

## Paroxysmal Hypertension Induced by an Insulinoma

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### Abstract

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Insulinoma is a rare, usually benign, pancreatic neuroendocrine tumor. The clinical features of an insulinoma are fasting hypoglycemia with neuroglycopenic symptoms including confusion and unusual behavior, while hypertension is usually not associated with the disease. We herein report a patient with insulinoma who manifested paroxysmal hypertension and neuroglycopenic symptoms. The possible etiology of hypertension induced by an insulinoma is catecholamine release in response to hypoglycemia, which may cause acute hypertension through activation of the sympatho-adrenal system. This case implies that sustained hyperinsulinemia due to insulinoma can be functionally linked to the induction of paroxysmal hypertension.

**Key words:** insulinoma, hypertension, hypoglycemia

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### Introduction

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Insulinoma is a rare pancreatic islet cell tumor with an estimated incidence of 0.4 per 100,000 person-years (1). The characteristic clinical manifestation of insulinoma is fasting hypoglycemia with neuroglycopenic symptoms including confusion, visual changes, and unusual behaviors (2). However, hyperinsulinemia has not been generally considered to be a causal factor in the development of hypertension (3-5). We herein report a rare case of hypoglycemia-induced paroxysmal hypertension that was ameliorated by the surgical removal of an underlying insulinoma.

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### Case Report

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A 65-year-old woman was admitted to our hospital because of episodes of altered mental status and high blood pressure. Initially, the patient had been referred due to uncontrolled blood pressure rising to 196/114 mmHg during her dental treatments. Forty days prior to admission, the patient was taken to the emergency department of another hospital with an altered mental status and hypertension despite the fact that etizolam had been administered for stress-

induced hypertension. At that time, her blood pressure was 226/129 mmHg, while her blood glucose level was 48 mg/dL. A solution of 50% dextrose in water was administered intravenously, resulting in improvement in the patient's level of consciousness. After that, the patient suffered four similar attacks with high systolic blood pressure >200 mmHg as well as lowered plasma glucose (PG) <70 mg/dL. Since her blood pressure at home was 154/92 mmHg on average, treatment with 25 mg losartan was commenced. Four days prior to admission, she had been transported to another hospital due to an altered mental status, with a very low glucose level of 25 mg/dL and inappropriately high level of immunoreactive insulin (IRI) of 19.8 µl/mL. She was then referred to our hospital.

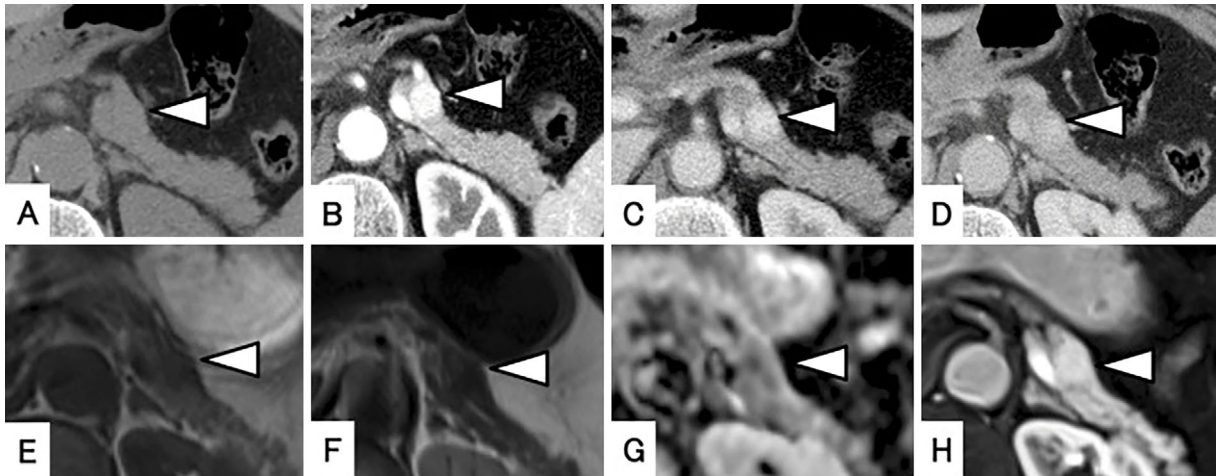
Her blood pressure on admission was 140/94 mmHg, pulse rate was 84 beats/min, respiratory rate was 20/min, and axillary body temperature was 36.6°C. The patient was alert and oriented to person, place, and time. Her lungs were clear to auscultation bilaterally, and her heart sounds were regular, without any cardiac murmur. Her abdomen was soft and flat without tenderness. A neurological examination revealed no abnormalities. Laboratory tests on admission showed the following values: hemoglobin A1c, 4.5%; fasting plasma glucose (FPG), 55 mg/dL; IRI, 45.2 µU/mL; and C

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**Figure 1.** The radiological findings of a pancreatic tumor. A contrast-enhanced CT image of the abdomen demonstrating a lesion 15 mm in diameter in the pancreatic body (A: arrowhead). The tumor was strongly enhanced in the arterial phase (B: arrowhead) and slightly enhanced in the portal phase (C: arrowhead) and venous phase (D: arrowhead). T1-weighted (E) and T2-weighted (F) MRI and diffusion-weighted imaging (G) showed a lesion in the pancreatic body that had a low signal (arrowheads). The tumor was slightly enhanced in a gadolinium-enhanced image (H: arrowhead).

peptide, 4.4 ng/mL. By endocrine workup, no dysfunction of the anterior pituitary, thyroid, or adrenal glands was found. The diagnostic indicators of insulinoma, including the Fajan: IRI/PG >0.3, Grunt: PG/IRI <2.5, and Taminato indices:  $(100\text{-PG}) \times (\text{IRI}-3) \geq 280$ , were positive, at 0.792, 1.26, and 1,260, respectively, while the Turner index  $\text{IRI} \times 100 / (\text{PG}-30) > 200$  was negative, at 180.8. In addition, the patient had Whipple's triadic signs: hypoglycemic symptoms, low glucose level at the time of the symptoms, and the amelioration of the symptoms after glucose administration. After admission, glucose 30 mg/h was administered intravenously via a peripherally inserted central catheter, considering her several hypoglycemic episodes. Octreotide administration reduced the serum IRI and C peptide levels by 33% and 39%, respectively, for 2 hours. Enhanced abdominal computed tomography (CT) was performed and showed a lesion 15 mm in diameter in the pancreatic body that was strongly enhanced in the arterial phase (Fig. 1A-D). Magnetic resonance imaging (MRI) of the abdomen showed a lesion in the pancreatic body, exhibiting a low signal on T1- and T2-images and slight enhancement on the Gd-enhanced image (Fig. 1E-H). Significant accumulation of the tracer was not detected in the pancreatic tumor by  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/CT.

Based on the diagnosis of a solitary insulinoma, laparoscopic resection of the pancreatic body and tail was performed. There was no evidence of gross invasion, abnormal lymph nodes, or metastases. The resected specimen contained a well-circumscribed white round mass, 15 mm in diameter, in the pancreatic body with the absence of a surrounding capsule (Fig. 2A). The mass was pathologically found to be a well-differentiated tumor with amyloid deposition showing 1% Ki-67-positive cells and <2 mitoses (/10 high-power field (HPFs)) (Fig. 2B). Immunohistochemical

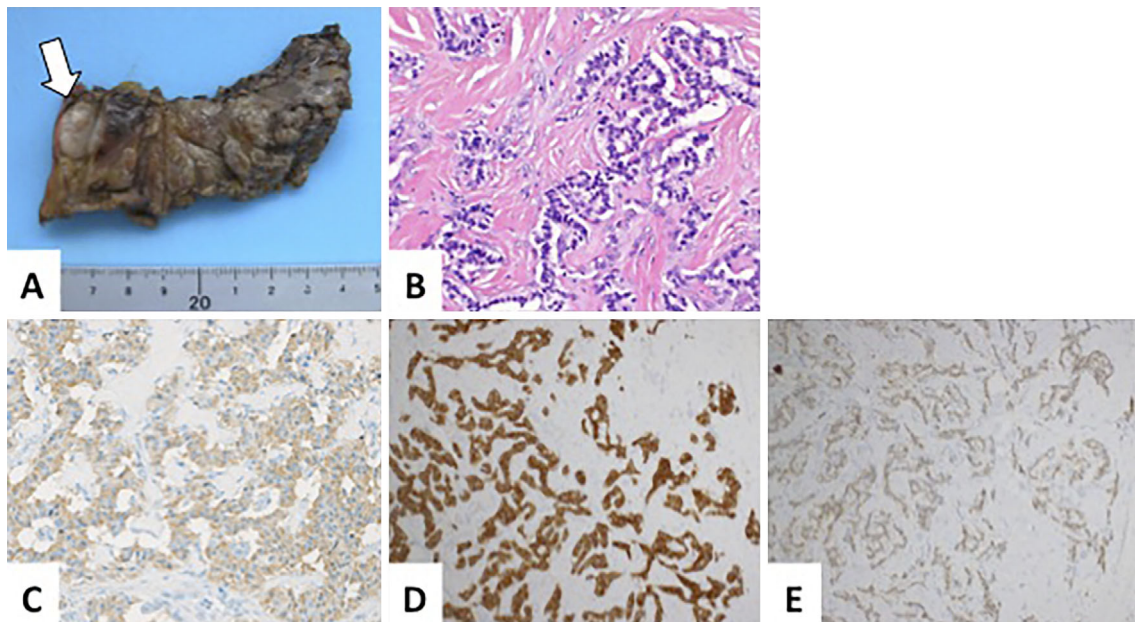
studies showed positive staining for insulin and the neuroendocrine markers synaptophysin and chromogranin A but not for glucagon or gastrin (Fig. 2C-E), leading to the diagnosis of the insulinoma as a grade 1 neuroendocrine tumor based on the 2010 WHO Classification for Pancreatic Endocrine Neoplasms (6).

After surgery, the patient's FPG and IRI normalized to 116 mg/dL and 5.3  $\mu\text{L}/\text{mL}$ , respectively. Her systolic blood pressure (SBP) and diastolic blood pressure (DBP) during hospitalization gradually normalized (Fig. 3). The established indicators for insulinoma, including the Fajan, Grunt, and Turner indexes, were normal, at 0.046, 21.9, and 33.1, respectively. The levels of plasma noradrenaline (NA) and urinary NA also normalized after surgery. She has not had paroxysmal hypertension that seemed to be related to hypoglycemia since the surgery. Although administration of anti-hypertensive agents was discontinued 1 week after the surgery, her SBP has been maintained at less than 140 mmHg, and her home blood pressure (100-110 mmHg) and mental condition have also clearly stabilized.

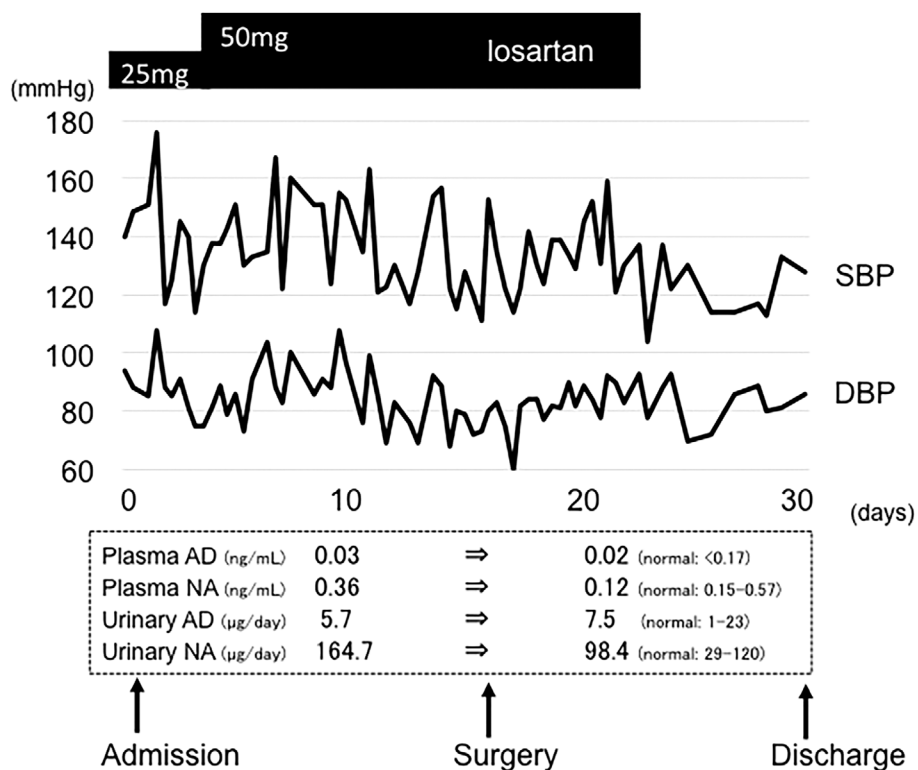
## Discussion

We report a case of insulinoma manifesting paroxysmal hypertension. Insulinoma is a rare, usually benign, pancreatic neuroendocrine tumor that can occur sporadically or as a part of the MEN type 1 (2, 7). The majority of patients with an insulinoma are between 30 and 60 years of age, with women accounting for 59% of the patients (8, 9). The most common clinical features of an insulinoma are fasting hypoglycemia with discrete episodes of neuroglycopenic symptoms (3). Interestingly, our patient showed both hypoglycemic episodes and paroxysmal hypertension.

Hyperinsulinemia accompanying insulin resistance has



**Figure 2.** The pathological findings of the resected insulinoma. The pancreatectomy specimen contained a well-circumscribed white round mass 15 mm in diameter in the pancreatic body with the absence of a surrounding capsule (A: arrow). In Hematoxylin and Eosin staining, a well-differentiated tumor with amyloid deposition was observed histopathologically (B). The tumor had 1% Ki-67-positive cells per 10 HPFs and less than 2 mitoses per 10 HPFs. Immunostaining was positive for insulin (C). Immunostaining for synaptophysin (D) and chromogranin A (E) was also positive. The tumor was thus classified as a grade 1 neuroendocrine tumor based on the WHO classification.



**Figure 3.** Clinical course. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) during hospitalization and the plasma and urinary adrenaline (AD) levels and noradrenaline (NA) level are shown. The levels of plasma NA and urinary NA were decreased after surgery. Although administration of losartan was discontinued 1 week after surgery, the SBP remained lower than 140 mmHg.



been reported to be associated with hypertension (10, 11). However, most of the studies conducted in the 1990s showed that there is no association between hyperinsulinemia and hypertension in the setting of insulinoma (4, 5, 12-14). To cite an example, Sawicki et al. investigated the hypothesis that insulin is a causal and independent risk factor for blood pressure elevation in humans by comparing pre- and post-operative blood pressures of 34 patients with insulinoma. They concluded that correction of hyperinsulinemia after surgery for insulinoma did not result in blood pressure changes (5). To our knowledge, there is only one documented report regarding insulinoma accompanying significant hypertension. Kaul et al. reported that a 10-year-old girl presented with hypoglycemia with a high insulin level, distal symmetrical motor-sensory axonal neuropathy and hypertension, although her urine catecholamine levels were normal. That patient's hypertension showed remarkable improvement one year after tumor excision (15).

There are a few possible mechanisms of hypertension caused by insulinoma. First, hypoglycemia due to insulinoma can induce catecholamine release, which may cause paroxysmal hypertension through activation of the sympathoadrenal system (16). Tsujimoto et al. reported that one-third of 414 patients with diabetes who presented with hypoglycemia to the emergency room had severe hypertension higher than 180/120 mmHg. Their article suggested that catecholamine hypersecretion as a result of severe hypoglycemia might contribute to severe hypertension (17). Our patient also showed high plasma and urinary levels of catecholamine on admission. In addition, the reduction in the plasma and urinary sodium after surgery indicated that the removal of the insulinoma impaired the secretion of catecholamine.

Another hypothesis is that the sodium-retaining effect of insulin may contribute to a rise in blood pressure (18). Accumulating data have shown that insulin stimulates renal sodium reabsorption primarily at the distal nephron, playing an important role in the development of hypertension and possibly of salt sensitivity (19). In our case, this hypothesis is, in part, supported by the fact that the patient's home BP was stabilized after tumor excision without any medication. Our case exhibited both symptoms of neurologic features due to hypoglycemia and emergent hypertension with SBP >180 mmHg. These symptoms might have been challenging for the emergent unit to differentiate from cerebrovascular disorders such as cerebral hemorrhage or infarction (20).

Collectively, we experienced a case of insulinoma with paroxysmal hypertension as well as neuroglycopenic symptoms, despite the fact that hypertension is not usually considered to be related to insulinoma. A hypoglycemic state should therefore always be considered when a patient manifests acute hypertension and neurologic symptoms, such as an altered mental status.

**The authors state that they have no Conflict of Interest (COI).**

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