleman, who is a retired car mechanic with unremarkable medical history, was admitted to the medical unit for fever and lower abdominal pain for 2 weeks. He had intermittent low-grade fever up to 38 degrees Celsius, malaise, weight loss of 4kg over 2 weeks and night sweats. He also had urinary frequency and urgency but no dysuria or hematuria. He did not have any cough, sputum or hemoptysis. On physical examination, his blood pressure was 130/80mmHg, pulse was 80 beats per minute, and oxygen saturation was 94% in room air. There was no finger clubbing or palpable cervical lymph node. Chest and abdominal examinations were normal, and with no focal neurological signs. Urine multi-stix was positive for white blood cells but negative for nitrite. Chest X-ray showed tiny nodular infiltrates over bilateral lung fields. The hemoglobin (Hb) level was 10.4 g/dL (ref 12.6-16.1), white blood cell (WBC) count was mildly elevated to 10.4 x 10^9/L (ref 4.2-9.6 x10^9/L), C-reactive protein (CRP) was 26.1mg/L (ref <9.9). Renal and liver functions were normal. Mid-stream urine analysis showed a moderately raised WBC of 10,000-100,000 cells/ml, but the culture was negative. Sputum culture and acid-fast bacilli (AFB) were negative, and blood culture was negative. Contrast computed tomography (CT) of the abdomen and pelvis was unrevealing and did not show any features of pyelonephritis, hydronephrosis, spondylitis or intraabdominal lymph node

enlargement.

The patient was initially managed as having a urinary tract infection and was started on intravenous co-amoxiclav, but the fever persisted with up-trending CRP and WBC despite 3 days of antibiotic treatment. In view of sterile pyuria, early morning urine (EMU) for AFB was saved, which revealed a positive AFB smear and *Mycobacterium tuberculosis* (MTB) DNA by polymerase chain reaction (PCR). The blood test for anti-HIV was negative. Diagnosis of urogenital tuberculosis (TB) was made, and the patient was started on anti-TB treatment including isoniazid, rifampicin, ethambutol and pyrazinamide. The patient had absolute compliance and good tolerance to anti-TB treatment during hospitalization. 10 days after initiation of anti-TB treatment, the fever subsided, the CRP level normalized and the EMU AFB smear was converted to negative.

On day 14 of anti-TB treatment, the patient developed acute retention of urine requiring a urinary catheter. No other focal neurological deficit was detected at that time. He was thus managed as a complication of urogenital TB, but he failed to wean off the urinary catheter over the next week. On day 21 of anti-TB treatment, the patient developed sudden onset bilateral hypertonic, hyperreflexic paraparesis (power 1 out of 5), loss of pain and proprioception from T12 downwards and reduced anal tone suggestive of spinal cord damage over the lumbosacral region. The mental state of the patient was normal and there was no focal neurological deficits of the cranial nerves and upper limbs.

Contrast magnetic resonance imaging (MRI) of the whole spine showed diffuse leptomeningeal enhancement along the contour of the length of the spinal cord, around the conus and nerve roots in the cauda equina. (Figure 1.) The leptomeningeal enhancement filled the sacral canal and extended directly into the posterior bony aspect of the sacral vertebrae. (Figure 2.) Lumbar puncture yielded turbid cerebrospinal fluid (CSF) and the opening pressure was 29 cmH_2O. CSF analysis showed low glucose 1.8mmol/L (blood glucose 6mmol/L), raised protein 4.1g/L (ref 0.15-0.45), markedly raised WBC 111 x 10^6/L (100% monocyte), while CSF Gram smear, bacterial culture, AFB smear, AFB culture and MTB PCR were negative. Contrast MRI brain showed multiple tiny enhancing foci in bilateral cerebral hemispheres. Sputum AFB smear and AFB culture were negative. Urine mycobacterium culture later yielded a pan-sensitive strain of MTB.

In view of the development of new tuberculous lesions after initial improvement

following anti-TB treatment, a diagnosis of paradoxical reaction with TB spondylitis and meningitis was made. The patient was started on high-dose dexamethasone 24mg/day (ie. 0.4mg/kg/day) with gradual tapering over 1 month and was continued with anti-TB treatment. He was transferred to a convalescence hospital, where he gradually regained mobility and was able to walk with a stick after 2 months of intensive rehabilitation. A follow-up MRI brain and whole spine was arranged 6 months after initial treatment to assess the degree of cerebral and leptomeningeal disease response.

Discussion and literature review

Vigilance towards paradoxical reactions in tuberculous infections is crucial as failure to recognize it may lead to incorrect clinical diagnosis and delayed treatment. Our patient developed acute retention of urine at day 14 anti-TB treatment for disseminated TB, which initially only presented with urogenital symptoms. Whether the acute retention of urine was caused by worsening of urogenital TB or part of manifestation of TB spondylitis, paradoxical reaction should be considered as one of the differential diagnoses early. Diagnosis of paradoxical reaction involves several definitions agreed upon across published case series. These include initial improvement of TB-related symptoms or radiographic findings after initiation of adequate anti-TB treatment, paradoxical deterioration of TB-related symptoms or radiologic findings either at the primary site or at new locations, absence of interference of anti-TB drugs such as compliance and resistance issues, and lack of alternative explanations for clinical deterioration. [1] Paradoxical reactions may occur as early as 10 days to 10 years after initiation of treatment, with the peak incidence at day 28 to 50. [2, 3]

Paradoxical reaction is believed to be an immune response event. While there is no fully established pathogenesis for it, the most-proposed mechanism involves an initially immunocompromised environment, following an exaggerated immune response towards high bacteria antigen levels from rapid TB killing. [4] There are some terminologies that are not to be mixed up. Paradoxical reaction is an umbrella term referring to the deterioration or development of new lesions after the initial response to TB treatment which can occur in human immunodeficiency virus (HIV) or non-HIV patients. While TB-immune reconstitution inflammatory syndrome (TB-IRIS) usually refers to exacerbation of TB after initiation of highly active antiretroviral therapy (HAART) in HIV patients which can be a cause of paradoxical reaction. [4]

Currently, there are no published guidelines or randomized trials for the

treatment of paradoxical reactions in non-HIV TB patients. Treatment of paradoxical reactions towards TB in non-HIV patients is mainly extrapolated from the evidence available from HIV-coinfected patients. The most common practice from case series is to continue anti-TB treatment with concurrent tapering moderate-to-high dose corticosteroid starting at prednisolone 20-40mg/day or equivalent.[5] This treatment regime is extrapolated from the PredART trial published in the New England Journal of Medicine in 2018. In this study with 240 participants, it was found that among HIV-coinfected TB patients receiving anti-TB treatment who were at high risk for TB-IRIS, the incidence of TB-IRIS was lower among those who received a 4-week course of prednisone (prednisolone 40mg/day for 2 weeks then 20mg/day for 2 weeks) at the start of antiretroviral treatment, than those who received placebo.[6]

As for our patient, a much-higher initial dose of steroid (dexamethasone 24mg/day), which was equivalent to prednisolone 180mg/day, was used after diagnosis of paradoxical reaction with TB spine and meningitis was made. The decision to use a higher dose steroid was based on the clinical and radiological evidence of meningitis, and the rapid deterioration in neurological function. A randomized, double-blind, placebo-controlled trial study in Vietnam with 545 participants demonstrated that adjunctive treatment with dexamethasone 0.3-0.4mg/kg/day can improve survival in patients over 14 years of age with TB meningitis.[7]

In summary, this is a case illustrating an uncommon complication of TB infection following initial successful treatment. High vigilance towards paradoxical reactions, early diagnosis and treatment with steroids is crucial for patient recovery. Consideration of alternative causes of deterioration in TB patients such as drug compliance and absorption, the presence of resistant strain TB is also important.

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

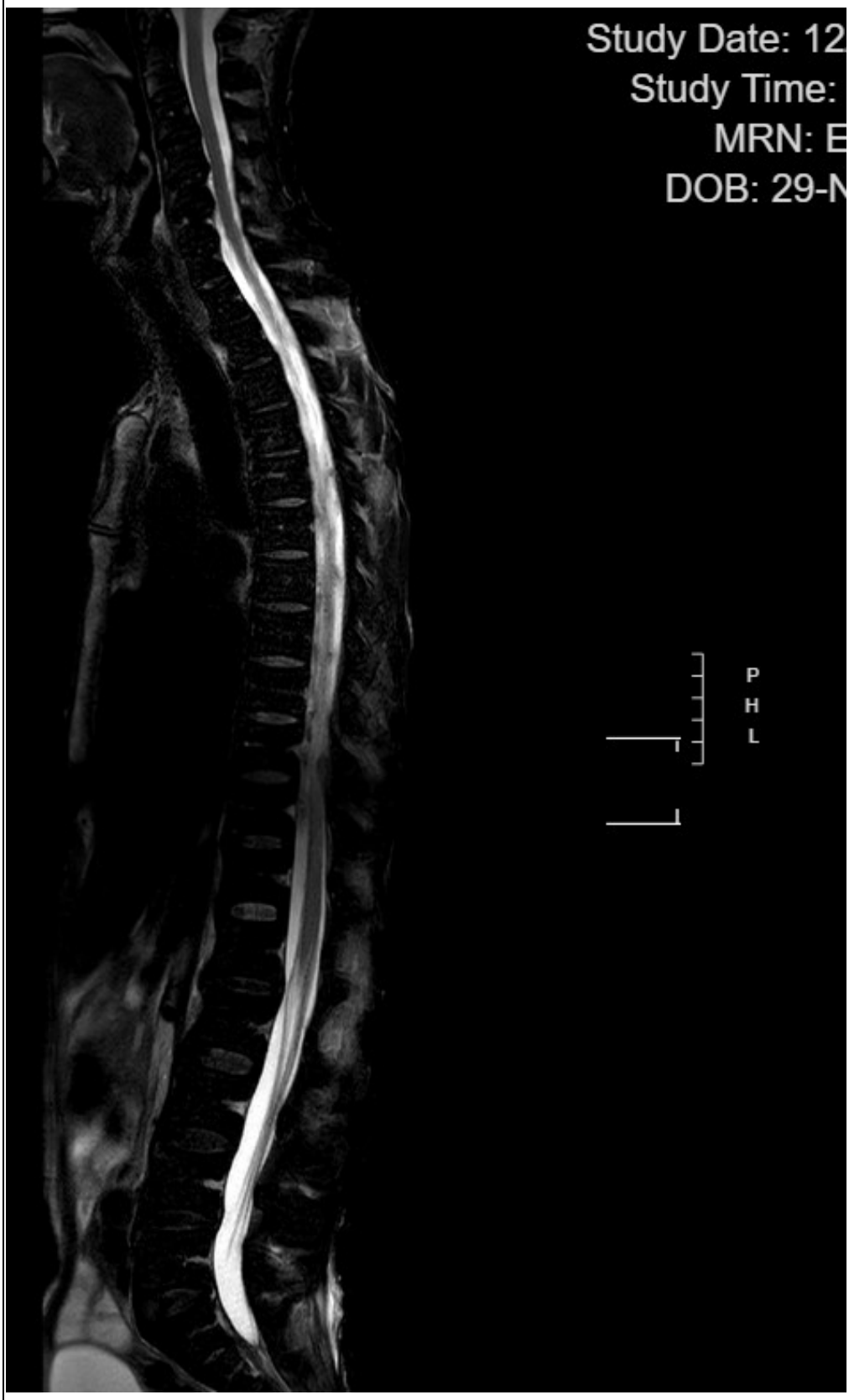

Figure 1: MRI spine sagittal view showed T2 enhancement signals along the

contour of the length of the spinal cord, around the conus and nerve roots in the cauda equina.

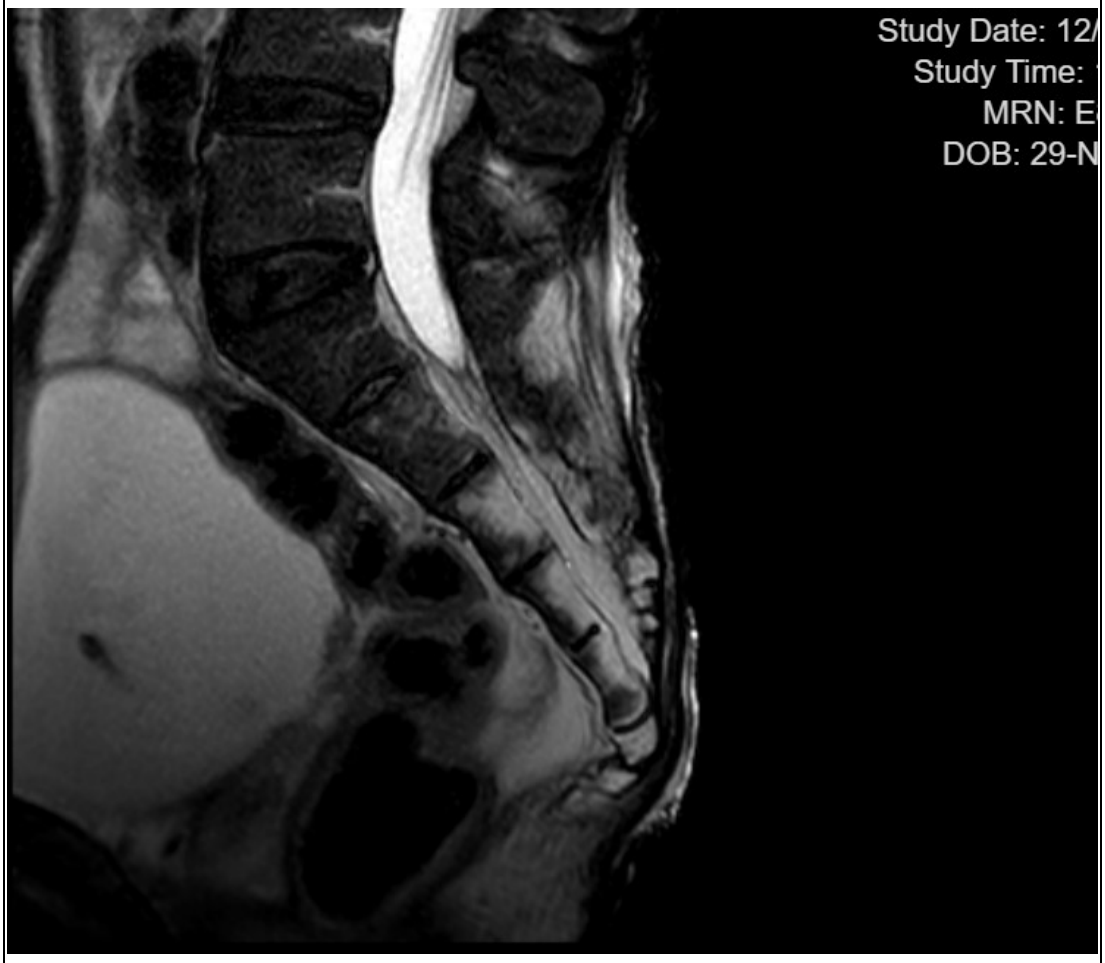

Figure 2: MRI spine sagittal view showed T2-weighted leptomeningeal enhancement filling the sacral canal and extending directly into the posterior bony aspect of the sacral vertebrae.

Reference (not more than 10)

1. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis. 2008; 8:516–523.

2. Machida A, Ishihara T, Amano E, et al. Late-onset paradoxical reactions 10 years after treatment for tuberculous meningitis in an HIV-negative patient: a case report. BMC Infect Dis. 2018; 18(1):313.
3. Tai MLS, Nor HM, Kadir KAA, et al. Paradoxical manifestation is common in HIV-negative tuberculous meningitis. Medicine (United States). 2016; 95(1).
4. Bell L, Breen R, Miller RF, et al. Paradoxical reactions and immune reconstitution inflammatory syndrome in tuberculosis. J. Infect. Dis. 2015; 32: 39-45
5. Done MM, Akkerman OW, Al-Kailany W, et al. Corticosteroid therapy for the management of paradoxical inflammatory reaction in patients with pulmonary tuberculosis. Infection. 2020; 48: 641–645.
6. Meintjes G, Stek C, Blumenthal L, et al. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. NEJM. 2018; 379(20): 1915–1925.
7. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. NEJM. 2004; 351(17):1741-51.

No of words in Case History and Discussion (excluding references):___1761_____

(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.