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 TWELVE Weeks before the date of Interim Assessment

Name of candidate (print and sign): Wu Tsun Wai Jeffrey
Hospital and Unit: QMH Specialty: AIM and Nephrology
Name of supervisor (print and sign): Dr. Lee Chun Hong Alan
Date(s) and place (hospital) of patient encounter: July 2024, QMH MED
Date of report submission: 13 Mar 2025

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: An Elusive Diagnosis: Biochemically Confirmed Insulinoma With Challenging Localisation

Case history:

A 34-year-old woman, a domestic helper, was admitted for sudden loss of consciousness (LOC), lasting around 5 minutes with spontaneous recovery. Hemostix was 1.1 when she was on ambulance, for which she was immediately given dextrose 10% solution. Her LOC was not preceded by chest discomfort, palpitations, dyspnoea. She did not present with twitching, incontinence, uprolling of eyeballs or tongue bites.

She reported a similar episode 3 months before this admission. She also noticed 4kg-weight gain over past one and a half year, associated with increased appetite. She had a few episodes of sweating and palpitations, relieved by food intake. She regularly took over-the-counter multivitamins and denied exogenous steroids uses.

Neurological and cardiovascular examinations were unrevealing. She did not any cushingoid features or hyperpigmentation. She was at 53.9kg with BMI of 23.3.

She developed recurrent hypoglycaemia after hospitalization. A set of bloods was taken at H'stix 2.3. The plasma glucose, C-peptide, insulin level and

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beta-hydroxybutyrate were 2.1mmol, 1.04 nmol/L (≥0.2), 16.4 mIU (≥3) and <0.1 mmol/L (<0.6 during fasting) respectively. 9am cortisol was 125 nmol/L (morning 130-600) and ACTH was 5 pmol/L (morning 1.6-13.9). 1mcg short synacthen test (SST) yielded adequate response with cortisol rising from 215 to 716 nmol/L at 60 minutes. Urine toxicology screening was unrevealing. The impression was endogenous hyperinsulinaemic hypoglycaemia. The patient was educated on cornstarch diet and was started on diazoxide. She was discharged and scheduled outpatient follow-up.

The diazoxide was titrated gradually from 25mg twice per day up to 125mg thrice per day (max dose 8mg/kg/day i.e. 440mg/day for the patient). Hydrochlorothiazide was later introduced for diazoxide-induced lower limb oedema. The patient however still developed recurrent LOC and hypoglycaemia despite lifestyle modification and medical treatment. She was re-admitted and put on dextrose infusion. Octreotide, a somatostatin analogue was further added, which was then switched to monthly lanreotide. Her hypoglycaemia remained refractory and she eventually required a peripherally inserted central venous catheter (PICC) for prolonged dextrose infusion. She was later put on oral prednisolone and was finally able to wean off the dextrose infusion.

Meanwhile, she had been undergoing localization studies for a possible insulinoma. Computed tomography (CT) of the pancreas with contrast did not show any pancreatic lesions. 66Ga-DOTA-TATE positron emission tomography (PET)-CT revealed no 68Ga DOTA-TATE avid lesions. Endoscopic ultrasound (EUS) was done [figure 1] and fine needle aspiration was performed on a 1.2cm hyperechoic lesion at the pancreatic head, yet the aspiration yield was inadequate for analysis. EUS-guided biopsy was attempted again on the pancreatic lesion later. Microscopic examination of the specimen revealed ubiform cuboidal cells with eosinophilic cytoplasm. Immunohistochemistry study showed positive stains for chromogranin A and synaptophysin, wth low Ki67 expression at ~1%. This is histologically compatible with a well-differentiated pancreatic neuroendocrine tumour (pNET).

She was referred to hepatobiliary and pancreatic (HBP) surgery team, an elective laparoscopic Whipple operation was performed in June 2025. The specimen section showed a well-circumscribed tumour organized in trabeculae and glandular pattern, supported by a rich vascular network. The tumour cells possess eosinophilic to amphophilic cytoplasm. They are again positively stained

for chromogranin A and synaptophysin. Features are those of a well-differentiated pNET. The resection margin was clear.

Diaxozide, hydrochlorthiazide and lanreotide were stopped after the operation. Prednisolone was switched to maintenance hydrocortisone, later stopped when subsequent SST result two months later was not suggestive of adrenal insufficiency.

Discussion and literature review

The case illustrates stepwise approach to hypoglycaemia workup and medical/surgical management of insulinoma.

To establish the diagnosis of a hypoglycaemic disorder in a non-diabetic patient, history taking should begin by focusing on the Whipple's triad, which should include (1) hypoglycaemic symptoms; (2) documentation of low blood glucose; and (3) resolution of symptoms after ingestion of carbohydrates or administration of glucose. While patients may present with autonomic symptoms such as sweating, weakness, hunger and tachycardia, these symptoms may disappear after prolonged recurrent hypoglycaemia due to "hypoglycaemic unawareness". Clinicians also need to pay heed to other symptoms of neuroglycopenia, including seizure, cognitive impairment, focal neurological deficits (mimicking stroke), LOC[1].

Biochemical investigations should follow a well-documented history fulfilling the Whipple's triad. Serum insulin and C-peptide should be taken in patients with documented hypoglycaemia <2.5-3 mmol/L. Fasting test was not indicated in this patient who had already presented with spontaneous hypoglycaemia. Insulin ≥3 mIU/L, C-peptide ≥ 0.2 nmol/L along with suppressed beta-hydroxybutyrate are indicative of endogenous hyperinsulinaemic hypoglycaemia.

The presence of hypoglycaemic agents should be assessed if factitious hypoglycaemia is suspected. Exceedingly high insulin level (>100-1000mIU/L) and a history of recurrent postprandial hypoglycaemia may warrant evaluation of autoimmune insulin antibody or insulin receptor antibody. The interpretation of the laboratory tests is summarized in figure 2.

In confirmed cases of endogenous hyperinsulinaemic hypoglycaemia, imaging studies should be pursued to localize the lesion and detect metastases. 90% of

insulinoma are benign solitary tumours and 90% are intra-pancreatic. Extra-pancreatic insulinoma are usually situated at the duodenal wall and rarely causes hypoglycaemia[1]. CT is the preferred initial imaging modality, with newer evidence suggesting a better sensitivity with MRI. EUS is another well-established diagnostic method with high sensitivity, albeit operator dependent. Selective arterial calcium stimulation test with hepatic venous sampling (SACST/ASVS) is typically reserved for cases with negative CT/MRI findings. The injection of calcium in the supplying vessels of the tumour causes cellular degranulation and insulin release into the portal vein, resulting in elevated insulin level measured at hepatic vein[1].

Somatostatin receptor (SSTR) imaging, such as 68Ga-DOTA-TATE PET-CT used in this patient, may be useful in diagnosing pNET. However, insulinomas sometimes have lower SSTR expression than other pNETs, leading to false negative result. There is an increased popularity of Glucagon-like peptide-1 receptor (GLP-1R) targeted imaging. It is built on the principle that almost all benign insulinomas express GLP-1R at much higher density (~5 times) than normal beta cells. While GLP-1 is readily degraded by Dipeptidyl peptidase-4 (DPP-4), the exendin-4 is resistant to such degradation and serves as a targeting molecule. GLP-1R PET/CT reportedly has above 90% sensitivity, showing promises for non-invasive tumour localization and hopes to avoid invasive SACST/ASVS[2].

Management of insulinoma begins with prevention of hypoglycaemia. Meals and snacks rich in slow carbohydrates are recommended. A meal before bed should be included, and in severe cases, nocturnal tube feeding. Central venous catheter should be ensured in patient with anticipated prolonged need of intravenous glucose administration.

Diazoxide is a benzothiadiazine derivative which inhibits adenosine triphosphate (ATP)-dependent potassium channels of the beta islet cells. This leads to hyperpolarization of the cell membrane and inhibition of insulin secretion. The main dose-limiting side effect is fluid retention and oedema, which is commonly mitigated by the concurrent use of thiazide diuretics. Female patients should also watch out for hirsutism.

Somatostatin analogues such as octrotide and lanreotide may suppress insulin secretion in a subgroup of insulinomas with increased SSTR2 expression. Glucocorticoids are reserved in refractory causes due to unfavourable long-term

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side effect profile. Beta blockers, non-dihydropyridine calcium channel blocker and phenytoin have been tried with variable efficacy. Ersodetug (RZ358), a human monoclonal antibody that allosterically and reversibly binds the insulin receptor (INSR), has shown to reduce hypoglycaemic events in a phase 2 study in patients with congenital hyperinsulinism, showing potential for a novel insulinoma treatment[3].

Curative surgical excision remains the treatment of choice for localized non-metastatic insulinomas[4]. Enucleation, distal pancreatectomy and Whipple procedure are possible options depending on tumour location and size. Radiofrequency ablation (RFA) or stererotactic body radiotherapy (SBRT) may be considered in patients at high risk for surgeries.

This case highlights both the diagnostic and therapeutic challenges of insulinoma, particularly when conventional cross-sectional and SSTR-based functional imaging are non-localizing. Nevertheless, workup should always aim at first confirming endogenous hyperinsulinaemic hypoglycaemia with appropriately paired biochemical sampling during symptomatic hypoglycaemia, followed by tumour localisation and definitive therapy. The patient's prolonged, refractory course also underscores the importance of a structured approach to hypoglycaemia prevention and escalation of medical therapies as bridging measures while localisation is pursued, alongside vigilance for treatment-related complications. With emerging modalities such as GLP-1R–targeted imaging and novel insulin-action attenuating therapies under study, future algorithms may reduce reliance on invasive sampling and shorten time to cure. However, early recognition of neuroglycopenic presentations and adherence to stepwise biochemical confirmation remain the cornerstone of safe and effective management.

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

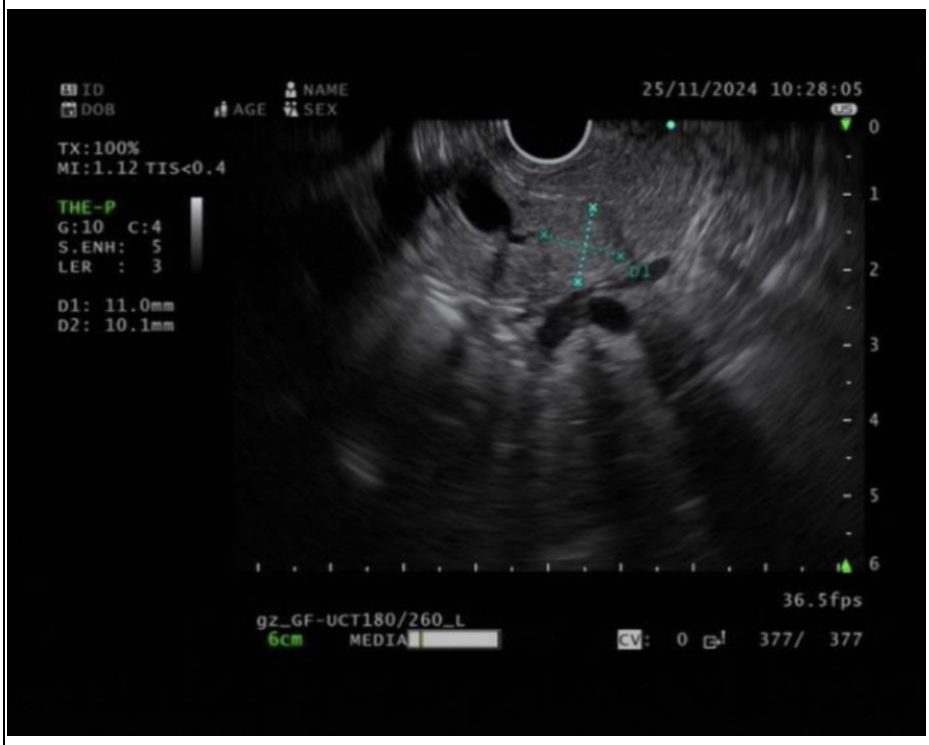


Figure 1 – endoscopic ultrasound showing pancreatic head hyperechoic lesion, with biopsy taken

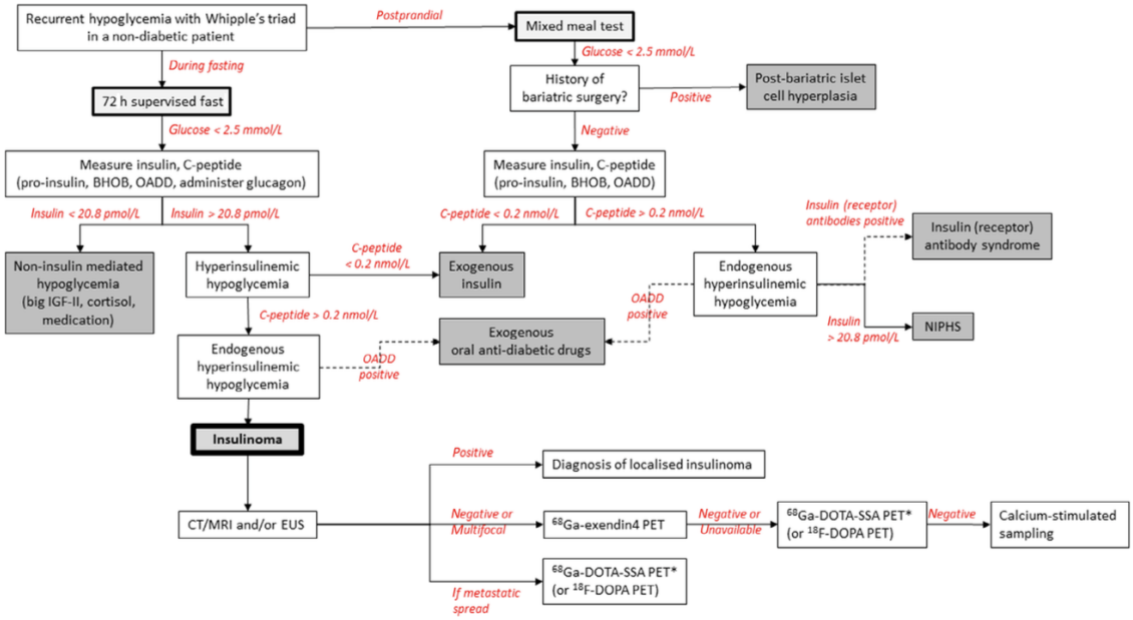


Figure 2 – diagnostic algorithm for hypoglycaemia suggested in European Neuroendocrine Tumour Society 2023 guidance paper[5]

Reference (not more than 10)

1. Okabayashi T. Diagnosis and management of insulinoma. *WJG*. 2013;19(6):829. doi:10.3748/wjg.v19.i6.829

2. Christ E, Antwi K, Fani M, Wild D. Innovative imaging of insulinoma: the end of sampling? A review. *Endocrine-Related Cancer*. 2020;27(4):R79-R92. doi:10.1530/ERC-19-0476

3. Demirbilek H, Melikyan M, Iotova V, et al. Global, multi-center, repeat-dose, phase 2 study of RZ358 (ersodetug), an insulin receptor antibody, for congenital hyperinsulinism. *Med*. 2025;6(6):100611. doi:10.1016/j.medj.2025.100611

4. Hofland J, Refardt JC, Feelders RA, Christ E, De Herder WW. Approach to the Patient: Insulinoma. *The Journal of Clinical Endocrinology & Metabolism*. 2024;109(4):1109-1118. doi:10.1210/clinem/dgad641

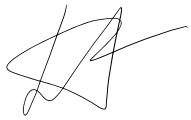
5. Hofland J, Falconi M, Christ E, et al. European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. *J Neuroendocrinology*. 2023;35(8):e13318. doi:10.1111/jne.13318

No of words in Case History and Discussion (excluding references):_____1357_____.

(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 *

Dr Lee Chun Hong Alan 

(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.