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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Hospital and Unit: Prince of Wales Hospital Specialty: AIM and Haematology & Haematological Oncology
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Date(s) and place (hospital) of patient encounter:6 January 2022 Prince of Wales Hospital Medical Ward
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 ectopic Cushing's Syndrome

Case history:

A 75-year-old woman with unremarkable past medical history was referred to our medical clinic for newly diagnosed diabetes mellitus and hypertension. She presented with persistent elevation in home systolic blood pressure and attended a private clinic. Workup for metabolic syndrome revealed an HbA1c of 9%, hence diagnoses of essential hypertension and type II diabetes mellitus were made. She also volunteered symptoms of malaise, muscle weakness, acne, lower limb swelling and progressive weight gain. She denied the use of over-the-counter medications or exogenous steroid. She had no family history of endocrinopathies.

On physical examination, patient had moon face with acneiform eruption, thick purple abdominal striae, pedal oedema and a buffalo hump. Neurological examination revealed proximal muscle weakness with Medical Research Council (MRC) grading of 4/5 over her bilateral upper and lower limbs. Visual field examination did not show bitemporal hemianopia. Laboratory investigations showed hypokalemia of 3.2mmol/L. Complete blood count, liver function and serum calcium level were unremarkable. Thyroid stimulating hormone and thyroxine level were normal. Serum morning cortisol saved in the early morning was 1076 nmol/l (ref 102-535 nmol/l), which excluded the possibility of iatrogenic adrenal insufficiency due to exogenous steroid use.

Owing to the clinical suspicion of endogenous glucocorticoid excess, an overnight 1mg dexamethasone suppression test was arranged as a screening test, which showed an unsuppressed cortisol level of 568nmol/l after 1mg oral dexamethasone. 24-hour urinary free cortisol was markedly elevated, with a urinary cortisol level of 1133mcg (ref. 3.5-45mcg). A 9am adrenocorticotropic hormone (ACTH) was 205pmol/l (ref. 6-50pmol/l), which supported the diagnosis of ACTH dependent Cushing's Syndrome. MRI pituitary showed a cystic lesion of size 0.22x0.36x0.27cm in the pituitary gland, suggestive of pituitary cyst or rathke cysts .

Patient was admitted later for corticotropin releasing hormone (CRH) test. The results of serial testings for ACTH/ cortisol levels after CRH was administered are stated in table 1. The serial increase in ACTH was smaller than 40% , and the rise in cortisol was less than 20%[8]. As CRH test showed the absence of ACTH and serum cortisol response to CRH stimulation, suspicion of ectopic Cushing's syndrome was raised. Inferior petrosal sinus test for confirmation and localization of ACTH origin was offered, but the patient declined due to the fear of endovascular complications.

Positron emission tomography and computer tomography (PETCT) raised the radiological suspicion of metastatic ovarian carcinoma with pulmonary and sigmoid colon metastasis (figure 1). After the diagnosis of metastatic ovarian carcinoma with ectopic ACTH secretion has been made, a debulking surgery involving total abdominal hysterectomy with bilateral salpingo-oophorectomy, omendectomy, and sigmoidectomy was performed by a private gynecologist. Histology confirmed high grade ovarian cancer. However, persistently elevated serum ACTH (17.94pmol/L) and cortisol levels (1126nmol/l) were observed 6 days after the surgery, suggestive of residual ectopic ACTH release. Metyrapone was prescribed as medical therapy for residual ectopic Cushing's syndrome. She was referred to oncology department for consideration palliative chemotherapy. Blood pressure and glycaemic control were stabilized with metyrapone, calcium channel blockers and metformin. She was started on carboplatin and bevacizumab for her metastatic ovarian carcinoma.

Discussion and literature review

Cushing's syndrome (CS) is an endocrine disorder caused by excessive level of glucocorticoids. The most common etiology of CS is exogenous steroid use. Other causes include ACTH dependent Cushing's with pituitary origin, ectopic orgin, or ACTH independent Cushing's with adrenal pathology. Ectopic ACTH secretion is an uncommon cause of Cushing's syndrome, accounting for approximately 15% of all the cases of CS[1]. Among cases of ectopic ACTH-secreting tumor, around 50% of the primary lesions were small-cell lung carcinoma[9]. Other less common tumor types include thyroid medullary carcinoma, pancreatic tumor, thymic tumor, and rarely ovarian carcinoma in the reported case[9].

Diagnosis of CS is difficult due to the lack of awareness of the insidious nature of the disease and the complexity of the diagnostic tests. The cardinal clinical features of CS include truncal obesity, hypertension, diabetes mellitus, hirsutism, oligomenorrhea or amenorrhea, facial plethora, muscle weakness, easy bruising, violaceous abdominal striae and osteoporosis. Recognition of clinical signs remains crucial to initiate appropriate diagnostic algorithms. Thorough history regarding clinical features and possible complications should be assessed, together with detailed drug history, to look for possible source for exogenous glucocorticoid.

After detailed history taking and physical examination, in case of suspicion of underlying CS, we proceed to biochemical screening and confirmatory tests. Screening laboratory tests for CS include: Late night salivary cortisol, overnight 1mg dexamethasone suppression test and 24 hour urinary free cortisol. There is no single laboratory test that best screens or diagnoses CS. Latest consensus guideline from *Lancet* suggests a combination of the aforementioned screening tests to confirm the state of glucocorticoid excess[2]. After excluding the possibility of pseudocushing's, a diagnosis of Cushing's syndrome can be established with abnormal result in 2 or more of the screening tests. Possible causes of pseudocushing's include depression, polycystic ovarian syndrome, alcohol use and obesity. These cases are identified with relevant history taking, and repeated screening tests at regular intervals for monitoring[2]. Differentiating CS and pseudocushing's can be difficult. Biochemical test with combined low dose dexamethasone suppression plus CRH test had been advocated to exclude pseudocushing's, in which patients with pseudocushing's have blunted response to CRH stimulation while patient with genuine CS often demonstrate exaggerated response.

Serum ACTH level should be checked when the diagnosis of CS is confirmed. It will help clinicians to differentiate between ACTH dependent and ACTH independent CS. An elevated ACTH level indicates the endogenous glucocorticoid excess is driven by uncontrolled release of ACTH. In cases of biochemically ACTH dependent CS, differentiation of pituitary origin i.e. Cushing's disease, versus ectopic CS is essential.

CRH test is a non-invasive dynamic test for localization of disease. After the administration of CRH, a 35-50% increase of ACTH or more and 20% increase of cortisol concentrations from baseline indicate the pituitary gland

as the origin of hypercortisolemia[8]. A recent review in 2022 carried out in Germany reviewed the sensitivity and specificity of CRH in 469 patients with ACTH dependent CS. Compared to high does dexamethasone suppression test (HDDST), CRH was equally sensitive, and more specific non-invasive localization test when compared to HDSST[3]. Guidelines suggested inferior petrosal sinus sampling when the CRH is not conclusive, depending on individual center expertise[2].

Appropriate imaging should be arranged to localize the origin of excessive ACTH secretion. MRI pituitary should be arranged if Cushing's disease is suspected biochemically to look for any pituitary adenoma. In case of biochemical suspicion of ectopic ACTH secretion, whole body imaging, including CT or PETCT, as in our reported case, maybe considered to localize the ectopic ACTH origin. Alternatively, ^{68}Ga-DOTATAE imaging if neuroendocrine tumor is suspected, or if no tumor is detected with cross-sectional imaging[2]. ^{68}Ga-DOTATAE has a better sensitivity to detect neuroendocrine tumor as the radioactive contrast has high affinity to somatostatin receptor type 2, which is usually overexpressed in neuroendocrine tumor.[10]

Cushing's syndrome is associated with considerable comorbidities, including cardiovascular risks, bone density loss and immunosuppression. Timely diagnosis and treatment for CS is important. For ectopic CS, the treatment of choice would be resection of the underlying ACTH-secreting tumor. Medical therapy could be considered when there is a need to rapidly suppress the state of hypercortisolism to avoid complications of CS, or as a bridging treatment before definitive surgical treatment. Medical therapy may also be indicated for patients with metastatic diseases which are beyond surgical cure.

Medical treatment of CS includes: adrenal steroidogenesis inhibitor, somatostatin receptor ligands, dopamine receptor agonist and glucocorticoid receptor blocker. A few examples of the medical treatment including Metyrapone, osilodrostat, and mifepristone will be reviewed here.

Metyrapone is a pyridine derivative. Functionally, metyrapone acts as an 11β-hydroxylase inhibitor. A review that included five studies of metyrapone suggested with a dosage of 500 to 6000 mg per day (mean, 2127.5 mg/d; median, 1750 mg/d), metyrapone achieved a remission rate ranging from 45.4% to 100%. Another prospective study showed that up to 66% of patients reported symptomatic improvement[5]. Common side effects include hirsutism, dizziness, arthralgia and hypokalemia.

Osilodrostat is an 11β-hydroxylase and aldosterone synthase inhibitor. According to a phase 3 double-blind randomized study in 2020, 31 (86%) patients in the osilodrostat group maintained normal urinary free cortisol versus 10 (29%) patients who received placebo (OR 13·7, 95% CI 3·7–53·4; $p<0·0001$) by 48 weeks[6]. Common side effects of osilodrostat include nausea, anemia and headache.

Mifeprestone is a glucocorticoid receptor blocker. In an open-label study involving 50 patients over a 24-week treatment period, 60% and 28% of

patients' glucose and diastolic blood pressure improved respectively[7]. However, up to 24% of patient developed hypokalemia and required spironolactone, 14% needed dexamethasone due to adrenal insufficiency. Mifepristone may also precipitate hypothyroidism and drug-drug interactions with drugs such as losartan, celecoxib, pioglitazone as mifepristone is a strong CYP450 2C8 and 2C9 inhibitor. Concurrent use of mifepristone would result in reduced clearance of these drugs.

The choice of medical therapy should be personalized, taking into account the patient background, drug potency and onset of the treatment. For instance, orlidrostat and metyrapone have a rapid onset, which may be preferred if early surgery is indicated. Parenterally administered drugs, such as pasireotide, maybe considered if the patient is intolerant to oral medications. Cabergoline may be preferred in pregnancy patients[2].

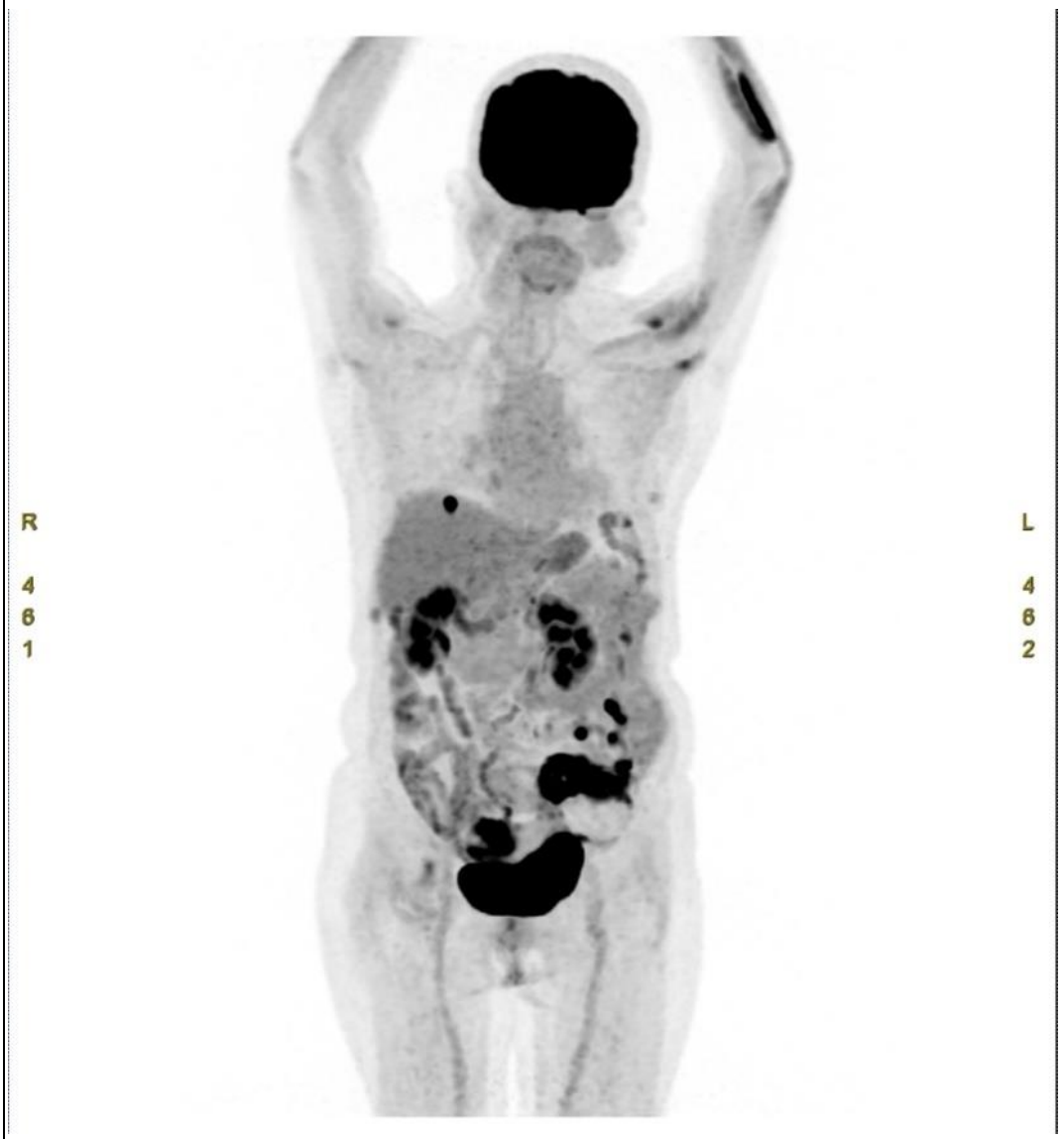
This clinical case demonstrated the complex diagnosis and treatment algorithms of Cushing's syndrome due to ectopic ACTH secretion by metastatic ovarian carcinoma. Our case illustrated the importance in recognition of the clinical syndrome, arrangement of relevant biochemical tests and appropriate imaging modalities. Furthermore, biochemical monitoring of ACTH and cortisol levels may guide medical treatments before and after surgical resection of ACTH secreting tumours, or in patients who are not fit for surgery.

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

Table 1. CRH stimulation test results of ACTH and cortisol levels against time.

8/8/2022	09:30	09:48	10:04	10:19	10:51	11:54
ACTH (pmol/l)	17.0	11.7	13.0	11.1	10.8	12.3
Cortisol(nmol/l)	739	696	678	619	572	592

Figure 2. PETCT image illustrating increased uptake in bilateral ovaries, sigmoid colon, peritoneal nodules and right lung.



Reference (not more than 10)

1. Wajchenberg BL, Mendonca BB, Liberman B, et al. Ectopic adrenocorticotropic hormone syndrome. Endocr Rev 1994;15:752-87.
2. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, Boguszewski CL, Bronstein MD, Buchfelder M, Carmichael JD, Casanueva FF, Castinetti F, Chanson P, Findling J, Gadelha M, Geer EB, Giustina A, Grossman A, Gurnell M, Ho K, Ioachimescu AG, Kaiser UB, Karavitaki N, Katznelson L, Kelly DF, Lacroix A, McCormack A, Melmed S, Molitch M, Mortini P, Newell-Price J, Nieman L, Pereira AM, Petersenn S, Pivonello R, Raff H, Reincke M, Salvatori R, Scaroni C, Shimon I, Stratakis CA, Swearingen B, Tabarin A, Takahashi Y, Theodoropoulou M, Tsagarakis S, Valassi E, Varlamov EV, Vila G, Wass J, Webb SM, Zatelli MC, Biller BMK. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021 Dec;9(12):847-875. doi: 10.1016/S2213-8587(21)00235-7. Epub 2021 Oct 20. PMID: 34687601; PMCID: PMC8743006.
3. Detomas, M., Ritzel, K., Nasi-Kordhishti, I., Wolfsberger, S., Quinkler, M., Losa, M., Tröger, V., Kroiss, M., Fassnacht, M., Vila, G., Honegger, J. B., Reincke, M., & Deutschbein, T. (2022). Outcome of CRH stimulation test and overnight 8 mg dexamethasone suppression test in 469 patients with ACTH-dependent Cushing's syndrome. *Frontiers in Endocrinology*, *13*.
4. Pivonello R , De Leo M , Cozzolino A , Colao A. The treatment of Cushing's disease. *Endocr Rev.* 2015; 36: 385-486
5. Nieman L, Boscaro M, Scaroni C, et al. Metyrapone treatment in endogenous Cushing's syndrome: results at week 12 from PROMPT, a prospective international multicenter, open-label, phase III/IV study. 2021 Virtual Meeting of the Endocrine Society (ENDO 2021); March 20–23, 2021 (abstr OR14-2).
6. Pivonello R, Fleseriu M, Newell-Price J et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. *Lancet Diabetes Endocrinol.* 2020; 8: 748-761
7. Fleseriu M, Biller BM, Findling JW et al. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *J Clin Endocrinol Metab.* 2012; 97: 2039-2049
8. Chrousos GP, Schulte HM, Oldfield EH, et al. The corticotropin-releasing factor stimulation test. An aid in the evaluation of patients with Cushing's syndrome. N Engl J Med 1984; 310:622.
9. Wajchenberg BL, Mendonca BB, Liberman B, et al. Ectopic adrenocorticotropic hormone syndrome. Endocr Rev 1994;15:752-87.
10. Jaïs P, Terris B, Ruszniewski P, et al. Somatostatin receptor subtype gene expression in human endocrine gastroentero-pancreatic tumours. **Eur J Clin Invest** 1997; 27(8):639–644.

No of words in Case History and Discussion (excluding references):____1655_____
(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.

_____
(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)

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