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Patient with Recurrent Hypoglycemia Caused by Malignant Giant Insulinoma

Clareza Arief Wardhana, Anak Agung Wiradewi Lestari, I Nyoman Wande

Department of Clinical Pathology, Faculty of Medicine, Udayana University/Sanglah Hospital, Denpasar, Indonesia. E-mail: clareza.arief@yahoo.com

ABSTRACT

Insulinoma is a functional endocrine tumor in the pancreas and the most common cause of hypoglycemia due to endogenic hyperinsulinism. Insulinoma is a rare case, with an incidence of 1-4 cases per million people each year. Malignant insulinoma is an insulinoma that is proven to metastasize to other tissues and only happens in 5-10% of insulinoma cases. Insulinoma with a size >9 cm is classified as giant insulinoma. Since 1927, fewer than 40 cases of giant insulinoma have been reported. 56 years old female was referred from a private hospital with the chief complaint of decreased consciousness due to recurrent hypoglycemia. On physical examination, palpable ±12x4 cm solid mass with an uneven surface in the epigastric region. Laboratory tests found an increase in c-peptide, fasting insulin, and liver function tests. A contrast CT scan found a heterogeneous solid mass 7.6x8.6x13.6 cm in cauda of the pancreas and hepatomegaly with multiple metastatic nodules. Results of pancreas and liver biopsy showed poorly differentiated carcinoma that metastasizes to the liver. In this case, based on patient history, physical and other examinations, it can be concluded that the patient was diagnosed with an observation of recurrent hypoglycemia caused by giant insulinoma with liver metastases.

Keywords: Endocrine tumor, hypoglycemia, malignant giant insulinoma

INTRODUCTION

Insulinoma is a functional endocrine tumor in the pancreas and the most common cause of hypoglycemia due to endogenic hyperinsulinism. Insulinoma is a rare case, with an incidence of 1-4 cases per million people each year. This tumor is usually benign (>90%) and is < 3cm (96%). Only 10% of insulinoma cases are malignant and can metastasize to other tissues such as the liver and lymph nodes.[1] According to the World Health Organization (WHO), insulinoma can be stated malignant if there is proof of metastasis to other tissues. Malignant insulinoma is associated with a high relapse and mortality rates.[2] Since 1927, less than 40 cases of giant insulinoma have been reported, with the largest one being > 9 cm.[3,4]

CASE REPORT

A-56-year-old female patient, was referred from a private hospital with a diagnosis of recurrent hypoglycemia due to suspect of hypoglycemia. The patient's family claimed that she had a decrease in consciousness every morning for the last 2 weeks. The decrease in consciousness was in the form of being silent and not being able to respond appropriately when being talked to. The patient suffered from weight loss of as much as 10 kg in the past 2 months. The patient had a history of admittance to a private hospital in Tabanan due to fainting caused by a drop of blood sugar below 40 mg/dL and the patient regained consciousness after getting an IV drip. The patient has been hospitalized two times before with the same complaint and received intravenous glucose 10 times. History of drug consumption such as diabetic medicine, herbal or traditional medicine was also denied.

The patient arrived conscious but weak. Heart rate 98 x/minute, respiratory rate 18 x/minute, body temperature 36.5°C. Physical examination found a distended abdomen, normal bowel movements, liver palpated + 10 cm, spleen unpalpable, a solid mass + 12 x 4 cm with an uneven surface was palpable in the epigastric region (Figure 1).

Complete blood count and hemostatic results were within normal limits. Random blood glucose when the patient showed hypoglycemic symptoms at the hospital was < 50 mg/dL (Table 1,2,3).

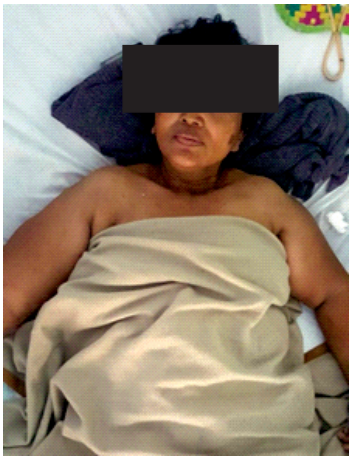


Figure 1. Patient with malignant giant insulinoma

Clinical chemistry results showed an increase of AST 67.2 U/L, ALT 59.1 U/L, ALP 117 U/L, GGT 150 U/L, fasting insulin 154 µIU/mL, and c-peptide 7.1 ng/mL (Table 4).

Abdominal ultrasonography on June 18th, 2019 showed hepatomegaly with multiple nodules in the right and left lobes of the liver, suspected metastatic nodules, observation of a solid mass in the epigastric region with calcification and positive intralesional vascularization, a mass in the head of the pancreas that could not be ruled out, bilateral nephritis, and observation of a heterogeneous solid mass with indistinct boundaries at the lower pole of the left kidney.

Table 1. complete blood count

Parameter	Results		Reference Range
	14/06/2019	25/06/2019	
WBC (10^3/µL)	10.04	10.14	4.1-11.0
% Neu	**90.34**	**72.22**	47-80
% Lym	**8.06**	19.33	13-40
% Mono	**1.38**	5.20	2.0-11.0
% Eos	0.06	2.09	0,0-5,0
% Baso	0.16	1.17	0.0-2.0
RBC (10^6/µL)	4.68	4.20	4.0-5.2
HGB (g/dL)	12.39	**11.12**	12.0-16.0
HCT (%)	40.72	36.40	36.0-46.0
MCV (fL)	87.07	86.58	80.0-100.0
MCH (pg)	26.49	26.46	26.0-34.0
MCHC (g/dL)	**30.42**	**30.56**	31-36
RDW (%)	13.60	13.76	11.6-14.8
PLT (10µ/µL)	358.70	349/60	140-440
MPV (fL)	**4.98**	**4.58**	6.80-10.0

Table 2. Hemostasis results

Parameter	Results	Reference Range
	25/6/2019	
PPT (seconds)	14.0	10.8-14.4
INR	1.13	0.9-1.1
APTT (seconds)	26.4	24-36

Table 3. Random blood glucose results

Date	Symptomatic RBG	RBG Following Intravenous D40%	Reference Range
14/06/19	**37** mg/dL	**370** mg/dL	70-140 mg/dL
15/06/19	**44** mg/dL	**234** mg/dL	70-140 mg/dL
17/06/19	**30** mg/dL	108 mg/dL	70-140 mg/dL
18/06/19	**27** mg/dL	87 mg/dL	70-140 mg/dL
21/06/19	**22** mg/dL	**218** mg/dL	70-140 mg/dL
22/06/19	**21** mg/dL	**146** mg/dL	70-140 mg/dL

Table 4. Clinical chemistry results

Parameter	Results			Reference Range
	14/06/2019	16/06/2019	25/06/2019	
Potassium (mmol/l)			3.71	3.5-5.1
Sodium (mmol/l)			140	136-145
AST (U/L)	**59.1**		**46.5**	11-27
ALT (U/L)	**67.20**		**46.7**	11-34
BUN (mg/dL)	8.00		4.2	10-20
Serum creatinine (mg/dL)	0.82		0.69	0.5-1.2
Total bilirubin (mg/dL)			0.45	0.2-1
Direct bilirubin (mg/dL)			0.17	<0.2
Alkali phosphatase (U/L)			**117**	42-98
Gamma GT (U/L)			**150**	7.00-32.00
Albumin (g/dL)			3.40	3.40-4.80
HbA1c (%)	4.9			4.8-5.9
LDH (U/L)	321			240-480
Fasting insulin (µIU/mL)		**154**		3.2-28.5
C-peptide (ng/mL)		**7.1**		0.9-4.4
Free T4 (ng/dL)	1.65			0.93-1.70
TSHs (IU/mL)	1.84			0.27-4.2

AST: Aspartate aminotransferase; ALT: Alanine transaminase; ALP: Alkali phosphatase; GGT: Gamma GT

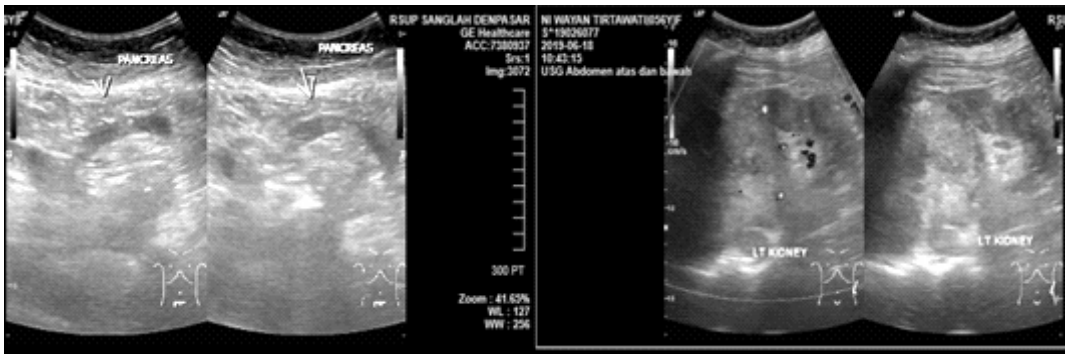


Figure 2. Abdominal USG, pancreatic mass (red), liver mass (blue)

Abdominal CT scan examination on June 19th, 2019 showed a heterogeneous solid mass measuring 7.6x8.6x13.6 cm in the cauda pancreas, which infiltrated the upper pole of the left kidney, IVC thrombus +/- 6.7 cm long, and in the left gonadal vein causing dilation of the gonadal veins to the left ovarian vein, left multiple perirenal and para-aortic lymphadenopathy, hepatomegaly with multiple metastatic nodules, no thrombus seen in the portal vein, grade I hydronephrosis in the right kidney, suspected due to partial stenosis of the right proximal ureter at L2-3 level, and lumbar spondylosis (Fig. 2 and 3).

Pancreatic tissue biopsy showed a proliferation of neoplastic cells forming infiltrative solid islands structure with 49/10 high powered field (HPF) mitosis. The liver biopsy found proliferation of

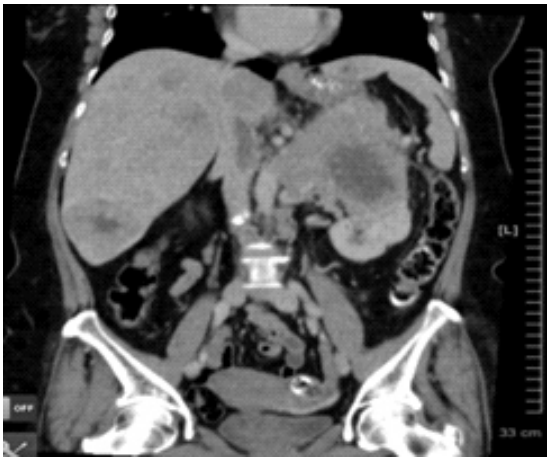
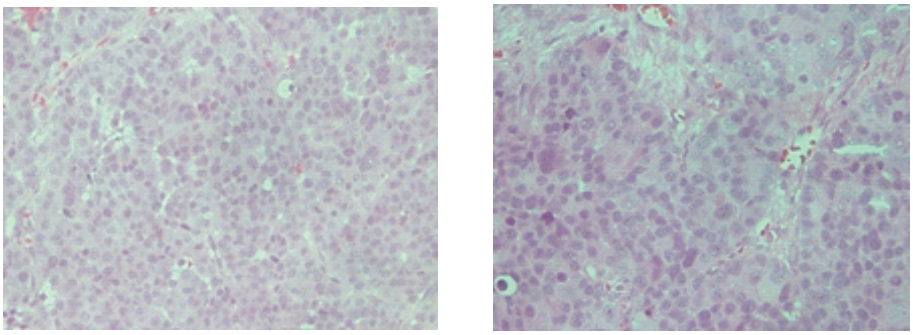


Figure 3. CT scan picture of the axial section, vein phase, pancreatic mass (red), multiple liver masses (blue)



(a) (b)

Figure 4. (a) Liver biopsy (b); Pancreas biopsy, arrows pointing at neoplastic cells

neoplastic cells forming solid trabecular islands and some forming solid island and glandular, infiltration between desmoplastic connective tissue stroma, and focus on bizarre cells with 39/10 HPF mitosis. The conclusion of the liver and pancreas tissue biopsy on June 26th, 2019 showed a poorly differentiated carcinoma type neuroendocrine carcinoma NEC (G3) that metastasized to the liver with a differential diagnosis of poorly differentiated adenocarcinoma (Figure 4).

The management of this patient was an intravenous fluid drip of D10% 20 drops per minute, a free diet with extra snacks and sugar water, if blood glucose was <60 mg/dL patient was given a bolus of 2 flasks of D40%, and then check the blood glucose every hour, subcutaneous octreotide 50 mcg every 12 hours, education to eat every 1-2 hours, and chemotherapy according to the digestive surgery section.

DISCUSSION

Insulinoma is the most common neuroendocrine tumor, in 40% of cases, and most patients are diagnosed with insulinoma between 30 and 60 years old. The highest prevalence is in females (59%).[4] Frequent clinical manifestations are the "Whipple triad" consisting of fasting hypoglycemia (<50 mg/dL or <2.7 mmol/L); symptoms of hypoglycemia; and immediate relief of symptoms after the administration of intravenous glucose. Patients can show autonomic disorder symptoms such as palpitation, tremor, and diaphoresis, also neuroglycopenic symptoms such as confusion, behavioral changes, seizures, and coma.[5,6]

This patient showed a history of a decrease in consciousness almost every morning when waking up 2 weeks before admittance. A decrease of consciousness appeared in the form of being silent and not being able to respond appropriately when being talked to. The patient suffered from weight loss as much as 10 kg in the past 2 months. The patient had a history pf admittance in a private hospital in Tabanan due to fainting caused by a drop of blood sugar below 40 mg/dL and the patient regained consciousness after getting an IV drip. The patient has been hospitalized two times before with the same complaint and received intravenous glucose 10 times. This fulfills all criteria for the Whipple triad that shows the patient had recurrent hypoglycemia, especially when waking up in the morning.

The gold standard examination to diagnose an adult patient with insulinoma, neuroglycopenic symptoms or a history of low plasma glucose were plasma insulin, c-peptide, and proinsulin.[7,8] This patient had a history of low glucose 2 weeks prior to admittance. While the patient was hospitalized in a private hospital, the patient had a history of blood glucose <40 mg/dL and when referred, an intravenous drip of D10% was administered. While admitted at Sanglah General Hospital, the patient also had a blood glucose <40 mg/dL several times due to sleeping soundly and forgetting to eat every 1 - 2 hours to maintain glucose stability. This patient has increased c-peptide and insulin at 7.1 ng/mL and 154 µIU/mL respectively. These results support the diagnosis of insulinoma because in insulinoma there is an increase in both c-peptide (>0.6 ng/mL) and insulin (>6 µIU/mL) due to endogenic hyperinsulinism that is produced by the tumor. Hypoglycemia occurs due to an increase of the hormone insulin in the blood causing an increase of glucose into the tissue. An increase in liver function tests (SGOT/SGPT/ALP/GGT) in this patient is in line with the metastasis of malignant insulinoma to the liver.

Insulinoma appears spontaneously, but about 10% of cases are related to the Multiple Endocrinal Neoplasia type-1 (MEN-1) gene. MEN-1 is a

dominant autosomal syndrome that can affect the parathyroid gland, anterior pituitary anterior, pancreas endocrine, and duodenum due to inactivation from the MEN-1 gene of chromosome 11q13.[7] Thyroid function tests in this patient showed normal results for TSH (1.84 IU/mL) and FT4 (1.65 ng/dL).

Radiologic examinations such as abdominal ultrasonography (USG), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) can also be performed to help establish the diagnosis with a sensitivity of 9-64%, 33-64%, and 40-90%, respectively. USG performed on this patient showed hepatomegaly with multiple nodules in the right and left lobes of the liver suspected of metastatic nodules and a solid mass in the epigastric region with calcification and intralesional vascularization. CT scan with contrast showed a heterogeneous solid mass measuring 7.6x8.6x13.6 cm in the cauda pancreas, multiple left perirenal and para-aortic lymphadenopathy, and hepatomegaly with multiple metastatic nodules. The results of these radiological examinations support the diagnosis of a tumor in the cauda pancreas. Insulinoma with the largest dimension >9 cm can be categorized as a giant insulinoma. Since 1927, less than 40 cases of giant insulinoma have been reported.[3,4] This tumor generally metastasizes to the liver and lymph nodes, and this is shown in this patient, as there is hepatomegaly with multiple metastatic nodules. According to the WHO, an insulinoma is said to be malignant, if it has been proven to metastases to other tissues.[2]

A laparotomy was performed on this patient for a biopsy of a pancreatic tumor and nodules in the liver. Pancreatic tissue biopsy showed proliferation of neoplastic cells forming infiltrative solid islands structure with 49/10 High Powered Field (HPF) mitosis. The liver biopsy found proliferation of neoplastic cells forming solid trabecular islands and some forming solid island and glandular, infiltration between desmoplastic connective tissue stroma, and focus on bizarre cells with 39/10 HPF mitosis. The result of this biopsy is a poorly differentiated carcinoma with hepatic metastases. According to the 2017 WHO criteria regarding pancreatic neuroendocrine neoplasia, patients with poorly differentiated and mitotic status > 20/10 HPF are classified as high-grade (G3) neuroendocrine carcinoma (NEC).[9]

The management of malignant insulinoma is very challenging for clinicians. According to an epidemiologic study in San Paolo, Brazil, the five years survival rate of insulinoma that has metastases to the liver is 16%. Another study by Mayo Clinic found the 10 years survival rate of malignant insulinoma to be 29%.[2,5] The palliative care approach is recommended for patients with malignant insulinoma with metastasis.[10] The aim of insulinoma management is to control hormone secretion and tumor growth. Insulin secretion can be controlled by using analog somatostatin such as octreotide. Hypoglycemia can be prevented by consuming food regularly, especially during the night/when malaise symptoms appear, and must be supervised by a family member. In cases with insulinoma where resection is not possible, antitumor treatment can be carried out with radiotherapy and chemotherapy.[6,7] This patient received intravenous D10% 20 drops per minute, a free diet with extra snacks/sugared water, education to eat every 1-2 hours, subcutaneous octreotide 50 mcg every 12 hours and a chemotherapy plan according to the digestive surgery division. Resection was not appliable in this patient due to the size of the tumor and liver metastasis. Current treatment aims to control insulin secretion and prevent hypoglycemia.

CONCLUSION

A female of 56-years-old has been reported with recurrent hypoglycemia due to giant malignant insulinoma. Laboratory results show an increase in c-peptide and fasting blood glucose. Radiology results show a >9 cm tumor that is categorized as giant insulinoma with liver metastasis. Biopsy results show a poorly differentiated carcinoma with liver metastasis. This patient met the WHO 2017 criteria regarding pancreatic neuroendocrine neoplasia as high-grade (G3) neuroendocrine carcinoma (NEC).

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