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Challenges in Managing Insulinomas and Hyperparathyroidism in MEN1: A Clinical Case Study

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Abstract

Pancreatic insulinoma is an uncommon neuroendocrine tumor with an incidence of approximately 1 per million people annually. While the majority of insulinomas are sporadic, a minority are associated with Multiple Endocrine Neoplasia type 1 (MEN1), a rare genetic disorder transmitted in an autosomal dominant pattern. MEN1 is characterized by the presence of hyperplastic or adenomatous parathyroid glands, pancreatic islet cell tumors, and pituitary tumors. The disorder can also involve lesions in the duodenum, adrenal glands, thymus, and bronchi.

We report a case of MEN1 presenting with multiple insulinomas in a 37-year-old male, who exhibited symptoms of intermittent hypoglycemia over a decade. Diagnostic workup included biochemical assays , and imaging studies that revealed elevated insulin and C-peptide levels and hypervascular pancreatic lesions, , and pathological findings consistent with MEN1. Surgical intervention involved the enucleation of insulinomas and distal pancreatectomy, followed by removal of parathyroid adenomas. The postoperative evolution was marked by the resolution of hypoglycemic episodes and the persistence of primary hyperparathyroidism.

This case underscores the complexity of diagnosing and managing insulinomas within the context of MEN1. It highlights the importance of a multidisciplinary approach to treatment and the need for ongoing surveillance to address both endocrine manifestations and psychological impacts. The findings advocate for comprehensive management strategies and support systems to improve patient outcomes and quality of life.

Keys word: Hypoglycemia, Pancreatic Insulinoma, Multiple Endocrine Neoplasia Type 1 (MEN1), Primary Hyperparathyroidism, Genetic Disorders

Introduction

Pancreatic insulinoma is a rare condition, with an incidence of 1 case per million people per year. It occurs sporadically in over 90% of cases and is associated with Multiple Endocrine Neoplasia type 1 (MEN1) in fewer than 10% of cases. MEN1 is a rare hereditary disorder transmitted in an autosomal dominant manner, characterized by hyperplasia or adenomas of the parathyroid glands, tumors of the pancreatic islet cells (also known as pancreatic neuroendocrine tumors), and/or pituitary tumors [1, 2].

Additional lesions may be observed in the duodenum, adrenal glands, thymus, and bronchi. Insulinoma is an uncommon presentation of MEN1. Differentiating between the sporadic form and that associated with MEN1 is based on the patient's family history, associated lesions, histopathological features, and genetic analysis. The diagnosis of MEN1 requires meeting at least one of the following criteria: the presence of two or more endocrine neoplasms related to MEN1 (including intrapancreatic tumors, parathyroid adenoma, pituitary adenoma, and others), the occurrence of MEN1-related neoplasms in first-degree relatives, or a positive MEN1 gene mutation test in a patient who may be asymptomatic and have no abnormal findings [1].

Surgical treatment is complex and is often not curative. Management of other associated conditions should be individualized. We report here a rare case of MEN1 associated with multiple insulinomas discovered during the evaluation of intermittent hypoglycemia that had been ongoing for over 10 years.

Case Report

A 37-year-old patient, with a history of bilateral renal lithiasis and a family history of digestive neuroendocrine tumor in his sister. He was admitted to our service for evaluation and management of hypoglycemia, presenting with a positive Whipple's triad. The symptoms began 10 years ago during Ramadan when the patient experienced fatigue, pallor, tremors in the extremities, visual disturbances, and occasional episodes of altered consciousness. At the time of these symptoms, his blood glucose level was 0.30 g/L. Hypoglycemia occurred both in fasting and postprandial states. The patient sought medical attention multiple times and was eventually referred to our service for further management.

On clinical examination, the patient was conscious and in good general condition. His conjunctivae were normochromic, and there were no signs of dehydration. He was normotensive and normocardic. The capillary blood glucose at admission was 0.38 g/L. His weight was 88 kg, with a BMI of 30.4 kg/m². The rest of the clinical examination was unremarkable.

Biological tests showed normal renal, hepatic, thyroid, and adrenal functions. However, serum insulin and C-peptide levels were abnormally elevated at 235.4 pmol/L and 3.06 pmol/mL, respectively (normal ranges: 17.8–173 pmol/L and 0.37–1.47 pmol/mL), with a Turner index of 678. The serum parathyroid hormone (PTH) level was also elevated at 696 pg/mL (normal range: 15.00–68.30 pg/mL). Additionally, blood calcium levels were elevated at 127 mg/L (normal range: 88–105 mg/L), while blood phosphorus levels were low at 17 mg/L (normal range: 25–45 mg/L). The hypophysiogram was without abnormality.

Given the biochemical findings suggestive of insulinoma, a topographic assessment was initiated. The abdominal CT scan revealed three hypervascular pancreatic lesions in the body and uncinate process, measuring 28 mm, 17 mm, and 23 mm, respectively (Figure 1). Endoscopic ultrasound identified two hypoechoic oval lesions in the pancreatic body. Due to the discrepancy between the CT and endoscopic ultrasound findings, an abdominal MRI was performed. It revealed three hypervascular pancreatic lesions in the uncinate process, body, and body-tail junction (Figure 2).

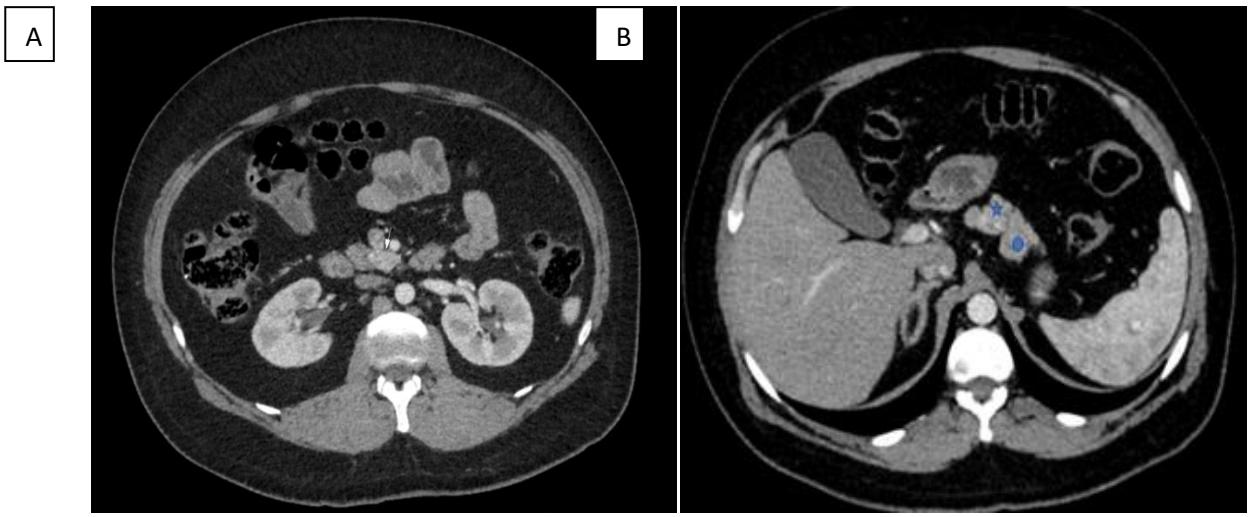

Figure 1 : **Abdominal Angio-CT Scan: Intense and homogeneous enhancement during the arterial phase. A: Isthmic mass B: Body and body-caudal mass**

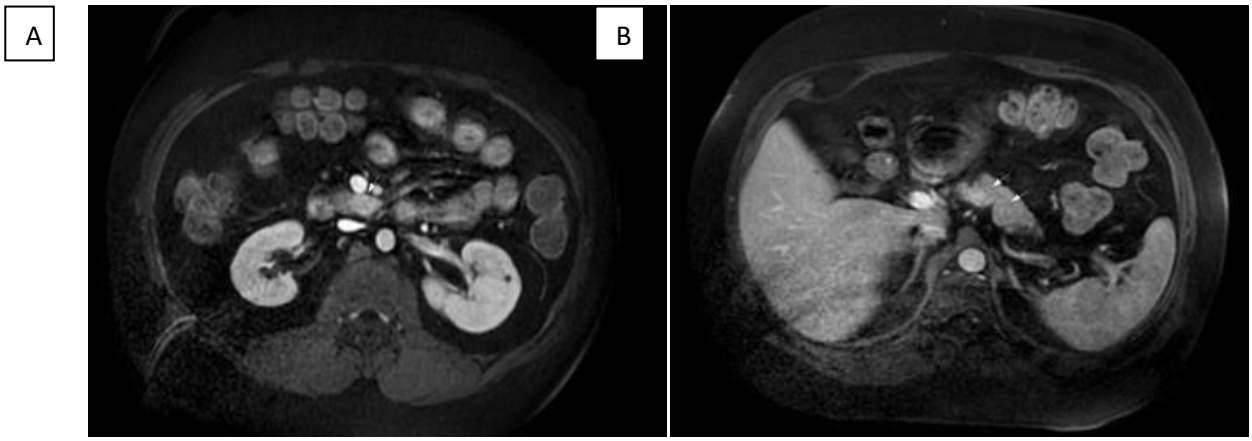

Figure 2 : **Abdominal Angio-MRI: Intense and homogeneous enhancement during the arterial phase. A: Isthmic mass B: Body and body-caudal mass**

Parathyroid imaging, including ultrasound and sestamibi scan, showed pathological processes in the lower poles of both the right and left parathyroid glands. Pituitary MRI revealed a 4 mm microadenoma on the left side.

The patient's history, clinical symptoms, laboratory results, and imaging findings suggested the possibility of MEN-1 (Multiple Endocrine Neoplasia type 1).

The patient underwent enucleation of the insulinoma in the uncinate process, followed by a distal pancreatectomy. Histopathological and immunohistochemical studies confirmed a well-differentiated neuroendocrine tumor, graded 1–2 according to the 2019 WHO classification.

Postoperatively, the patient experienced transient hyperglycemia, which later normalized without further episodes of hypo- or hyperglycemia. After multidisciplinary consultation and with the patient's consent, resection of the two parathyroid adenomas was performed. Histopathological examination confirmed the presence of two parathyroid adenomas.

"The postoperative period showed a decrease in PTH levels, with a reduction of more than 50% (H1: 43.62 pg/m). However, the six-month follow-up indicated persistent primary hyperparathyroidism, with

PTH levels at 426 pg/mL, serum calcium at 116 mg/L, and serum phosphorus at 16 mg/L. Management will be discussed. in multidisciplinary staff.

Discussion

Hypoglycemia is a heterogeneous metabolic syndrome with a complex pathogenesis. Insulinoma is the most common cause of hyperinsulinemic hypoglycemia, with an incidence of 1 to 4 cases per million patients. This endocrine pancreatic tumor leads to excessive and inappropriate insulin secretion, resulting in hypoglycemic episodes. While rare, insulinoma is the most frequent cause of organic hypoglycemia.

Insulinoma is sporadic in over 90% of cases and is associated with Multiple Endocrine Neoplasia type 1 (MEN1) in less than 10% of cases. MEN1, also known as Wermer's syndrome, is a rare disorder caused by an inactivating mutation of the MEN1 gene located on chromosome 11q13, which encodes the nuclear protein menin. Certain mutations are thought to be linked to a higher rate of pancreatic islet cell tumors, increased risk of distant metastases, and more aggressive disease [3-4].

MEN1 is characterized by the presence of tumors in the parathyroid glands, endocrine pancreas, and pituitary gland, among other sites [5]. In recent years, with a deeper understanding of MEN1 syndrome, it has also been observed in other locations such as the breast, bronchi, and uterus.

Insulinoma is the second most common functional pancreatic islet cell tumor associated with Multiple Endocrine Neoplasia type 1 (MEN1), occurring in 10 to 30% of cases [6,7], following gastrinoma. In contrast, only 4 to 6% of patients with insulinoma will develop MEN1 [1,8].

Sporadic insulinomas typically develop after the age of 40, while those associated with MEN1 often present before the age of 40, and sometimes even before 20 [9,10]. There is a slight female predominance (60%) . In our case, the patient is a 37-year-old male.

The diagnosis of insulinoma is suggested by a symptomatology that is somewhat characteristic but non-specific, including signs of hypoglycemia, often occurring in a fasting state. The diagnosis is confirmed biologically. Once endogenous hyperinsulinemic hypoglycemia is confirmed, preoperative imaging studies are required to localize the pancreatic tumor. In sporadic cases, the tumor is usually solitary and benign, whereas in MEN1, tumors are multiple and generally small.

In our case, the initial reason for consultation was a symptomatology consisting of signs of hypoglycemia (neurovegetative and neuroglycopenic symptoms) occurring both in a fasting state and postprandially. The biological assessment (insulin and C-peptide levels measured during hypoglycemia) supported the diagnosis of insulinoma. The preoperative imaging, including CT, abdominal MRI, and endoscopic ultrasound, identified three insulinomas.

The primary concern when diagnosing an insulinoma is to recognize the presence of MEN1. The clinical and biochemical presentation of hyperinsulinism alone is not sufficient for diagnosis. MEN1 is diagnosed based on family history, associated lesions (such as hyperparathyroidism and pituitary tumors), and genetic testing [11, 12].

Thus, the diagnosis of MEN1 is based on the presence of tumors in at least two of the three main sites mentioned, or in one of the three main sites in first-degree relatives of MEN1 patients, or the presence of MEN1 germline mutations in asymptomatic individuals [13]. Consequently, further steps in the diagnosis of insulinoma should include investigating family history of MEN1, conducting a calcium-phosphorus metabolism evaluation, and measuring pancreatic and pituitary hormones [14].

Most patients with MEN1 present with primary hyperparathyroidism (HPP) as the initial clinical manifestation, occurring in ≥95% of cases. Hypercalcemia is often asymptomatic, but in 25% of cases, it may present symptoms such as nephrolithiasis or nephrocalcinosis [1]. Our patient, with a family history of neuroendocrine tumors in his sister, showed HPP as the second manifestation following insulinoma. This was symptomatic HPP with two parathyroid adenomas, accompanied by nephrolithiasis and osteopenia.

Pituitary tumors occur in 15 to 42% of patients with MEN1 [1]. They can be functional, but are generally non-functional. Pituitary tumors associated with MEN1 may be larger and more aggressive compared to sporadic pituitary tumors; however, some studies suggest they are more indolent, similar to sporadic pituitary tumors [15]. Our patient had a non-functional pituitary microadenoma.

Other manifestations may be observed in MEN1. Carcinoid tumors (thymus, lungs, stomach) occur in 5 to 15% of cases. Adrenal hyperplasia or tumors, which can be unilateral or bilateral and functional or non-functional, are present in 33% [15]. Skin lesions (subcutaneous lipomas, angiofibromas), meningeal tumors, leiomyomas, sarcomas, and breast cancer may also occur [16,17]. In our case, no additional manifestations were noted.

Genetic testing for mutations in the MEN1 gene located on chromosome 11q13 is useful for confirming the diagnosis. However, some patients with MEN1 may have a negative genetic test, and the diagnosis can only be made based on clinical manifestations, imaging studies, and other information.

In our case, the diagnosis was based on the patient's family history, clinical presentation, and radiological findings. Genetic testing for MEN1 was not performed. First-degree relatives of patients with MEN1 have a 50% risk of developing the syndrome [1], highlighting the importance of family genetic screening.

Once the diagnosis of insulinoma within the context of MEN1 is established, a tailored therapeutic strategy should be developed for both the insulinoma and associated lesions. Treatment typically involves surgical resection and/or pharmacological therapy, often in combination with radiotherapy or chemotherapy, depending on the various manifestations.

Sporadic insulinomas typically present as a single, monosecretory lesion, usually small in size, and can often be cured with simple enucleation. In the context of MEN1, the lesions are multiple, polysecretory, and require complex surgical treatment that is often not curative.

The type of surgery depends on the location of the tumors and the risk of metastasis: options include left pancreatectomy and enucleation of tumors in the head of the pancreas, with or without lymphadenectomy; simple enucleation; and, rarely, duodeno-pancreatectomy or total pancreatectomy.

Diazoxide or a somatostatin analogue may be used to manage hypoglycemia. Chemotherapy can alleviate symptoms by reducing tumor burden.

In our case, the patient underwent enucleation of the uncinate adenoma and a distal pancreatectomy without splenectomy. Histopathological examination classified the gastro-entero-pancreatic neuroendocrine tumors (NETs) according to the World Health Organization's grading system, which includes well-differentiated NETs (G1, G2, and G3). Poorly differentiated neuroendocrine carcinoma, similar to NET G3, is characterized by poor differentiation and a poor prognosis. In our case, the NETs were classified as G1-G2.

The prognosis is generally favorable for benign tumors, with a cumulative incidence of postoperative recurrence at 20 years being 8% (7% for isolated benign tumors and 21% for cases associated with MEN1).

In cases of malignant metastatic insulinoma, the recurrence rate is approximately 60% after 3 years, and survival after reoperation for tumor recurrence ranges from 1 to 4 years.

Treatment for hyperparathyroidism is primarily surgical, though the type of intervention remains debated. Options include total parathyroidectomy with partial autotransplantation [1], which carries a risk of hypoparathyroidism, or subtotal parathyroidectomy, which has a risk of recurrence. Octreotide and cinacalcet may help manage recurrent or persistent postoperative hypercalcemia. Kartini et al. [18] suggested that subtotal parathyroidectomy should only be considered if there is precise localization of the parathyroid glands on at least two imaging modalities with consistent results. In our case, we opted for the removal of both parathyroid adenomas; however, the postoperative course was marked by persistent primary hyperparathyroidism

Some studies indicate that individuals under surveillance for MEN1 frequently encounter a reduced quality of life, primarily due to anxiety over the emergence of new tumors or the potential onset of the disease in their relatives. This underscores the importance of integrating psychological support into the medical management of the condition [19].

MEN1 is a condition that necessitates a multidisciplinary approach and ongoing clinical, biochemical, and radiological monitoring.

Conclusion

Pancreatic insulinoma, while rare, presents significant challenges in diagnosis and management, particularly when associated with Multiple Endocrine Neoplasia type 1 (MEN1). This case highlights the complexity of diagnosing and treating insulinoma in the context of MEN1, emphasizing the need for a comprehensive, multidisciplinary approach. MEN1, a rare autosomal dominant disorder, often involves a constellation of endocrine tumors including insulinomas, parathyroid adenomas, and pituitary tumors.

In this patient, the presence of multiple insulinomas alongside primary hyperparathyroidism and a pituitary microadenoma underscores the multifaceted nature of MEN1. The diagnosis was supported by a combination of family history, clinical symptoms, biochemical markers, and imaging studies, although genetic testing was not performed in this instance.

Surgical intervention, including enucleation of the insulinomas and resection of parathyroid adenomas, was undertaken with the goal of symptom relief and disease management. Despite successful surgical outcomes, persistent primary hyperparathyroidism remains a concern, reflecting the ongoing challenge of managing MEN1.

Furthermore, the psychological impact of MEN1, including anxiety over tumor recurrence and familial risk, highlights the necessity for integrated psychological support within the treatment plan.

The case illustrates the critical importance of ongoing monitoring and a tailored, multidisciplinary approach to managing MEN1. Continued research and a collaborative care strategy are essential to optimize treatment outcomes and improve the quality of life for affected individuals.

References

1. Thakker RV, Newey PJ, Walls GV, et al. Clinical Practice Guidelines for Multiple Endocrine Neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990–3011.
2. Gracanin A, Dreijerink KM, van der Luijt RB, et al. Tissue Selectivity in Tumorigenesis Associated with Multiple Endocrine Neoplasia type 1. Cancer Res. 2009;69(16):6371–4.

3. Perrier ND. From Wermer's Initial Description to Current MEN1: What Have We Learned? World J Surg. 2018;42(4):1031–1035.
4. Marx SJ. Recent Topics in Multiple Endocrine Neoplasia Type 1. J Clin Endocrinol Metab. 2018;103(4):1296–1301.
5. El-Maouche D, Welch J, Agarwal SK, et al. A Patient with Typical MEN1 Features and MEN2-Like Characteristics. Int J Endocr Oncol. 2016;3(2):89–95.
6. Okabayashi T, Shima Y, Sumiyoshi T, et al. Diagnosis and Management of Insulinoma. World J Gastroenterol. 2013;19(7):829–37.
7. Iglesias P, Díez JJ. Management of Endocrine Diseases: A Clinical Update on Tumor-Induced Hypoglycemia. Eur J Endocrinol. 2014;170 R147–57
8. Placzkowski KA, Vella A, Thompson GB, et al. Temporal Trends in the Presentation and Management of Functional Insulinoma at the Mayo Clinic, 1987-2007. J Clin Endocrinol Metab. 2009;94(3):1069–73.
9. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functional Insulinoma: Incidence, Recurrence, and Long-Term Survival of Patients: A 60-Year Study. Mayo Clin Proc. 1991;66(8):711–9.
10. Machens A, Schaaf L, Karges W, et al. Age-Related Penetrance of Endocrine Tumors in Multiple Endocrine Neoplasia Type 1 (MEN1): A Multicenter Study of 258 Gene Carriers. Clin Endocrinol (Oxf). 2007;67(5):613–22.
11. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional Cloning of the Gene for Multiple Endocrine Neoplasia Type 1. Science. 1997;276(5311):403–7.
12. Lemmers I, Zhang CX, Parente F, et al. Identification of the Multiple Endocrine Neoplasia Type 1 (MEN1) Gene. The European Consortium of MEN1. Hum Mol Genet. 1997;6(7):1177–83.
13. Turner JJ, Christie PT, Pearce SH, et al. Diagnostic Challenges Due to Phenocopies: Lessons from Multiple Endocrine Neoplasia Type 1 (MEN1). Hum Mutat. 2010;31: E1089–101
14. Cougard P, Calender A, Carnaille B, et al. Screening for Multiple Endocrine Neoplasia Type 1 (MEN1). Reflections from the GENEM Group. Ann Chir. 1995;49(7):500–6.
15. de Laat JM, Dekkers OM, Pieterman CR, et al. Long-Term Natural History of Pituitary Tumors in MEN1 Patients: Results from the Dutch MEN1 Study Group (DMSG). J Clin Endocrinol Metab. 2015;100(9):3288–96.
16. Waguespack SG. Beyond the "3 P's": A Critical Evaluation of Non-Endocrine Manifestations of Multiple Endocrine Neoplasia Type 1. Front Endocrinol (Lausanne). 2022;13:1029041.
17. Dreijerink KM, Goudet P, Burgess JR, Valk GD, International Breast Cancer in MEN1 Study Group. Breast Cancer Predisposition in Multiple Endocrine Neoplasia Type 1. N Engl J Med. 2014;371(6):583–4.
18. Kartini D, Dasawala F, Ham MF. Inferior to Subtotal Parathyroidectomy in Multiple Endocrine Neoplasia Type 1: Case Report and Literature Review. Int J Surg Case Rep. 2020;77:337–40.
19. Leeuwaard R, Pieterman CRC, Bleiker EMA, et al. High Disease Fear Associated with Poor Quality of Life in Multiple Endocrine Neoplasia Type 1 Patients: Results from the Dutch MEN1 Study Group. J Clin Endocrinol Metab. 2018;103(6):2354–61.