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CASE SERIES

Experience in the Approach to Insulinoma: A Case Series

Ángela María Victoria[1]*, Karen Daniela Cándelo[1], Pedro Tomás Argüello[2], Karen Milena Feriz[3], Luz Ángela Casas[3], Luis Guillermo Arango[3], Alejandro López[3], Veline Martínez[4], Guillermo Edinson Guzmán[3]

[1]*Medical Intern, Universidad Icesi, Health Sciences Faculty, Calle 18 No. 122-135, Cali 760031, Colombia - Fundación Valle del Lili, Cra 98 #18-49, Cali 760032, Colombia*
[2]*Gastrointestinal Surgery Unit, Fundación Valle del Lili, Cra 98 #18-49, Cali 760032, Colombia*
[3]*Internal Medicine Unit – Department of Endocrinology, Fundación Valle del Lili, Cra 98 #18-49, Cali 760032, Colombia*
[4]*Internal Medicine Unit, Fundación Valle del Lili, Cra 98 #18-49, Cali 760032, Colombia*

Corresponding Author: Angela María Victoria, E-mail: angelamav7@hotmail.com

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ABSTRACT

Introduction: Insulinomas are rare pancreatic neuroendocrine tumors derived from beta cells responsible for insulin secretion. These tumors are typically manifested by hypoglycemia signs and symptoms, which might be non-specific leading to a delay in the diagnosis. The present study describes the experience in the approach of patients with insulinoma at Fundación Valle del Lili, Cali, Colombia. **Case Presentation:** A retrospective search of patients with the diagnosis of insulinoma within the database of the pathology service was performed between March 2002 and February 2017. Parameters such as the lesion size and localization, the immunohistochemistry findings, the serum levels of glucose, the insulin and C-peptide levels, the presence of metastasis, and the development of diabetes after surgery were evaluated. A total of nine patients with a diagnosis of insulinoma were enrolled in the study. The cohort comprised of seven men and two women, aged 30–50 years. Whipple triad was present in seven patients. The most common symptom was hypoglycemia-related syncope. All patients underwent surgical resection of the tumor with subsequent resolution of the symptoms. Only one patient was diagnosed with diabetes in the postoperative period. **Conclusion:** In the last 15 years, only nine cases of insulinoma were detected at the Fundación Valle del Lili, which is consistent with the low incidence of the disease. A higher frequency of the disease is noted in men, unlike that in the literature. However, other clinical and pathological features from large studies are in agreement with the current data. Nevertheless, continual experience in the management and identification of these cases is essential as common clinical manifestations may not be observed.

INTRODUCTION

Insulinomas are rare neuroendocrine tumors derived from insulin-producing beta pancreatic cells (1) with an annual incidence of four cases per million individuals (2). The principally affected individuals are between 41 and 50-years-old (3), of which, 57% are women. A majority of these tumors (90%) are benign (2,4). Up to 6% of the cases are related to the genetic syndrome known as multiple neuroendocrine neoplasia type 1 (MEN-1) (5,6). The clinical manifestations of insulinomas are those typical of hyperinsulinemic hypoglycemia (4). Thus, the initial identification of the Whipple triad is essential. It consists of neuroglycopenic symptoms secondary to low blood glucose levels that are promptly relieved after glucose administration (7-9). Occasionally, the symptomatology could be non-specific leading to a delayed diagnosis. Herein, we describe our experience with the diagnosis and treatment of insulinomas at Fundacion Valle del Lili (Cali, Colombia) depicting the demographic characteristics and clinical course and comparing it with the available literature in order to identify the putative patterns in the local population.

CASE PRESENTATION

A retrospective search of the database of the pathology service at Fundacion Valle del Lili was conducted, and cases of patients diagnosed with insulinoma between March 2002 and February 2017 were retrieved. The variables assessed included sociodemographic information, symptoms, glycemia, serum C-peptide levels, insulinemia, tumor characteristics, metastasis, and the onset of diabetes after surgical resection.

Continuous variables were expressed as median and interquartile range (IQR) or as mean and standard deviation (SD). Categorical variables were expressed as frequencies and percentages. All statistical descriptions were performed using STATA 12.

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The report of these case series was approved and supervised by the Ethics Committee on Biomedical Research of Fundacion Valle del Lili.

A total of nine patients, diagnosed with insulinoma were included in this study. The cohort comprised of seven (77%) men and two (22%) women, and 44.4% of the group was between 30 and 50-years-old. The median time-lapse between the initial appearance of symptoms of hypoglycemia and the surgical intervention was 8 (range, 3–60) months. The most frequent signs and symptoms were fasting hypoglycemia (100%), Whipple triad (77%), and hypoglycemia-related syncope (66%). All diagnosis were confirmed by the 72-hour-fast test. The mean glycemia was 43.3 mg/dL. In addition, the serum C-peptide level was measured in only six patients, and the median level was found to be 5.4 ng/mL, while the mean insulinemia was 32.84 µIU/mL. All patients underwent surgical resection of the tumor that was commonly localized in the tail of the pancreas in 33% of the cases, followed by body and head localization in the pancreas. None of the tumors were metastatic or malignant. Furthermore, different staining techniques were used for the immunohistochemistry of the resected specimens. Consequently, the staining for synaptophysin was positive in all the 6 samples, staining for insulin was positive in 3/4 samples, and staining for chromogranin was positive in all 5 samples. Only one patient was diagnosed with diabetes mellitus postoperatively, and although it was new onset, the medical record revealed insulin-dependent type 2 diabetes mellitus before the diagnosis of insulinoma, which in turn, favored persistent hypoglycemia (Table 1).

Peptide C levels were reported in only six patients from the cohort included in the study.

Table 1. Demographic and clinical characteristics of patients with insulinoma

Variable	Patients (n=9)
Age, Median (IQR)	40 (27.5–63)
Gender, n (%)	
Male	7 (77)
Female	2 (22)
Time-lapse between diagnosis and surgical removal (months), Median (IQR)	8 (6–12)
Hypoglycemic symptoms, n (%)	
Syncopes	6 (66)
Paresthesias	4 (44)
Seizures	4 (44)
Glycemia (mg/dL), Mean (SD)	43.3 (22.44)
Serum C peptide (ng/mL), Median (IQR)	5.4 (2.0–5.7)
Insulinemia (µUI/mL), Mean (SD)	32.8 (21.5)
Localization of the tumor, n (%)	
Tail	3 (33)
Body	2 (22)
Head	2 (22)
Neck	1 (11)
Uncinate process	1 (11)
Diameter of the lesion, n (%)	
<2 cm	6 (66)
>2 cm	3 (33)
Ki-67 cellular proliferation index n (%)	
<2	3 (33)
2–20	3 (33)
>20	0 (0)
No report	3 (33)

IQR: Interquartile range, SD: Standard deviation

DISCUSSION

In the last 15 years, only nine cases of insulinoma were detected at Fundacion Valle del Lili, which is consistent with the low incidence of the disease. Male patients comprised 77% of the cohort in contrast to other studies that reported female predominance, which accounted for up to 57% of the cases (3,7). Additionally, the most frequent age of onset was 30–50 years (44%), coinciding with data from large cohort studies that reported a mean onset age of 47 years (2-3).

Documenting the classic Whipple triad is a key diagnostic approach to hypoglycemia (10). Insulinomas are one of the most frequent causes of this manifestation after factitious hypoglycemia is excluded (11). Herein, this manifestation was detected in 77% of the patients. Furthermore, insulinoma-related hypoglycemia is typically described as fasting hypoglycemia. However, the clinical presentation has evolved, and up to 6% of the cases might present only postprandial hypoglycemia, while 21% exhibited a combination of fasting and postprandial hypoglycemia (7).

The final diagnosis was established by unusually high insulinemia associated with hypoglycemia that was further confirmed by a 72-hour fasting test (12,13). The mean plasma insulin level in our patients was 32.84 µIU/mL, exceeding the 5 µIU/mL insulin threshold established for diagnosis (5,12).

A majority of these tumors are benign (90%) and are presented as single lesions (87%), <2 cm, with homogeneous localization in the head, body, or tail of the pancreas (2,4,14). In the current case series, a significant proportion of tumors was >2 cm (33%) with a slight predominance of localization in the tail of the pancreas (33%). Herein, no malignant processes were found, which might be attributed to the small number of cases retrieved from our database.

The surgical resection of the tumor is considered as the treatment of choice due to a 95% efficacy in the resolution of the symptoms (4). All patients underwent successful surgical removal of the tumor, with no relapse during the follow-up, indicating a satisfactory prognosis. Therefore, pharmacological alternatives such as diazoxide, everolimus, and octreotide were not necessary for the treatment of the tumor (4,10,15-18).

The coexistence of diabetes mellitus with insulinoma has been rarely reported in the literature. The casuistry of the Mayo Clinic consisting of 313 patients presented only one

patient with both diseases. In the current study, one case was reported to be persisting with diabetes mellitus after tumor resection.

In conclusion, insulinoma is rare and should be suspected in unusual situations; for example, as a differential diagnosis of hypoglycemia in the diabetic patient, since this disease can lead to fatal outcomes. In the current study, we identified cases with general characteristics that match with the data from large studies. Nevertheless, common clinical manifestations may not be detected frequently, and hence, continual experience is essential with respect to the management and identification of these cases.

STUDY LIMITATIONS

The pathology service database from Fundación Valle del Lili, Cali, Colombia was reviewed. Only nine cases of insulinoma were reported in the last 15 years. This small number of cases was a limitation of the current study.

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AUTHOR CONTRIBUTIONS

All author contributed equally in this study.

CONFLICT OF INTERESTS

The authors have no conflicts of interests to declare.

ETHICAL STANDARDS

This case report was approved and supervised by the Ethics Committee at Fundación Valle del Lili and was deemed to be a risk-free study due to the retrospective design. Thus, written consent is not required, although informed consent was obtained from all participants included in these case reports.

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