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Olgu Sunumu / Case Report

Vague Behavioral and Personality Changes and a Misdiagnosis of Complex Partial Epilepsy

Şüpheli Davranış ve Kişisel Değişimler ile Karışık Kısmi Epilepsinin Yanlış Teşhisi

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ABSTRACT

Pancreatic insulinomas are rare endocrine tumors and their diagnosis needs a high index of suspicion. Several patients receive an initial misdiagnosis before the tumor is being finally detected. We report on two patients who presented with vague and bizarre personality and behavioral changes. One patient was initially diagnosed with hysteria and both eventually were diagnosed with complex partial epilepsy. They had not improved on anti-epileptic medications and their symptomatology continued to deteriorate. Their final diagnosis turned out to be pancreatic insulinoma. Because of the rarity of insulinomas as well as their diverse and non-pathognomonic symptoms, the diagnosis remains challenging and may quite well escape detection unless it is entertained.

Key Words: İnsulinoma; pancreatic islet cell tumor; complex partial seizures; behavioral changes; personality disorders

ÖZET

Pankreatik insülinom nadir görülen endokrin tümörü olup teşhisi ciddi anlamda yüksek şüphe gerektirmektedir. Hastaların çoğuna son aşamada gözlenen tümör bulgusundan önce yanlış teşhis konulmaktadır. Bu raporda belirsiz ve şüpheli davranış gösteren iki hastayı ele aldık. Hastanın birine ilk olarak histeri teşhisi konmasına ragmen sonunda her ikisine birden karışık kısmi epilepsi tanısı kondu. Her ikisine anti-epileptik ilaçlar verilmesine rağmen iyileşme gözlenmedi ve belirtileri bu durum daha kötü hale gelene kadar devam etti. Son olarak pankreatik insülinom hastası oldukları ortaya çıktı. İnsülinomlar farklı ve patognomonik olmayan belirtilerinin yanı sıra nadir görülmelerinden dolayı oldukça zor teşhis edilmektedirler ve çok belirgin olmadıkça gözden kaçabilmektedirler.

Anahtar Kelimeler: İnsülinom, pankteatik islet hücre tümörü, kompleks kısmi nöbet, davranışsal değişimler, kişilik bozuklukları.

INTRODUCTION

Insulinomas have been punctuating the medical literature for approximately one century and in spite of this long period of research, their etiology and pathogenesis are still unknown. Their diagnosis remains a challenge, as well. Insulinomas are the commonest functioning endocrine tumors of the pancreas and they represent 1-2-% of all pancreatic tumors. They secrete insulin and result in hypoglycemia. They affect 1-4 person per million in the general population. Both genders are afflicted equally and no age is exempt[1-11].

CASE REPORTS

Patient number one was a 35-year-old married woman who was brought to the emergency department after collapsing at home half an hour ago. The patient was diagnosed with complex partial seizures 3 weeks ago and she was prescribed levetiracetam 1000 mg per day since then. She was complaint with her medications as her sister had stated. Her past histories were unremarkable. The family denied any history of head trauma or illicit drug ingestion. The patient's Glasgow Coma Scale (GCS) was 6/15, blood pressure was 110/66 mmHg, pulse rate was 120 beats/minute, and her respiratory rate was 12 regular cycles/minute. Both planter reflexes were flexors and there were no focal or lateralizing signs. The patient's routine blood tests on admission were unremarkable apart from random plasma glucose of 37 mg/dl. The patient was given a continuous infusion of 50% glucose. An urgent non-contrast CT brain scan was normal. Urinary and blood toxicology screens (including for sulphonylureas) were negative.

Within a quarter of hour after infusing glucose, the patient made a remarkable recovery and her GCS went back to 13/15. We reviewed her past records; she had been visiting our emergency department over the past 3 months because of sudden behavioral changes; there were an average of 4 visits per week. She was given a diagnosis of hysteria and was asked to consult a psychiatrist. Each time she visited the emergency department, she received an injection of paracetamol and one pint of an intravenous fluid. We reviewed her past investigations during these visits; no blood sugar was done. Three weeks ago, a psychiatrist diagnosed complex partial seizures and he prescribed oral levetiracetam. The patient's brain MRI (with gadolinium) and a 20-minute 16-lead EEG examination were normal.

The patient was admitted to our hospital and investigated thoroughly. Her abdominal CT scan and MRI were unremarkable. However, her endoscopic ultrasonography revealed a mass within the pancreas, between its body and tail (figure 1). A 72-hour fasting tests for serum insulin, C-peptide, and proinsulin were done. After 7 hours, the plasma glucose went down to 34 mg/dl and serum insulin was 70.62 µU/mL, C-peptide was 48.2 ng/ml, and proinsulin was 68% of the immunoreactive insulin.

A diagnosis of pancreatic insulinoma was made and a work-up for multiple endocrine neoplasia type I (MEN1) was fruitless. Levetiracetam was stopped. Laparotomy was done and the pancreatic tumor was enucleated (figure 2). Glucose was continuously infused before and during the operation. A benign insulinoma was found at histopathological examination of the enucleated mass. Five minutes after removing the tumor, the patient's capillary glucose level went up to 153 mg/dl (figure 3).

The patient stayed at our hospital for a further period of 7 days. Her stay was uneventful and neither "hypos" nor any abnormal behavioral changes or lapses in consciousness were detected. She was discharged home on day 8 postoperatively. We asked her to check up her capillary glucose level using a glucometer at different times of the day and for a total period of 1 month; the values had never fallen down below 100 mg/dl. She scored 28/30 on mini-mental state examination.

Patient number two was a 14-year-old school girl. She presented to our emergency department for the very first time with agitated confusional state. One week ago, she was given a diagnosis of "epilepsy" and oral carbamazepine was started, 200 mg three times per day, at that day. The patient's father denied any improvement in the patient's overall condition; the reason behind visiting a neurologist was that he had noticed that his daughter had poor school records, had become anxious and irritable most of the time, and had poor night time sleep for the past 2 months. On examination, the patient was extremely agitated and shouting, using "obscene words;" therefore, we were unable to examine her neurologically. The

patient's mother denied any form of domestic violence or head trauma. Her complete blood counts, blood urea and electrolytes, and liver function were within their normal reference range; however, her capillary glucose level was 41 mg/dl. Immediately, an infusion of 50% glucose was given and she became calm and cooperative after approximately 15 minutes. The patient's urgent CT brain scan was normal-looking, as were her urinary and blood toxicology screen (which also included sulphonylureas). The blood pressure was 105/70 mmHg, pulse rate was 114 beats/minute, and her respiratory rate was 17 regular cycles/minute.

A preliminary diagnosis of insulinoma was made and she was admitted to our neurology ward. After 13 hours of fasting, her results were: serum glucose 34 mg/dl, serum insulin 59.31 µU/mL, and C-peptide 38.7 ng/ml. A battery of investigations to uncover other components of MEN1 was run and it was negative. Abdominal CT scan with contrast suggested the presence of a small "vascular lesion" within the pancreas (figure 1). However, endoscopic ultrasonography contradicted this and revealed a normal-looking pancreas (no image is available). A decision to do laparotomy was made and we found a mass within the distal pancreas. Distal pancreatectomy with lower partial splenectomy (to preserve immunity) was made. The patient's postoperative hospital stay was uneventful and her fasting blood glucose was between 83 to 102 mg/dl while the random blood glucose levels were between 94 to 137 mg/dl. Histopathological examination of the mass confirmed that the tumor was a benign insulinoma.

A regular follow-up visits at 2-week intervals (for a total of 3 months) revealed the achievement of a better school performance and a remarkable improvement in her previous personality changes.

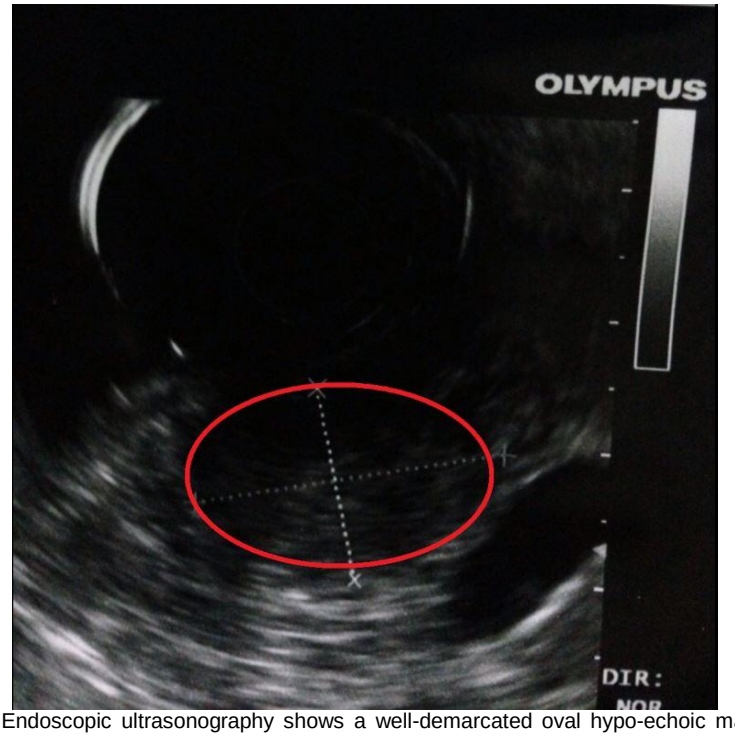

Figure 1. Endoscopic ultrasonography shows a well-demarcated oval hypo-echoic mass, 24 x 15 mm in maximum diameters (within the red circle), adjacent to the portal vein confluence. The mass is clearly separated from the vessel.

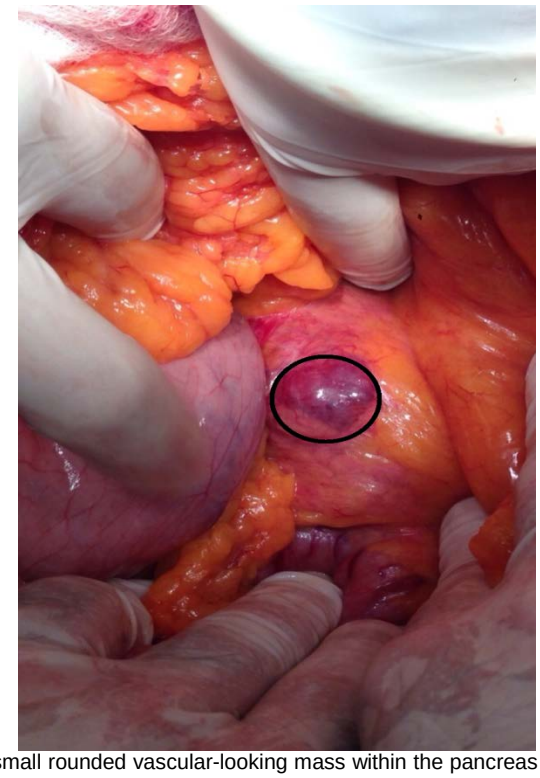

Figure 2. There is a small rounded vascular-looking mass within the pancreas (marked by black circle). The mass was enucleated and its histopathological examination confirmed that the mass was an insulinoma.

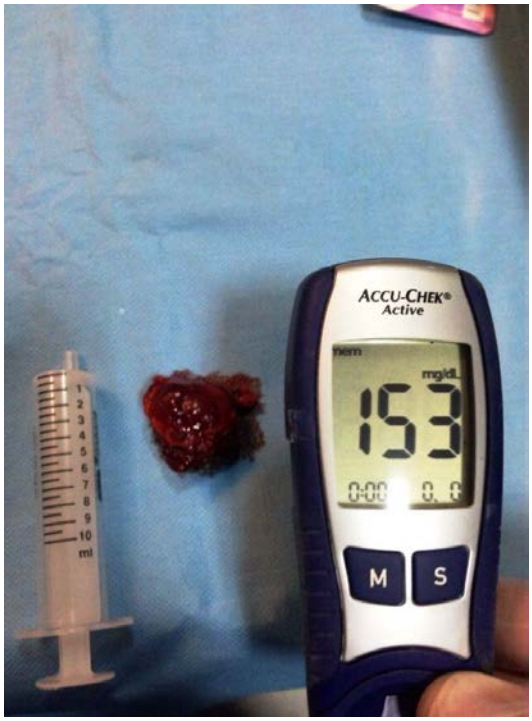

Figure 3. Five minutes after removing the tumor (which is placed between the syringe and the glucometer), the patient's plasma capillary glucose rose up to 153 mg/dl!

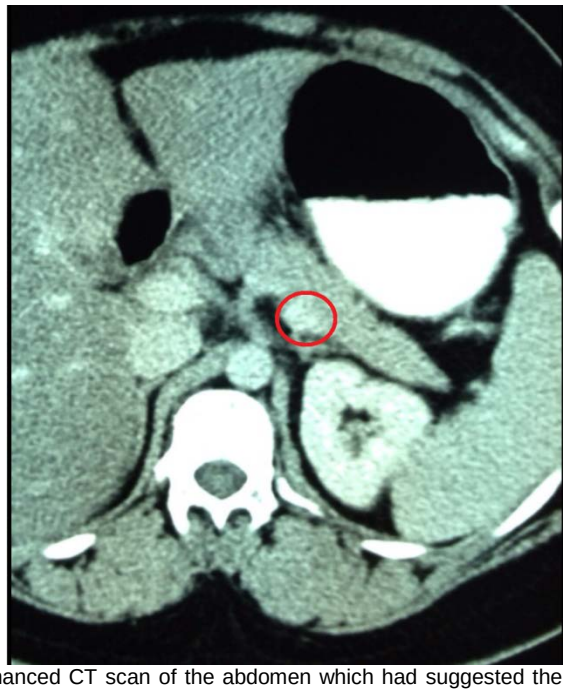

Figure 4. Contrast enhanced CT scan of the abdomen which had suggested the presence of a small vascular lesion (marked by the red circle) within the pancreas; no suggestion of insulinoma was made by the radiologist.

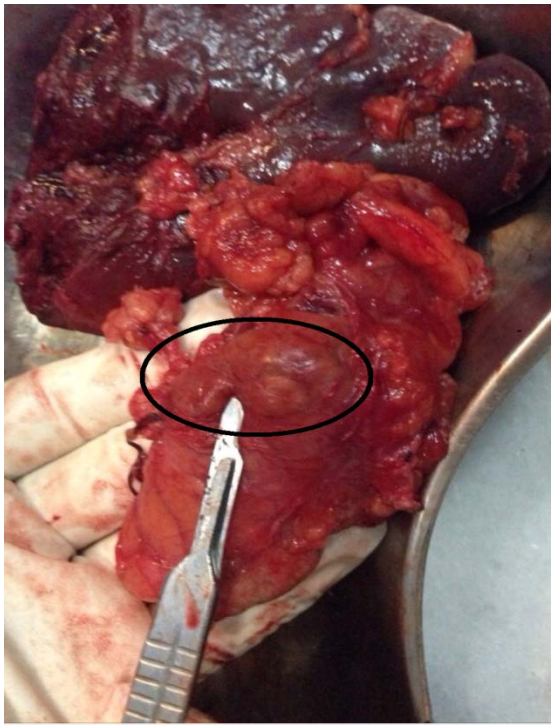

Figure 5. Distal pancreatectomy with partial lower splenectomy was made because the tumor couldn't be enucleated. The tip of the blade lies on the tumor (marked within the black circle). The splenic vascular pedicle was ligated and the lower part of the spleen became ischemic. The upper part of the spleen depended on short gastric arteries to maintain its nourishment. The lower part of the spleen was removed to maintain immunity in this young 14-year-old girl.

DISCUSSION

In the year 1869, the German pathological anatomist Paul Langerhans, while a medical student, described the pancreatic islet cells[1]. In 1922, Banting and Best were successful in isolating what they named “isletin” (modern insulin) from a solution extract of a dog’s pancreatic tissue[2]. After one year, Harris suggested a clinical possibility of hyperinsulinism and compared it with the hypoinsulinism of diabetes mellitus; he postulated the possibility of insulinoma[3]. In 1927, Wilder and coworkers were successful in establishing an association between hyperinsulinism and a functional pancreatic islet cell tumor; they did an operation in a patient with repeated hypoglycemia and they discovered multiple hepatic metastases from a pancreatic islet cell carcinoma[4]. Graham reported on the first surgically cured case of pancreatic islet cell tumor in the year 1929[5]. In 1935 Whipple noticed that the symptoms of hypoglycemia were provoked by fasting; patients became symptomatic when the blood glucose fell below 50 mg/dl and there was complete resolution of symptoms upon administration of glucose[6]. This was the basics of establishing the diagnosis of insulinoma by the Whipple’striad we use nowadays.

Insulinomas are the commonest functioning endocrine tumors of the pancreas and they represent 1-2-% of all pancreatic tumors. They secrete insulin and result in hypoglycemia (and its consequences). They target 1-4 person per million in the general population. Both genders are afflicted equally and no age is exempt; they can target any age. At least 90% of insulinomas are benign, solitary, less than 2 cm in maximum diameter, and develop within the pancreas. They are distributed evenly within the pancreatic tissue (i.e., there is no area of predilection). Extra-pancreatic insulinomas are extremely rare and comprise approximately 2% of all insulinomas; they are almost always found within the duodenal wall. The etiology and pathogenesis of insulinomas are still poorly understood[7-11].

The episodic nature of the signs and symptoms of hypoglycemia are related to the intermittent secretion of insulin by the tumor, i.e., the secretion is not continuous[11]. Most patients become symptomatic several hours after meal and in severe cases, the symptoms develop postprandially. Neuronal dysfunction and autonomic hyper-activation are the reason behind developing the variable combination of sweating, palpitation, tremor, visual disturbances, altered mental status, anxiety, irritability, confusion, seizures, and coma[10-13].

Altered mental status and confusional states are encountered in 75-80% of patients while vague personality changes and abnormal behavior are seen in 36% of the patients[10,12]. Seizures, including myoclonus ones, develop in 17-23% of the patients; these seizures may be focal, multifocal, or generalized.

The diagnosis of insulinoma may be easily missed if it is not entertained; because of its deceptive, masquerading, and non-pathognomonic symptomatology, insulinoma can pose a diagnostic dilemma even to a shrewd clinician and remain undiagnosed for years[14].

Jagadheesan and Suresh[15] reported on a 45-year-old male with insulinoma who presented with recurrent episodic confusional state, disorganized behavior, and restlessness; the patient was thought to have developed a psychiatric disorder. Likewise, Halder and colleagues[16] reported on a patient with episodic bizarre behavioral changes; the final diagnosis turned out to be pancreatic insulinoma. On the other hand, Nakamura and coworkers[17] reported on a 28-year-old woman who presented with sub-stupor, mutism, mannerism, restlessness, and incoherence. She was referred to the psychiatric department as a case of hysteria; the culprit was an insulinoma. Vig et al[18] reported on a 43-year-old man who presented with attacks

of altered behavior over a short period of time; he had insulinoma.

Graves and colleagues[19] reported on a 45-year-old female who had been diagnosed with complex partial seizures and secondarily generalized seizures. She was commenced on antiepileptic medication. Despite escalating treatment, her seizure frequency and pattern had worsened significantly during the previous 2 years. Her final diagnosis was insulinoma. Alemdar and coworkers[20] reported on a man who was diagnosed with epilepsy and anxiety disorders; he continued to deteriorate despite treatment with multiple anti-epileptics and anxiolytics. An insulinoma was found.

Four categories[15] of insulinoma-related symptoms have been recognized: acute neuroglycopenia;
subacute neuroglycopenia; chronic neuroglycopenia; and hyperinsulinemic neuropathy.

The biochemical hallmark of insulinoma is fasting hypoglycemia with simultaneous inappropriately elevated endogenous insulin levels. Classically, 72-hour fasts are performed. However, outpatient fasts can provide the required data and be much more cost-effective than inpatient fasts[21]. However, it should be noted that normal results from a prolonged fast do not preclude an insulinoma[22].

Druce and colleagues[23] found that preoperative localization of insulinomas remains challenging. A pragmatic combination of computerized tomography and especially magnetic resonance imaging predicts tumor localization with high accuracy. However, they concluded that radionuclide imaging and endoscopic ultrasound examinations were less helpful but may be valuable in selected cases. Calcium stimulation currently remains useful in providing an additional functional perspective.

Due to their hypervascular nature, these tumors have characteristic imaging appearances. Aggarwal and coworkers have emphasized the need for performing spiral CT scan whenever the diagnosis of insulinoma is suspected, due to the ability to image the pancreas in the early arterial as well as in the equilibrium phase. They also noted that water should be given instead of radio-opaque oral contrast, as islet cell tumors may also be found in the bowel wall[24].

In conclusion, because of the rarity of insulinomas as well as their diverse and non-pathognomonic symptoms, the diagnostic remains challenging and may well escape detection unless it is entertained. Both of our patients developed vague behavioral and personality changes and were diagnosed with complex partial seizures; their EEG and brain MRI were unremarkable. One patient was initially diagnosed with hysteria. Their final diagnoses turned out to be pancreatic insulinoma. They made a remarkable improvement and permanent cure when their tumor was surgically removed.

Conflicts of interests, grants, and permission: None.

REFERENCES:

1. Langerhans P. "Beitrage zur mikroscopischen anatomie der bauchspeichel druse". Inaugural-dissertation. Berlin: Gustav Lange; 1869.
2. Banting F, Best C. Internal secretion of pancreas. J Lab Clin Med. 1922;7:251-66.
3. Harris S. Hyperinsulinism and dysinsulinism. JAMA. 1924;83:729-33.
4. Wilder RM, Allan FN, Power MH, Robertson H. Carcinoma of the islets of the pancreas: hyperinsulinism and hypoglycemia. J Am Med Assoc. 1927;89:348-55.
5. Welbourn RB, Barabas AP. Hormone-secreting tumors of the pancreas. Postgrad Med J. 1976;43:24-30.
6. Whipple AO, Frautz VK. Adenomas of islet cells with hyperinsulinism: a review. Ann Surg. 1935;101:1299-335.

7. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc. 1991;66:711-9.

8. Lam KY, Lo CY. Pancreatic endocrine tumour: a 22-year clinico-pathological experience with morphological, immunohistochemical observation and a review of the literature. Eur J Surg Oncol. 1997;23:36-42.

9. Gumbs AA, Moore PS, Falconi M, Bassi C, Beghelli S, Modlin I, Scarpa A. Review of the clinical, histological, and molecular aspects of pancreatic endocrine neoplasms. J Surg Oncol. 2002;81:45-53; discussion 54.

10. Mathur A, Gorden P, Libutti SK. Insulinoma. Surg Clin North Am. 2009;89:1105-21.

11. Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa Y, et al. Diagnosis and management of insulinoma. World J Gastroenterol. 2013;19:829-37.

12. Boukhman MP, Karam JH, Shaver J, Siperstein AE, Duh QY, Clark OH. Insulinoma-experience from 1950 to 1995. West J Med. 1998;169:98-104.

13. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008;135:1469-92.

14. Mahabalshetti AD, Aithal KR, Patil BS, Patil PB. Insulinoma- a misleading neuroendocrine tumour. Int J Biol Med Res. 2013;4:2975-7.

15. Jagadheesan V, Suresh SS. Episodic confusional state: Due to insulinoma. Indian J Psychiatry. 2008;50:197-9.

16. Halder PJ, Hafeezunnisa P, Pai R, Samsi AB. Insulinoma. J Postgrad Med. 1992;38:202-4.

17. Nakamura Y, Doi R, Kohno Y, Shimono D, Kuwamura N, Inoue K, et al. High dose calcium stimulation test in a case of insulinoma masquerading as Hysteria. Endocrine. 2002;19:127-30.

18. Vig S, Lewis M, Foster KJ, Stacey-Clear A. Lessons to be learned: A case study approach insulinoma presenting as a change in personality. JR Soc Health. 2001;121:56-61.

19. Graves TD, Gandhi S, Smith SJ, Sisodiya SM, Conway GS. Misdiagnosis of seizures: insulinoma presenting as adult-onset seizure disorder. J Neurol Neurosurg Psychiatry. 2004;75:1091-2.

20. Alemdar M, Iseri P, Komsuoglu SS. Insulinoma in differential diagnosis of seizure disorder. J Neuropsychiatry Clin Neurosci. 2006;18:247-8.

21. Marney A, Jagasia S. Case study: Diagnostic dilemma in a patient with insulinoma. Clin Diab. 2007;25:152-4.

22. Soh AW, Kek PC. Insulinoma in a patient with normal results from prolonged fast and glucagon-induced hypoglycemia. Endocr Pract. 2010;16:838-41.

23. Druce MR, Muthuppalaniappan VM, O'Leary B, Chew SL, Drake WM, Monson JP, et al. Diagnosis and localisation of insulinoma: the value of modern magnetic resonance imaging in conjunction with calcium stimulation catheterisation. Eur J Endocrinol. 2010;162:971-8.

24. Aggarwal B, Gothi R, Aggarwal A, Doda S, Verma K. Spiral CT and MR appearances of pancreatic head insulinoma. Indian J Radiol Imaging. 2000;10:37-8

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