中文題目：胰島素瘤: 病例報告與文獻回顧

英文題目：Insulinoma: A Case Report and Literature Review

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Introduction:

According to the Endocrine Society Clinical Practice Guideline for Evaluation and Management of Adult Hypoglycemic Disorders, published in 2009, we recommend evaluation and management in adults in whom Whipple's triad documented. In patients with fasting hypoglycemia without diabetes mellitus, clinical clues to potential hypoglycemic etiologies, such as hyperinsulinemic (including endogenous or exogenous causes) or non-hyperinsulinemic status, should be considered.

Initially excluded drug-related hypoglycemia, patients with endogenous hyperinsulinemic etiologies and negative for insulin antibody or insulin receptor antibody, localization test for possible insulinoma should be arranged. Here, we report a case of insulinoma, documented by selective intraarterial calcium stimulation test (IACS), and make a systematic review to compare these diagnostic tools.

Case Description

A 47-year-old woman, a tuner, was generally healthy before and she suffered from tongue and bilateral arms numbness since the end of 2018, without any precipitating or palliating factors. She visited Shuang Ho Hospital (SHH) in early 2019 and myocardial bridge was told. She mentioned body weight gain, by 5 kg in recent one year and denied irregular menstrual cycle. Her numbness became more severe in 2020, partially subsided after taking snacks, but she still woke up in the middle of the night (around 2 AM) with sweating and hunger feeling. Her symptoms got worse with transient speech problems, slow response, problems using smart phones, and her elder sister observed her personality change, easy panic, increased in severity of insomnia and fluctuated appetite.

In the afternoon of May, 5, 2020, she became disoriented at first and then lost consciousness. She was then sent to the ER of SHH for help, where hypoglycemia was checked, but she recovered soon, after glucose infusion, and she came to OPD of AIR and neurologist's department of Mackay Memorial Hospital (MMH) due to personal reasons. Autoimmune disorders (AID) were first considered due to chief complaint of progressive numbness over tongue and bilateral arms, but then were ruled out based on the autoimmune profiles. She was admitted to neurologist's ward, where she received brain computed tomography (CT) and her outpatient brain Magnetic Resonance Imaging (MRI) displaced negative finding over pituitary area. Her complete blood count was unremarkable but biochemistry data yielded random

glucose 37 mg/dL, HbA1C: 4.8% (4.0-6.0 %), blood beta-ketone 0.1mmol/L (< 0.6 mmol/L), and endocrinologist was consulted with tentative diagnosis of hypoglycemia without diabetes.

Initial vital signs were body temperature 37.2℃, pulse rate 72 beats/min, respiratory rate 20/min and blood pressure 109/70 mmHg. Electrocardiogram showed normal sinus rhythm. Other biochemistry data showed normal renal/ liver function, normal lipid profile, no electrolyte imbalance (Na, K, Cl, Ca, P, Mg) and albumin 4/4 g/dL (3.5-5.0 g/dL). 72-hrs prolonged fasting test was indicated for recurrent hypoglycemia, refractory to glucose infusion, and was early terminated due to glycemic target achieved within 3 hours. Otherwise, her result of endocrine axis turned out to be within normal range, including cortisol 17.27 ug/ dL (morning 9.52-26.21 ug/ dL), ACTH 44.12 pg/mL (10.0-70.0 pg/mL); TSH 1.23 uIU/mL (0.25-4.00 uIU/mL), free-T4 1.30 ng/dL (0.89-1.79 ng/dL), T3 93.86 ng/dL (78.0-182.0 ng/dL); IGF-1 252.0 ng/mL (107-297 ng/mL), HGH 0.07 ng/mL (< 5.0 ng/mL); insulin antibody 4.2 % (< 5.5%).

72-hr prolonged fasting test			Post 1mg glucagon IV injection		
time	0 min	Sentinel event	10 min	20 min	30 min
Serum BG	65	51*	74	103	112
insulin	9.30	8.90	—	—	—
C-peptide	1.88	1.82	—	—	—
備註：BG: blood glucose (mg/dL), insulin (3.21-16.32 uIU/mL), C-peptide (0.8-4.2 ng/mL)					
* cortisol 24.73 ug/ dL, ACTH 66.25 pg/mL; HGH 0.81 ng/mL					

According to the result of data, listed above, endogenous hyperinsulinemia, insulinoma-related was highly suspected. Abdominal echo, pancreatic CT with contrast and IACS were arranged. Because multiple endocrine neoplasia, type 1 should also be ruled out, chromogranin A, gastrin, i-PTH, Ca/P, para/thyroid echo and panendoscope were also arranged, which later, turned out to be unremarkable finding. Octreotide was then administered due to recurrent, severe hypoglycemia refractory to glucose infusion. The pancreatic CT displaced a hypervascular lesion about 1.2*1.0cm in the pancreatic tail, consistent with the result of abdominal echo, compatible with clinical suspicion of insulinoma. The result of IACS, shown beneath, whose concentration of insulin, c-peptide, were sampled from the hepatic artery, also compatible with the insulinoma, localized at the tail of pancreas.

		0 sec	20 sec	40 sec	60 sec
SMA	insulin	16.50	15.90	14.40	13.10
	C-peptide	3.70	3.60	3.58	3.60
GDA	insulin	25.70	18.50	20.10	20.50

	C-peptide	4.65	4.56	4.46	4.43
SpA	insulin	15.40	88.90	106.40	78.30
	C-peptide	3.88	13.40	6.40	6.07
備註：SMA: superior mesenteric artery; GDA: gastroduodenal artery; SpA: splenic artery					

The patient was transferred to the division of general surgeon, where she received distal pancreatectomy. The pathological report turned out to be a neuroendocrine tumor, grade 2, which Ki-67 proliferation labeling index about 5%; immunohistochemically, positive for INSM-1, CD56, chromogranin A, synaptophysin and islet-2, consistent with pancreatic origin. She no more suffered from hypoglycemic, nor hyperglycemic episode during OPD follow, afterwards.

Discussion

Most insulinoma can be identified from conventional localizing preoperative study, such as ultrasonography, CT scan, or MRI, but still some occult one refers to a biochemically proven tumor with indeterminate anatomical site. These occult insulinoma, usually less than 1 cm, within the pancreatic head or uncinate process, only can be identified by further invasive tools, such as, IACS (its sensitivity 93%); combination of IACS and endoscopic ultrasound (EUS) (100%). Besides, EUS was specific to localized the insulinoma, near the head or uncinate process of pancreas.

Overall, the symptoms of hypoglycemic episodes of insulinoma occur in the fasting state in 73%; 6% postprandial; 21% both. Otherwise, IACS can differentiate insulinoma from adult-onset nesidioblastosis, termed noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), which is typical of postprandial hypoglycemia.

There is a strong tendency of performing intraoperative localization by palpation or using intraoperative ultrasonography (IOUS) for reconfirmation, which is especially useful in discriminating the proximity of the lesions to the pancreatic or bile duct; in guiding the dissection of tumors during enucleation.

Conclusion

CT is routinely used as formal staging, non-invasive, diagnostic tool, preoperatively. IACS or EUS can be consider if non-invasive examination cannot localize the insulinoma. IOUS was applied, routinely for confirmation, detection of distant metastasis, and guideline for enucleation.