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: June 2020
Date of report submission: 1/3/2021

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: A case of Cushing's syndrome with hepatitis B reactivation

Case history:

Miss Y is a 46 years old lady with good past health. She presented to the emergency department in January 2020 for first episode of loss of consciousness after 30 minutes of hiking. There were no preceding symptoms nor seizure activities witnessed by her friends. She spontaneously regained full conscious level after 10 seconds.

On admission, physical examination was unremarkable with full GCS and no focal neurological deficit. The only remarkable finding was high blood pressure with systolic blood pressure 180 mmHg.

Upon initial workup, there was noted hypokalaemia with plasma potassium of 2.8mmol/dL. Blood gas or work up for urine potassium loss were not arranged. . Potassium was subsequently replaced but magnesium was not checked during this episode of admission. ALT was slightly elevated at 52 IU/L.

ECG showed sinus rhythm with features of left ventricular hypertrophy, which was confirmed by transthoracic echocardiogram. Holter exam showed no

evidence for arrythmia and CT brain showed no ischaemic changes or intracerebral lesion to account for the loss of consciousness. Serial troponin T rose from 20 to 40 ng/mL and subsequently normalized. In the absence of chest pain and ECG changes, this was deemed likely related to extreme exertion from hiking. A CT coronary angiogram was arranged, where calcium score was 0, signifying no significant coronary artery disease.

Patient was commenced on amlodipine for control of her hypertension and potassium supplement to maintain normokalaemia. After control of her hypertension and correction of hypokalaemia, work up for endocrine causes for hypokalaemic hypertension was initiated and found to be unremarkable. Spot renin/aldosterone was renin 3.73ng/ml and aldosterone 297pmol/L with ARR ratio of 80. 24 hour urine for free metanephrine was saved after discharge, and urine metanephrine, normetanephrine and 3-methoxytyramine were all within normal range. Screening for Cushing's syndrome was intended upon follow up in out-patient basis when patient is out of acute stress.

However, during subsequent follow up in medical clinic 3 months after her discharge, she was noted to have cushingoid appearance. Blood test also showed alarmingly elevated ALT 699 IU/L, bilirubin 26 umol/L, ALP 107 IU/L. She was electively admitted for further workup. Further history revealed she had experienced progressive weight gain of 15 kg over a 1 year period with increased acne and hirsutism over face and back, associated with bilateral lower limb weakness and difficulty in climbing up stairs very suggestive of proximal muscle weakness. She also reported oligomenorrhea for half a year. There were no symptoms of headache or visual disturbance. She also reported occasional back pain, which vertebral fracture was excluded by x-ray.

For the deranged liver function, HBsAg was found to be positive with HBV DNA 6.13log and HBe antigen positive. Her mother had hepatitis B but she was unaware of her own hepatitis B status.

At this point it was suspected patient is suffering from Cushing's syndrome. Enquiry into medication use was unrevealing and she reported no intramuscular injections, use of over -the- counter medication or topicals that contained exogenous steroid. Screening test for Cushing's syndrome was initiated including 1mg overnight dexamethasone suppression test which was totally non-suppressible with cortisol of 710 nmol/L and 24 hour urine free cortisol was markedly elevated at 1147 nmol/L. In light of the florid Cushingoid phenotype and markedly positive abnormality on screening test, formal

confirmatory low dose dexamethasone suppression test was not performed. Additionally, there is concern that the dexamethasone that needs to be administered over two days during low dose dexamethasone suppression test may lead to further flare up of her HBV, and overall clinical picture is already very suggestive of Cushing's syndrome. Paired 9am morning cortisol was performed to differentiate between pituitary and adrenal dependent Cushing's which revealed 9am cortisol 615 nmol/L with ACTH <1.6 pg/ml which is strongly suggestive of adrenal dependent Cushing's. A dedicated CT adrenal scan with 3mm fine cut was performed showed bilateral adrenal nodules suggestive of lipid-poor adenoma. 1.06mCi I-131 iodocholesterol functional scan was arranged to determine laterality of the adrenal Cushing's. The scan subsequently confirmed intense bilateral adrenal uptake, compatible with hyperfunctioning bilateral adrenal lesions, either adenoma or hyperplasia.

The working diagnosis is therefore ACTH-independent Cushing syndrome, with underlying adrenal adenoma/ hyperplasia, which was further complicated by flare up of the underlying hepatitis B. She was started on metyrapone as medical treatment for Cushing's syndrome while awaiting definitive surgical treatment with bilateral adrenalectomy and entecavir for HBV flare up. The initial presentation of Cushing's syndrome can be subtle, yet when reviewed retrospectively can be very classical just like in our patient here. Under such circumstances, it is always very useful to refer to the old photographs of patients to look for any changes to facial appearances and to have a greater index of suspicion for patients presenting with young onset hypertension. She eventually presented with hypokalemic hypertension, complicated by left ventricular hypertrophy, dysmenorrhea and loss of consciousness, which could be due to intolerance to exercise due secondary to muscle wasting.

Discussion:

This case illustrates a case of endogenous Cushing syndrome which is ACTH independent. Compared with exogenous supra-physiological dose of corticosteroid use, endogenous Cushing's syndrome is uncommon, with an annual incidence of 0.7–2.4 per million population[1]. It is important to diagnose the disease in a timely manner because if undiagnosed, it may lead to long term and enduring complications to patients, including elevated cardiovascular risk, immunosuppression, musculoskeletal, ophthalmological complications etc. Furthermore, the underlying cause of Cushing syndrome may be due to the presence of a tumour which is potentially curable if diagnosed in a timely manner. For example ectopic ACTH producing small cell lung tumour, pituitary tumour, or in this case, from adrenal glands.

In a meta-analysis that included 5367 patients, the mean time needed to diagnose pituitary, adrenal and ectopic Cushing's syndrome was approximately 3, 2.5, and 1.3 years respectively[5]. If left untreated, the 5 year mortality can be up to 50%. Even after successful treatment, not all disease related complications can be completely reversed. To name a few, bone marrow density and cognitive dysfunction may not completely normalize in all patients after curative treatment of Cushing's. If surgical intervention is needed, the risk of operation has to be taken into consideration as well[6].

The elevated liver enzyme in this case proved to be due to hepatitis B reactivation due to chronic immunosuppression by excessive endogenous cortisol production.

It is known that use of long term corticosteroid can predispose hepatitis B reactivation by mechanism of glucocorticoid responsive transcriptional regulatory element in the HBV genome and depressed cytotoxic T-cell function[2]. High dose steroid such as prednisolone 20mg daily (or equivalent) for more than 4 weeks may give rise to more than 10% chance of reactivation in HBsAg positive cases. The chance of hepatitis B reactivation also depends on other factors including the anti Hb core antibody, anti-hepatitis B surface antigen status and the use of certain types of immunosuppressant. For instance, the risk due to CD20 depleting monoclonal antibody Rituximab or Obinutuzumab will have stronger immunosuppressive effect than traditional agents such as azathioprine or methotrexate. It is suggested to give hepatitis B prophylactic treatment in moderate to high reactivation risk patients, until at least 6 months after completion of the immunosuppressive treatment. The

suggested treatments include third generation nucleotide analog Entecavir or Tenofovir, where both are effective with low cumulative resistance rate.

However there is little evidence on how endogenous corticosteroid affects risk of hepatitis B reactivation in susceptible patients. Through literature search in Medline and Embase, I can only identify case reports of hepatitis B reactivations. One case report described a case of submassive liver necrosis in a hepatitis B carrier with underlying Cushing syndrome, in which the patient eventually succumbed[4]. Another report described a case of hepatitis B reactivation due to a sellar tumor with post traumatic stress disorder. The possible reason maybe due to the difficulty in quantifying the amount of endogenous steroid produced, which is used to correlate with the risk of hepatitis B reactivation. Given the risk of reactivation, checking hepatitis B status appears to be necessary in newly diagnosed Cushing syndrome patients. Through literature search, there are no standard guidelines on this aspect as yet and further studies are needed in this area.

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

Reference (not more than 10)

1. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. *Cushing's syndrome*. Lancet. 2006;367:1605–1617
2. Robert P Perrillo et al., . American Gastroenterological Association Institute Technical Review on Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy. Gastroenterology 2014
3. Lynnette K. Nieman. Recent Updates on the Diagnosis and Management of Cushing's Syndrome. Endocrinology and metabolism 2018.
4. Pei- Ling Tsou. Submassive liver necrosis in a hepatitis B carrier with Cushing's syndrome. Journal of Formos Med association 2002.
5. German Rubinstein et al., Time to Diagnosis in Cushing's Syndrome: A Meta-Analysis Based on 5367 Patients. Journal of clinical endocrinology and metabolism 2020
6. Lynnette K. Nieman et al., The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. Journal of clinical endocrinology and metabolism 2008
7. Ryosuke et al., Rapid Deterioration of Latent HBV Hepatitis during Cushing Disease and Posttraumatic Stress Disorder after Earthquake. Jornal of neurological surgery 2017.

No of words in Case History and Discussion (excluding references): **1354**

(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)

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