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Case Report

A Rare Case of Pancreatic Insulinoma, Sleep Apnea, and Hypertension

Milos Mijalkovic[1*], Dalila Sacic[2] , Slavica Pajovic[3]

[1]Polyclinic Kardio Medika, Nish, Serbia

[2]University Clinical Center of Serbia, Clinic for cardiology, Belgrade, Serbia

[3]University of Priština, Faculty of Medicine - Internal Medicine Clinic - Kosovska Mitrovica, Serbia

***Corresponding author:** Milos Mijalkovic, Polyclinic Kardio Medika, Vojvode Mišića 58, 18 000 Nish, Serbia

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Abstract

Introduction: Pancreatic insulinomas are rare, usually benign, small neuroendocrine tumors that occur more frequently in women, with an average age of 47 years. Insulinomas are characterized by chronic hyperinsulinemia leading to recurrent hypoglycaemia. There is evidence that hyperinsulinemia and insulin resistance may be initial events in the genesis of arterial hypertension. The presumed link between hyperinsulinemia and hypertension is more common in individuals of European descent than in those of African descent. On the other hand, sleep apnea is one of the common causes of secondary hypertension. **Case presentation:** In this study, we present a 61-year-old male of Roma ethnicity with pancreatic insulinoma, hyperinsulinemia, recurrent hypoglycaemia, arterial hypertension, and sleep apnea. The clinical features of insulinoma include hypoglycaemia with neuroglycopenic symptoms, including mental confusion and behavioural changes. In the case of this individual patient, due to the development of resistant hypertension accompanied by headaches and ringing in the ears, intensified antihypertensive drug therapy was implemented. However, despite these measures, blood pressure regulation remained highly challenging. **Conclusion:** Pancreatic insulinoma in a 61-year-old male of Roma ethnicity with neuroglycopenic symptoms and the development of paroxysmal hypertension is a rare occurrence, despite hypertension typically not being associated with insulinoma. Sleep apnea serves as an additional exacerbating factor for the onset of secondary hypertension, further complicating blood pressure regulation.

Keywords: pancreatic insulinoma, hypertension, hypoglycaemia, hyperinsulinemia, sleep apnea.

Introduction

Pancreatic insulinomas are rare neuroendocrine tumors with an estimated incidence of 1-4 cases per million population annually. The average age of patients is around 47 years, and they are more common in women than in men (1.4:1). Over the past few decades, the incidence of neuroendocrine tumors has been increasing compared to the overall incidence of carcinomas. The increase in incidence can largely be explained by improvements in diagnostics, including more sensitive imaging methods. Pancreatic insulinomas are mostly small benign lesions, with a diameter of less than 2 cm in 90% of cases. A malignant form of the disease with dissemination to local lymph nodes or the liver occurs in 10% of cases [1-3].

Pancreatic neuroendocrine tumors can be classified symptomatically into secreting and non-secreting (silent) tumors. Pancreatic insulinomas, which are functionally active, secrete insulin and lead to hypoglycemia as a consequence of endogenous hyperinsulinism. They may be associated with other tumors in endocrine glands as part of multiple endocrine neoplasia type I (MEN I), namely the parathyroid glands, pituitary gland, and endocrine pancreas [4].

Pancreatic insulinomas are characterized by chronic sustained hyperinsulinemia leading to recurrent hypoglycemia.

There is evidence suggesting that hyperinsulinemia and insulin resistance may be the initial events in the genesis of arterial hypertension. The presumed link between hyperinsulinemia and hypertension is more common in Caucasians than in African Americans [5,6].

It is well known that sleep apnea is one of the common causes of secondary hypertension. Hypertensive patients with sleep apnea are at an increased risk of developing resistant hypertension and adverse cardiovascular and cerebrovascular events. Epidemiological studies have shown that sleep apnea is more common in obese men, and the likelihood of developing sleep apnea likely increases with age [7].

Case presentation

A 61-year-old male patient of Roma ethnicity presents to the cardiologist's office due to high blood pressure readings both in the morning and evening, approximately 160/100 mmHg at home. He reports significant difficulty in controlling his blood pressure despite regular antihypertensive medication therapy. The patient complains of headaches, dizziness, ringing in the ears, difficulty breathing, daytime sleepiness, fatigue, weakness, a weight gain of approximately 15 kg over the past year, impaired concentration, confusion, loud snoring, and nocturnal breathing interruptions (heteroanamnestic data provided by his wife). In the family history, he mentions that his mother was treated for type 2 diabetes mellitus.

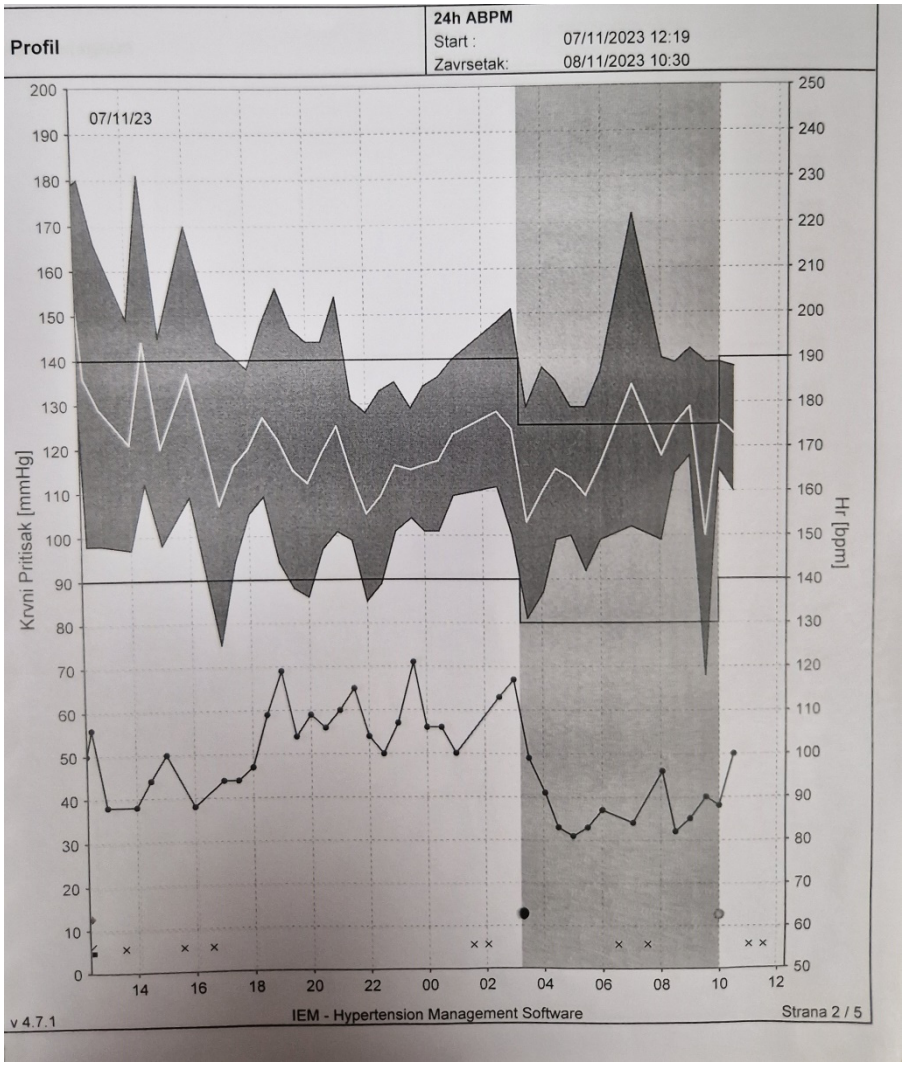
During auscultation of the lungs, there is a slightly diminished breath sound without accompanying findings. Cardiac examination reveals regular cardiac activity with clear tones and no murmurs. Blood pressure is measured at 160/95 mmHg with a heart rate of 86 beats per minute. On objective examination, the male patient is obese, with a height of 166 cm, weight of 94 kg, and a BMI of 34.1 kg/m².

On the EKG, sinus rhythm is recorded with a left axis deviation, SF:86 /min, left anterior fascicular block, normal cardiac rhythm, and no ST-T changes.

The echocardiographic examination of the heart reveals a left ventricle of normal size (EDD 5.1 cm, ESD 3.0 cm), with preserved global contractile function, EF: 55% (measured by 2D Simpson's method). There is mild hypokinesia of the apical septal segment and hypokinesia of the apical inferior wall. Myocardial thickness is normal, with a septum thickness of 1 cm and posterior wall thickness of 1 cm. Transmitral flow indicates slowed diastolic relaxation E/A 0.60 m/s. The mitral valve leaflets are slender with preserved amplitudes of motion. Trace mitral regurgitation is noted. The aortic annulus is partially calcified with a normal luminal width of 3.2 cm. The aortic valve is tricuspid with preserved leaflet separation. Flow velocity across the aortic valve is preserved. The left atrium is borderline in size, measuring 4.0 cm in the parasternal long-axis view. Right heart chambers are of normal dimensions, with a right ventricle measuring 2.4 cm. Trace tricuspid regurgitation is noted. Right ventricular systolic pressure RVSP is preserved. The pulmonary artery is of normal luminal width with preserved flow. The pericardium appears echogenic, thicker along the lateral wall, without layering or effusion.

A stress echocardiographic test was performed, which was negative for myocardial ischemia at the achieved SMF.

During 24-hour ambulatory blood pressure monitoring, the average arterial pressure was 145/99 mmHg (SF: 99/min). Throughout the daytime, it averaged at 147/100 mmHg (SF: 103/min), while during the nighttime, it averaged at 139/96 mmHg (SF: 87/min). The average value of mean arterial pressure was 120 mmHg (122 mmHg during the day and 116 mmHg at night). The average pulse pressure was 46 mmHg (47 mmHg during the day and 43 mmHg at night). The maximum recorded blood pressure values during the day were 181/112 mmHg at 14:30, and during sleep, they were 172/102 mmHg at 07:03. The circadian rhythm is disrupted, classified as a non-dipper pattern. This examination was conducted under the therapy of Nebilet (Nebivolol) 5 mg 1x1 in the morning and Prexanor (Perindopril/Amlodipine) 10/5 mg 2x1 (Picture 1).

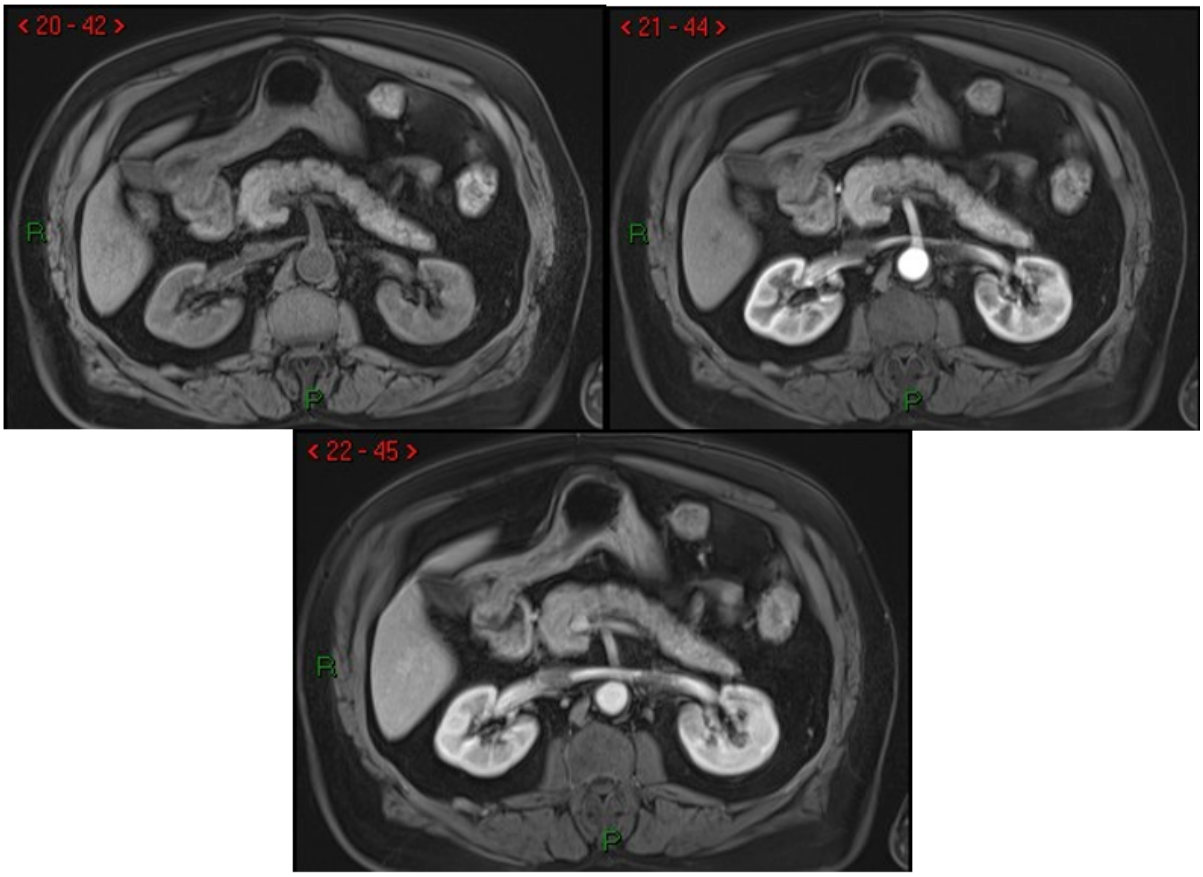


Picture 1: 24-hour ambulatory blood pressure monitoring

The patient was referred to a pulmonologist for further investigation due to respiratory symptoms. A polysomnography was performed, revealing a severe degree of sleep-disordered breathing with significant desaturations, even down to 51%. The use of a CPAP machine was recommended.

Subsequently, the patient was referred to an endocrinologist due to recurrent hypoglycemia. Laboratory analyses showed the following results: Complete blood count and sedimentation rate were within normal limits. Blood glucose level was decreased to 2.6 mmol/L. Lipid profile showed slightly elevated levels: total cholesterol 5.9 mmol/L, HDL cholesterol 1.2 mmol/L, LDL cholesterol 3.7 mmol/L, triglycerides 2.3 mmol/L. Liver function tests were within normal limits: AST 19 IU/L, ALT 26 IU/L, GGT 22 U/L. Renal function tests were within normal limits: urea 7.1 mmol/L, creatinine 103 μmol/L. Electrolytes were within normal limits: Na 139 mmol/L, K 4.7 mmol/L, Ca 2.51 mmol/L. Thyroid function tests (TSH, FT4) were normal. ACTH and cortisol levels were within normal range: ACTH 37.3 pg/mL, cortisol 8.408 μg/dL. Vanilymandelic acid, metanephrine and normetanephrine in 24- hour urine were normal. C-peptide was elevated at 5.6 ng/mL (reference range: 0.8–3.85 ng/mL). Initial insulin level was elevated at 26.6 μIU/mL, and insulin after two hours was elevated at 64.7 μIU/mL.

Six months earlier, an abdominal and pelvic magnetic resonance imaging (MRI) was performed, revealing a pancreas with normal parenchyma of the head, body, and tail, with clear and well-defined contours. The adrenal glands were of normal size and morphology (Picture 2).



Picture 2: The abdominal MRI shows a pancreas with normal parenchyma of the head, body, and tail

Following that, an attempt was made to perform an endoscopic ultrasound of the pancreatobiliary system due to suspicion of pancreatic insulinoma. However, during the examination, a hypertensive crisis occurred with blood pressure reaching 230/130 mmHg and desaturation of the patient, leading to the discontinuation of the procedure.

A month later, an endoscopic ultrasound of the pancreas was performed again, revealing a poorly defined area with a diameter of 20x25 mm in the projection of the pancreatic head. A fine-needle aspiration biopsy was performed, and the histopathological examination revealed a well-differentiated neuroendocrine tumor of the pancreatic head, categorized as "NET-G1." Upon consultation with an abdominal surgeon, surgical treatment of the pancreas was indicated.

The patient's antihypertensive therapy was intensified as follows: Concor (Bisoprolol) 5mg tablet once daily in the morning, Prexanil combi (Perindopril/Indapamide) 10/2.5 mg tablet once daily in the morning, Norvasc (Amlodipine) 10 mg tablet once daily in the evening, Spirinolactone 25 mg tablet once daily in the morning, Lasix (Furosemide) 40 mg tablet half in the morning, Methyldopa 3x500 mg tablets daily, Tamsol (Tamsulosin) 0.4 mg tablet once daily in the morning, and advised weight reduction. Gradually, there was stabilization of blood pressure values, although it remained difficult to maintain, and there was a reduction in subjective symptoms such as headaches and ringing in the ears.

Discussion

The majority of insulinomas are typically solitary, small, benign, well-encapsulated tumors that are not easily detected. The clinical diagnosis of pancreatic insulinoma is based on the "Whipple's triad," which consists of symptoms caused by hypoglycemia, low serum glucose levels during hypoglycemic episodes, and rapid improvement of symptoms after glucose administration. Symptoms of neuroglycopenia include changes in behavior, mental confusion, visual changes, fatigue, convulsions, and loss of consciousness. The most significant biochemical parameters for diagnosis are plasma glucose measurement, insulin, C-peptide, and proinsulin levels during a 72-hour fast. The most important diagnostic methods include transabdominal ultrasound, abdominal CT, and abdominal MRI. Endoscopic ultrasound (EUS) is currently the method of choice in Western centers, with reported detection rates of pancreatic insulinomas ranging from 86.6% to 92.3%. Angiography combined with arterial stimulation and venous sampling, using calcium as an insulin secretagogue, is probably the most sensitive available method, with an accuracy ranging from 94% to 100% [8-10]. Surgical resection is the preferred method for treating pancreatic insulinomas, with the choice of surgical technique depending on the tumor's localization. If surgery poses severe complications with a high risk of mortality, stereotactic ablative radiotherapy is a highly precise alternative method [11,12].

Several possible mechanisms may underlie the development of arterial hypertension caused by pancreatic insulinoma. Firstly, severe hypoglycemia due to insulinoma can trigger the release of catecholamines, leading to paroxysmal hypertension via activation of the sympathoadrenal system. Secondly, insulin can increase sodium retention in the kidneys, primarily in the distal nephron, as well as induce changes in the vascular system, contributing to an increase in blood pressure. Only a small number of studies have been published regarding insulinoma associated with significant hypertension. Kaul et al. reported a case of a 10-year-old girl presenting with hypoglycemia, high insulin levels, distal symmetric motor-sensory axonal neuropathy, and hypertension, with normal urinary catecholamines. Ko Harada et al. described a case of a 65-year-old woman with pancreatic insulinoma, hypoglycemia, paroxysmal hypertension, and elevated plasma and urinary catecholamines [13-16]. However, on the other hand, there are studies that have shown no association between pancreatic insulinoma, hyperinsulinemia, and hypertension [17-19].

Sleep apnea is a common and widespread factor in the development of secondary hypertension. The mechanism underlying the development of arterial hypertension in sleep apnea involves multiple factors, including increased sympathetic tone, peripheral vasoconstriction, increased activity of the renin-angiotensin-aldosterone system, and altered baroreceptor reflexes. CPAP therapy is the primary treatment option for sleep apnea. However, in cases where a patient develops resistant hypertension and there is an inability to control blood pressure with medication, renal denervation may be considered as an alternative treatment option [20-22].

Conclusion

In this study, we presented a rare case of pancreatic insulinoma with neuroglycopenic symptoms and the development of paroxysmal hypertension, despite the fact that hypertension is not typically associated with insulinoma. Therefore, hypoglycemia should always be further investigated, especially when hypertensive reactions and neurological symptoms occur in patients. Sleep apnea represents an additional exacerbating factor for the development of secondary hypertension and complicates the regulation of blood pressure values.

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