

A Malignant Metastatic Insulinoma as the First Clinical Presentation of Multiple Endocrine Neoplasia Type 1: A Case Report

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Authors' contributions

This case report was carried out in collaboration among all authors. Author VSNN wrote the case report and wrote the first draft of the manuscript. Authors VSNN and CRN performed the genetic analysis. Authors FB, FRKO, GMFSM managed the literature searches. All authors read and approved the final manuscript.

Article Information

Editor(s):

(1) Vania dos Santos Nunes Nogueira, Motilal Nehru Medical College, India.

Reviewers:

(1) Emre Bozkirli, Acibadem University, Turkey.

(2) Rana Choudhary, India.

(3) Sudeb Mukherjee, IPGMER and SSKM Hospital, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/57049>

Case Study

Received 10 March 2020

Accepted 18 May 2020

Published 01 June 2020

ABSTRACT

Aim: We report the case of a patient who had a malignant insulinoma as the first presentation of Multiple Endocrine Neoplasia type 1 (MEN1).

Case Presentation: A 54-year-old male patient has reported palpitations, tremor, weight loss (approximately 20 kg) and seizures for one year. A blood sample taken during a fasting hypoglycemic episode revealed a low plasma glucose (35 mg/dL), an elevated immune reactivity insulin (> 300 μ UI/ml) and a high C-peptide concentration (7 ng/mL, normal range 1,1 to 4,4 ng/ml). A computed tomography scan of abdomen detected a pancreatic tail tumor of 4 cm. The patient underwent pancreatic surgery and hepatic biopsy that revealed malignant insulinoma with lymphnode and liver metastases. The screening for MEN1 showed an adrenal and pituitary adenoma clinically nonfunctioning. After obtaining informed consent from the patient, mutational analysis of *MEN1* gene was performed using genomic DNA isolated from peripheral blood

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leukocytes. The sequencing analysis showed a heterozygous intronic mutation in intron 3, IVS3-6 C>T. Her daughter and son were evaluated for the IVS3-6 C>T mutation and only the daughter presented the alteration.

Conclusion: We report an uncommon case whose early diagnosis of MEN1 allowed the genetic study, and consequently helped the genetic counseling and early diagnosis of the affected relatives.

Keywords: Multiple endocrine neoplasia type 1; insulinoma; MEN1 mutation.

1. INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a genetic disease, inherited in the dominant autosomal form and characterized by the presence of tumors in at least two of the following endocrine tissues; parathyroid, enteropancreatic and adeno-pituitary [1]. Alternately, we consider as MEN1, a case with MEN1 in a first-degree relative and with tumor in one of the three main tissues [1]. Besides the main components, adrenocortical and carcinoid tumors, subcutaneous lipomas, facial angiofibromas and collagenomas have been associated with the disease [2].

Enteropancreatic tumors have a prevalence of 30% to 40% in MEN1, with gastrinoma being most frequently followed by insulinoma [1,2]. Insulinomas represent 10% to 30% of all pancreatic tumors in patients with MEN1, and they are usually a single lesion more than 5 mm in diameter [1]. Insulinomas may be the first manifestation of MEN1 in 10% of patients, and approximately 4% of patients with insulinomas will have MEN1 [2].

Mutations on MEN1 gene are responsible for this neoplasia. This gene is located in the 11q13 chromosome, it consists of 10 exons and encodes a protein, composed of 610 amino acids, called menin [2]. Even though the functional role of this protein has not yet been totally elucidated, inactivating mutations in this gene are associated with the development of endocrine tumors [3].

1.1 Aim

We report the case of a patient who had a malignant insulinoma as the first presentation of MEN1.

2. CASE PRESENTATION

A 54-year-old male patient has reported palpitations, tremor, weight loss (approximately

20 kg) and seizures for one year. During investigation it was diagnosed recurrent hypoglycemia but no history of liver disease, alcohol abuse or use of hypoglycemic drugs. On admission, his body weight, height, and body mass index were 80 kg, 178 cm, and 25 respectively.

A blood sample taken during a fasting hypoglycemic episode revealed a low plasma glucose (35 mg/dL), high immune reactivity insulin (> 300 μ U/ml) and high C-peptide concentration (7 ng/mL, normal range 1.1 to 4.4 ng/ml).

A computerized tomography scan of the abdomen detected a pancreatic tail tumor of 4 cm, with necrosis and calcification areas with probable hepatic metastases.

The patient underwent pancreatic surgery and hepatic biopsy that revealed malignant insulinoma with lymphnode and liver metastases (T1bN1M1). As the surgical treatment could not be curative, the patient suffered transarterial hepatic chemoembolization with doxorubicin and streptozotocin.

The screening for MEN1 showed an adrenal and pituitary adenoma clinically nonfunctioning, the levels of PTH and calcium were within the normal ranges.

After obtaining informed consent from the patient and the agreement of the Hospital Ethics Committee, mutational analysis of MEN1 gene was performed using genomic DNA isolated from peripheral blood leukocytes. Twelve pairs of primers were designed to amplify the 10 exons of MEN1 gene [4]. Amplification was performed with 500 ng of genomic DNA in a 25 μ L reaction containing 7.5 μ M of each primer (Invitrogen, SP, Brazil), 10 \times Buffer (1.5 M Tris pH 8.8, 1 M MgCl₂, 1 M (NH₄)₂SO₄, 11 μ L β -mercaptoethanol, H₂O qsp 1.5 mL), 10 mM dNTPs (Invitrogen, SP, Brazil), 0.875 U of Taq DNA polymerase (Invitrogen, SP, Brazil), and 10% DMSO (Sigma-Aldrich, MO, USA). PCR thermocycling conditions

were 5 min at 94°C, followed by 36 cycles of 94°C for 45 s, 63°C for 45 s, 72°C for 1 min, with a final extension at 72°C for 10 min. . The following PCR conditions were used: initial denaturation for 5 min at 94°C, 36 cycles with 45 s at 94°C, 45s at 63°C, 60s at 72°C and a terminal extension at 72°C for 10 min [4].

The entire coding regions of the MEN1 gene, including the exon-intron boundaries, were sequenced. The sequencing analysis did not reveal mutations in the coding regions. However, a heterozygous intronic mutation in intron 3 was found, IVS3-6 C>T (Fig. 1). Her daughter and son were evaluated for the IVS3-6 C>T mutation but the alteration was found only in the daughter. Her MEN1 clinical screening results were normal.

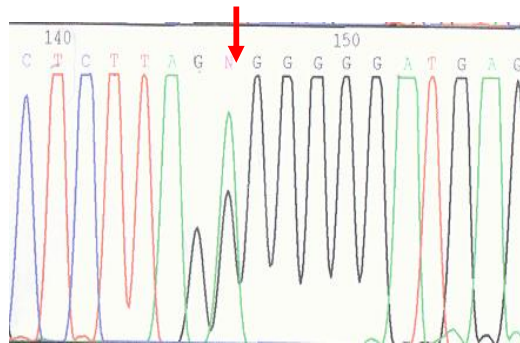


Fig. 1. The heterozygous intronic mutation found in intron 3, IVS3-6 C>T, antisense sequence

3. DISCUSSION

Insulinoma is the second most common hormone secreting enteropancreatic neuroendocrine tumor in MEN1, with an overall lifetime prevalence of 10% among adults with this neoplasia. MEN1 also accounts for approximately 15% of all patients with insulinoma [5]. In patients without MEN1, insulinomas generally occur in those older than 40 years old. Conversely, in MEN1, patients with insulinoma are usually younger than 40 years old but many of them are younger than 20 years old [1].

In contrast to other islet cell tumors such as gastrinoma and vasoactive intestinal peptide, most insulinomas are believed to be benign. Insulinoma can be malignant in approximately 10% of the cases [6]. The malignant metastatic form of insulinoma is an extremely rare pancreatic neuroendocrine tumor, being the

incidence rates reported from 5% to 15% of all insulinomas [7].

Intronic mutations can result in an abnormal messenger RNA, and the effect of this mutation was analyzed at the RNA level by Roijers et al. [8], the mutant mRNA had a deletion of exon 3, causing a frame shift at codon 149 and a premature stop codon 13 triplets further downstream.

MEN1 is a hereditary disease whose symptomatology can be initiated only by one of the associated tumors. Its screening in patients with only one of the related tumors may benefit many individuals with an early diagnosis of other diseases. Since this is a dominant autosomal disease, family members should be examined earlier for the presence of this neoplasia.

4. CONCLUSION

In summary, we report an uncommon case whose early diagnosis of MEN1 allowed the genetic study, and consequently helped the genetic counseling and early diagnosis of the affected relatives.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard guideline written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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