Jurnal RSMH Palembang
Journal Homepage: http://jurnalrsmh.com/index.php/JRP

Insulinoma

Ria Yuniarti[1*], Suly Auline

Departemen Patologi Anatomi, Fakultas Kedokteran Universitas Sriwijaya, Palembang, Indonesia

ARTICLE INFO

Keywords:
Insulinoma
Neuroendokrin
Insulin
Tumor Pankreas
Hipoglikemia
Hiperinsulinemia

Corresponding author:
Ria Yuniarti

E-mail address:
ria.alnika23@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/JRP.v1i2.10

ABSTRACT

Insulinoma is a functional neuroendocrine neoplasm consisting of insulin-producing cells, which produce insulin uncontrollably, causing a hypoglycemic syndrome. The Hypoglycemic syndrome is a result of hyperinsulinemia which causes adrenergic symptoms and neuroglycopenia. The clinical diagnosis is based on the Whipple triad, insulin, and C peptide levels in a 72-hour fasting state. Generally, insulinoma is a benign neoplasm with a proliferation index of Ki-67 <2%. On histological features, the growth pattern of the insulinoma is usually trabecular or solid. Some insulinomas show a *tubuloacinar* growth pattern with psammoma bodies. We reported one case of insulinoma in a 65-year-old woman, who had experienced fainting, cold sweats for 3 years, especially when the patient ate late or at midnight while sleeping. A CT scan showed a tumor mass in the pancreas possibly an insulinoma and a pancreatectomy was performed. The results of the histopathological examination are bu following peer under Insulinoma.

1. Introduction

Insulinoma is the most common functional endocrine neoplasm in the pancreas and accounts for 1-2% of all pancreatic neoplasms. Insulinomas occur in 1-4 per million people. Symptoms that arise are in the form of recurrent hypoglycemia, which can result in repeated loss of consciousness. Insulinomas can also be detected by radiological examination, and are treated by removing the tumor.

2. Case presentation

A 65-year-old woman came for treatment because she often experienced fainting, cold sweats, especially when eating too late or at midnight while sleeping. When the attack occurred, the face was pale with cold sweat, the tips of the fingers and toes were pale and cold. The patient regained consciousness after drinking sugar water.

Since ± one (1) year before admission to hospital, patients begin to learn to control dietary patterns and learn management when there are recurrent hypoglycemia symptoms. The hands are often numb, the neck feels tense occasionally. The patient feels that his weight is increasing, because his clothes are getting narrower, his face is wider and the skin folds in the neck area are also getting wider. During the last 3 years the patient's body weight increased from 60 kg to 105 kg. The patient had a history of hypertension for 5 years with the highest blood pressure 160/100 mmHg. Then the patient was referred to RSMH Dr. Moh. Hoesin to

do further examination regarding the condition of the disease

The examination at RSMH showed blood pressure 150/80 mmHg, pulse 88 beats per minute, breathing 22 times per minute, temperature 36.6 ^{o}C, height 151 cm, weight 105 kg, and body mass index (BMI) 46.1 kg/m^2, giving the impression of being overweight (*class 3 obesity, WHO BMI classification*). The patient's blood sugar level often ranges from 30-80 mg/dl, C-*Peptide* level is 14.36 ng/mL and insulin level is 101.3 uIU/ml.

The CT scan results showed a lobulated mass, well-defined (3x1.5 cm in axial size) which was enhanced by contrast, especially in the arterial phase of the cauda of the pancreas, the peripheral part of the anterior pancreas, seemed *benign*. The diagnosis is differential *Islet cell tumor* and insulinoma

During a laparotomy, a thick omentum is found in the abdominal cavity and closes the operative field of view. Furthermore, laparotomy and omentectomy conversion were performed. In gastrocolika, a pancreatic caudal tumor was found, then pancreatectomy was performed, then the excised tissue was sent to the Department of Anatomical Pathology for histopathological examination. Followed by washing the abdominal cavity.

On the macrosscopic examination, a piece of tissue covered with fat, yellowish in color, measuring 4x3x2 cm, found an *irregular* surface. In the cut, there was a well-defined, encapsulated mass, brownish yellow, measuring 2.8 x 1.6 x 1.4 cm, chewy, and there was no bleeding and necrosis **(Figure 1).**

On histopathological examination, it was found that tumor masses formed trabecular structures that partially anastomose each other, some were acinar, composed of cuboidal cells, round-oval nuclei, chromatin *salt and pepper*, granular eosinophilic cytoplasm, partly vacuole, clear. Mitosis is very rare, only 0-1 per 10 large field of view (TBSA). The mass of the tumor is surrounded by a desmoplastic stroma and in between appears an amorphous eosinophilic mass (possibly an amyloid). The stroma is mild to moderate inflammatory cells, lymphocytes, PMNs and plasma cells. There was the impression that a well-differentiated pancreatic neuroendocrine tumor (PanNET) *grade 1* (G1), supported insulinoma **(Figure 2).**

Immunohistochemical streaks were performed with several specific antibodies as neuroendocrine markers, namely anti-CD56, *Chromogranin, Synapthophisin and Ki-67*. All of these antibodies showed immunoreactive on tumor cells, whereas Ki-67 showed positivity in less than 2% (<2%) of tumor cells **(Figure 3).** Thus the diagnosis of this tumor is a *grade 1* (G1) well-differentiated pancreatic neuroendocrine tumor (PanNET), supporting insulinoma.

After removal of the tumor, the patient did not experience hypoglycemia again. A few days after that the patient experienced an increase in urea levels up to 213 mg / dl and 20.900 mg / dl of leukocytes. The patient's condition worsened and eventually died.

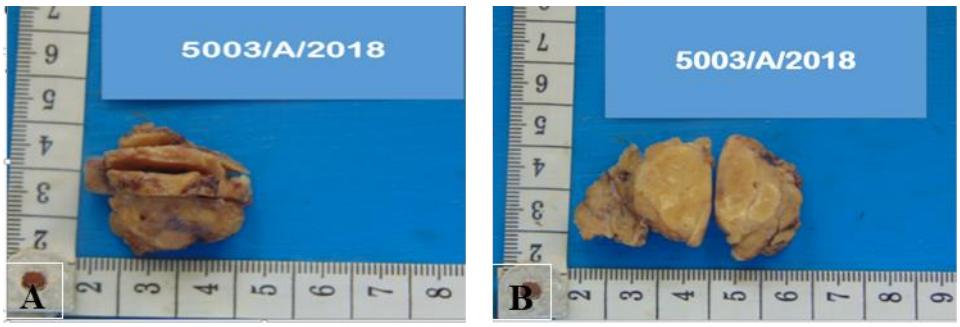

Figure 1. Macroscopic insulinoma. A. A piece of tissue covered with a little fat, yellowish in color, measuring 4 x 3 x 2 cm. B. Mass with firm boundaries, capsule, size 2.8 x1.6 x 1.4 cm brownish yellow, and chewy consistency.

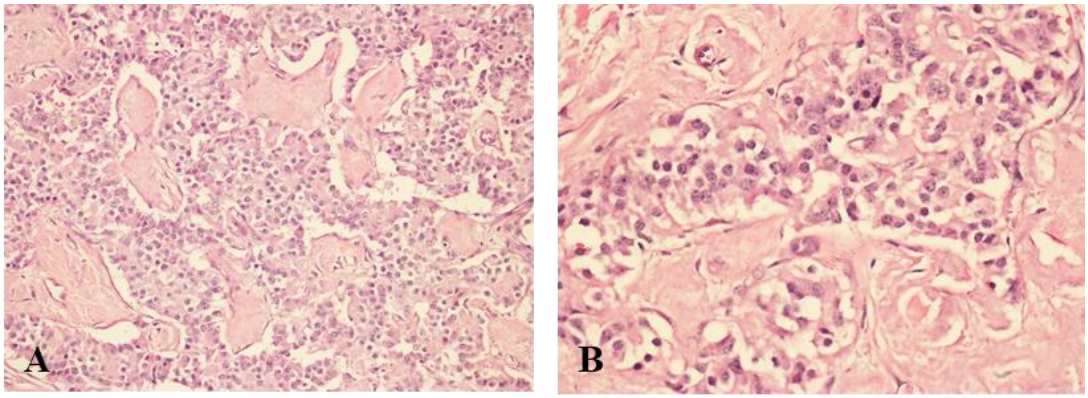

Figure 2. Histopathology of insulinoma A. The structure of the tumor mass is trabeculae (HE, magnification 100x). B. Tumor cells consist of cuboidal cells, round-oval nucleus, chromatin *salt and pepper*, granular eosinophilic cytoplasm, partly vacuole, clear, (HE, 200x magnification)

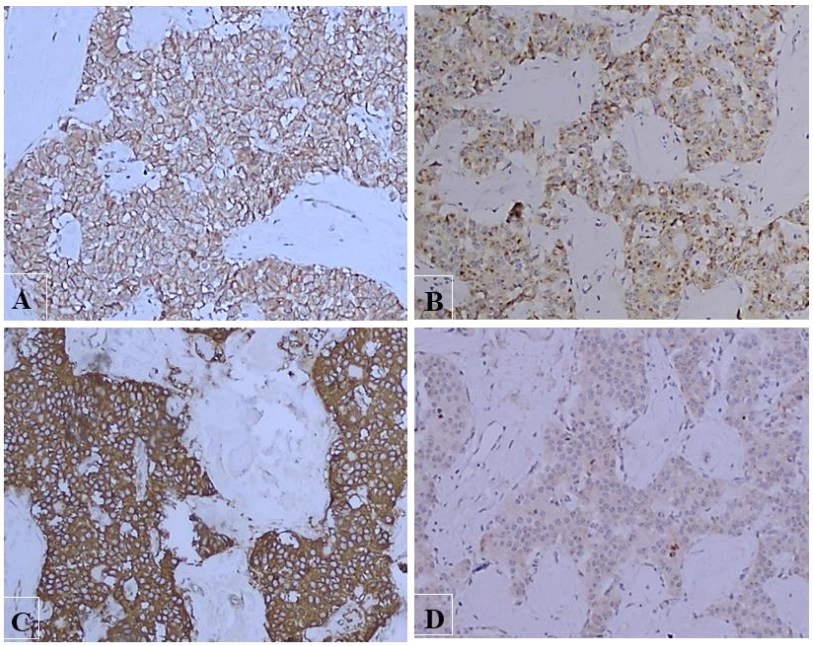

Figure 3. Immunoreactivity of CD56, *Chromogranin, synaphtophysin* and Ki-67 on tumor cells. A. Tumor cells show immunoreactive against CD56 with strong and diffuse expression. B. The cytoplasm of tumor cells shows immunoreactive against *Chromogranin.* C. Tumor cells show diffuse immunoreactive against *synaphtophysin.* D. Low Ki-67 proliferative index; 2% in insulinoma tumor mass. A, B, C, and D at 100x magnification.

3. DISCUSSION

Insulinomas as functional endocrine neoplasms are mostly found in the pancreas. The average age of most patients was 60 years. The ratio between male: female is 2: 3.[1,4,5] This is in accordance with the patient in this case, namely a woman aged 65 years. The locations of insulinomas are often in the pancreas (90%) and extrapancreas (10%). The most common locations were found in the pancreas, namely the corpus and cauda of the pancreas (57.1%); the head of the pancreas (42.9%). Extrapancreatic insulinoma is rare, but has been reported on the walls of the duodenum, ileum, jejunum and splenic hillus.[1] In this patient the lesions were in the cauda of the pancreas.

Correct diagnosis of insulinoma requires proper clinical observation and laboratory tests. Various clinical symptoms can arise in patients with this tumor, so that only 53% of patients can be diagnosed within 5 years after experiencing the first symptoms. Spontaneous hypoglycemia from insulinoma causes adrenergic symptoms and neuroglycopenia **(table 1).** Adrenergic symptoms include palpitations and tremors. Cholinergic symptoms include excessive sweating, hunger and / or paraesthesia. The symptoms of neuroglycopenia include severe weakness, psychiatric and neurological symptoms that vary. Other symptoms can include confusion, agitation, blurred vision, seizures, fainting and even coma.[1,2] In severe cases, patients may experience seizures and coma. Glucose levels below 55 mg/dL result in elevated catecholamine levels which in turn cause palpitations, shaking, diaphoresis, and tachycardia. All these symptoms disappear or can be prevented when the patient consumes a high-glucose diet, as described by Whipple and Frantz.[2] In this case, an insulinoma could only be diagnosed 3 years after the patient developed symptoms of neuroglycopenia in the form of decreased consciousness (recurrent fainting), adrenergic symptoms in the form of diaphoresis and weight gain.

Diagnosis in this case is based on symptoms of hypoglycemia, glucose levels less than 40 mg/dl or less than 2.2 mmol/L, and symptoms improve after glucose administration (whipple triad). The best test for this condition is fasting (48-72 hours) with measurement of blood glucose levels, serum insulin, *C-peptide* and pro-insulin **(table 2)**[3]. This patient experienced recurrent hypoglycemia and symptoms improved after being given glucose in the form of 40% dextrose. The tests carried out were in the form of random blood sugar which varied from 30-87 mg/dl, C-peptide levels = 14.36 ng/mL (0.78-5.19 ng/mL) and insulin = 101.3 uIU/ml (2.6-24.9 uIU / ml), this qualifies for an insulinoma diagnosis.

Radiological imaging plays an important role in detecting insulinoma in the pancreas. These tumors can be detected by *endoscopic ultrasonography* (EUS) with a sensitivity level of 77%, *Real time transabdominal high resolution ultrasonography* (sensitivity 50%), *intraoperative transabdominal high resolution ultrasonography* (detects more than 90% of insulinomas), CT scan (sensitivity 82-94%), *Magnetic resonance imaging* (MRI), *arteriography* (selective angiography has 82% accuracy, with 5% false positives), PET / CT *with gallium* -68 DOTA- (Tyr3) - *octreotate* (Ga-DOTATATE): 90% sensitivity.[6] A CT scan in this patient found insulinoma tumors after ultrasound showed no abnormalities.

On CT scan, the tumor is well-defined, with good vascularity. While on the MRI image, generally insulinomas give hypointense signals on T1FS and hyperintense on T2WI.[6,8]

Insulinoma is a tumor with small size, solitary and well-defined with a grayish-white to dark yellow color and a bleeding area is usually found in the section. About 80% of insulinomas are small compared to other PanNETs functional tumors (1-2 cm in diameter). Metastatic insulinomas usually measure more than 2 cm, with a mean of 3 cm.[1,4,5] However, in other literature it is reported that a tumor mass measuring 2 cm can occur even in 10-20% of insulinomas.[1,3] this was a brownish yellow mass, well-defined, measuring 2.8x1.6x1.4 cm, slightly larger than the mean tumor size.

In general, insulinomas showed a well-differentiated PanNETs pattern with a Ki67 proliferation index of less than 2%. Malignant

insulinoma is more often a neuroendocrine (G2) tumor. On histological features, the growth pattern of the insulinoma is usually trabecular or solid. Some insulinomas show a tubuloacinar growth pattern and there may be foci of *psammoma bodies*, such as those in somatostatin-producing PanNET. The normal pancreatic duct is sometimes trapped between the tumor cells, between which a sclerosed stroma and extensive hyalinization may be found. Stromal deposit *islet amyloid polypeptide* (IAPP, also called amylin) specific for insulinoma but only found in about 5% of cases.[1,4,5] Image of tumor cells with round nuclei, relatively small size, monotonous shape with chromatin *salt and pepper* and Eosinophilic cytoplasm, a classic cytomorphological feature of *Neuroendocrine Neoplasm* (NEN).[7] The microscopic appearance in this case shows a tumor mass with a trabecular structure, with cells showing the classic appearance of NEN among amyloid masses. The Ki67 proliferation index shows a well-differentiated neuroendocrine picture of tumors.

The presence of insulin is not mandatory in PanNET solitary cases. In multiple PanNET it is important to do insulin stain to detect insulinoma. Insulin staining is also needed to diagnose insulinomatosis, namely insulin-producing tumors that occur simultaneously or not simultaneously, rarely metastasize, often causing recurrent PHH *(persistent hyperinsulinemic hypoglycemia)*, which is shown to be a new primary insulinoma developing in the remaining pancreatic tissue in the patient.[14] About half of the patients Insulinoma showed limited positive staining for glucagon, PP (Pancreatic polypeptide), somatostatin and / or other hormones.[1] In this case insulin staining was not performed because this CPI test was not yet available at RSMH.

Immunohistochemical scans for diagnosis of NEN were performed to confirm that the tumor originated from neuroendocrine cell differentiation, rule out differential diagnosis (if any), and determine tumor grading. The antibody markers used to make the diagnosis are divided into first-line antibodies, namely chromogranin A and synapthophisin and second-line antibody markers CD56, CD57, and NSE. The diagnosis of NEN is made if the streak is positive in two of the 3 marker antibodies used. The antibody marker used to assess prognosis as well as to determine tumor grading was Ki-67.[7] Immunohistochemical tests performed on our patient showed a positive marker for chromogranin antibody, synaphtophisin, CD 56, thus meeting the NEN criteria.

Insulinoma staging, like all PaNENs, follows the TNM classification of *The Union for International Cancer Control* (UICC) and the *American Joint Committee on Cancer* (AJCC) *cancer staging manual*. Determining staging depends on the macroscopic location of the tumor, tumor size and metastasis. This approach is consistent with the classification of the *European Neuroendocrine Tumor Society* (ENETS).

The staging of this patient is T2NxMx (stage II). However, the staging was inadequate because in this specimen there were no lymph nodes and no other information or clinical examination.

Hypertension, which also occurred in this patient, was precipitated by catecholamine release in response to hypoglycemia, which can lead to acute hypertension through activation of the adrenal sympathetic system. Hypertension is a manifestation of hemodynamic balance of the cardiovascular system, and its pathophysiology is multi-factor so that it cannot be explained by a single mechanism.[11]

Obesity to insulinemia is associated with the effect of insulin action. In this case insulin causes SREBP-1 to increase the expression and action of the enzyme glucokinase, and consequently, to increase the concentration of glucose metabolites which is thought to be an intermediary for the effect of glucose on lipogenic gene expression.[11] The frequent consumption of sugar water as happened in this case also leads to accumulation. glycogen and causes obesity.

Differential diagnosis of clinical insulinoma includes nesidioblastosis which is hyperplasia of the pancreatic islet cells causing hyperinsulinemic hypoglycemia, which is a congenital abnormality. The microcopic image shows hyperplastic islet cells, forming a ductuloinsular structure.[11,12] Another

differential diagnosis is *non-insulinoma pancreatogenous hypoglycemia syndrome* (NIPHS), which is a condition of hyperplasia of the pancreatic islet cells, manifested by post prandial neuroglycopenia, negative fasting glucose test. pancreatic imaging within normal limits, and positive presence of *intra-arterial calcium stimulation of serum insulin*.[9] While the histopathological differential diagnosis is glucagonoma with a tumor mass structure that forms a dense trabecular structure, with little stroma[1,9]

At one day postoperative follow-up, the patient had an increase in the leukocyte count up to 18.200 mg / dl and urea up to 66 mg / dl, this was as a result of sepsis and acute renal failure. Although tests for microorganism resistance and hemodialysis were carried out in this patient, the patient eventually died of septic shock. In a state of hypoglycemia, the kidneys will experience a decrease in gluconeogenesis, and impaired degradation and *clearance* of insulin in the kidneys[12]

Table 1. Symptoms of neuroglycopenia and adrenergic insulinoma

Symptoms of neuroglycopenia	**Adrenergic symptoms**
Confusion (80%)	Diaforesis (69%)
Visual disturbances (59%)	Tremor (24%)
Coma, amnesia, decreased consciousness (47%)	Palpitations (12%)
Abnormal habits (36%)	Hyperphagia / Weight Gain (50%)
Seizures (17%)	

Table 2. Diagnosis of insulinoma based on clinical symptoms and ENETS consensus *(European Neuroendocrine Tumors Society)* [3,13]

Clinical symptoms (Whipple Trias): (1) Hypoglycemia (plasma glucose <50 mg / dL); (2) Neuroglycopenic symptoms; (3) Relief of symptoms after glucose administration.
ENETS consensus

- In times of hypoglycemia during the 72 hour fasting test:
  - Insulin threshold ≥ 3μU / mL, (in **patients** = **101.3 μU/mL**)
  - C-peptide threshold 0.6 ng / mL (**patient** = **14.36 ng/mL**)
  - Insulin / C-peptide ratio <1.0
  - Proinsulin cut-off level of 20 pmol / L
  - Absence of sulfonylurea (metabolites) in plasma or urine

Non-invasive imaging Transabdominal ultrasound CT MRI
Invasive imaging

Table 3. Staging in insulinoma[7]

Primary Tumor (T)	
TX	Primary tumors cannot be evaluated
T0	There is no evidence of a primary tumor
T1	Tumor Confined to the pancreas, measuring <2 cm
T2	The tumor was confined to the pancreas, measuring > 2cm but < 4cm
T3	Tumors confined to the pancreas, > 4 cm in size, or invade the duodenum or gallbladder
T4	The tumor invades surrounding organs (stomach, spleen, colon, adrenal glands) or large blood vessel walls (superior mesenteric artery, celiac axis)
Lymph gland	
NX	Regional lymph nodes cannot be evaluated
N0	There is no metastasis to regional lymph nodes
N1	There is metastasis to regional lymph nodes
Metastasis jauh	
M0	There are no distant metastases
M1	There are distant metastases
M1a	Only liver metastases
M1b	Only extrahepatic metastases
M1c	Hepatic and extrahepatic metastases

Pancreatic neuroendocrine tumor stage			
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

4. CONCLUSION

Insulinomas can be enforced based on clinical images, CT scans, macroscopic and microscopic images. In this case, diagnosis and treatment were carried out, but the patient died due to sepsis and acute renal failure.

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