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Insulinoma: A retrospective study analyzing the differences between benign and malignant tumors

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ABSTRACT

Background/objectives: Insulinoma is a rare pancreatic tumor and, usually, a benign disease but can be a malignant one and, sometimes, a highly aggressive disease. The aim of this study was to determine differences between benign and malignant tumors.
Methods: Retrospective study of 103 patients with insulinoma treated in a tertiary center. It was analyzed demographic, clinical, laboratory, localization and histologic analysis of tumor and follow up data of subjects in order to identify differences between individuals benign and malignant disease.
Results: Almost all patients (87%) had a benign tumor and survival rates of 100% following pancreatic tumor surgery. Those with malignant tumors (13%) have a poor prognosis, 77% insulinoma-related deaths over a period of 1–300 months after the diagnosis with a survival rate of 24% in five years. The following factors are associated with an increased risk of malignant disease: duration of symptoms < 24 months, fasting time for the occurrence of hypoglycemia < 8 h, blood plasma insulin concentration ≥ 28 μU/mL and C-peptide ≥ 4.0 ng/mL at the glycemic nadir and tumor size ≥ 2.5 cm.
Conclusions: Our data help to base the literature about these tumors, reinforcing that although insulinoma is usually a single benign and surgically treated neoplasia, the malignant one is difficult to treat. We highlight the data that help predict a malignancy behavior of tumor and suggest a long follow up after diagnosis in these cases.

Introduction

Insulinoma is pancreatic insulin-secreting tumor that, although rare, is the most common functioning neuroendocrine neoplasm of the pancreas. Hypoglycemia related symptoms are the main clinical manifestation and responsible for the great morbidity of this tumor. However, the malignant variant of this neoplasm can present additional morbidity and mortality due to their aggressiveness as neoplasia [1–4]. The diagnosis of malignancy is only defined out in the presence of metastasis but in patients who do not have extrapancreatic disease at initial presentation the prediction of their clinical behavior, following surgery of the primary tumor, is difficult unless the histological and immunohistochemical study reveals a poorly undifferentiated carcinoma [5–7].

Because malignant insulinoma is very rare, with the largest individual series having a maximum of 13 cases, comparative studies between benign and malignant tumors is quite limited [4–8]. Some authors have attempted to do make this distinction based on tumor

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evaluation with a smaller number in patient data. They suggest that some immunohistochemical or molecular markers of tumor are more common in malignant tumors, however, none of them are definitive for this definition [9–13]. Because these kinds of evaluation are not available in most services, it is of interest that the distinction between benignity and malignity can be made based on more available features, such as classic clinics, laboratories and morphological data.

The aim of this study was to evaluate the differences of clinical, laboratory, radiological and evolution data in the presentation of benign and malignant tumors.

Material and methods

Study design and patients

A retrospective cohort study using data collection from medical records of 103 patients with diagnosis of insulinoma attended by Endocrine Service and Pancreatic-Biliary Service at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), a tertiary care center in São Paulo, Brazil, since 1987 to 2017.

Study protocol

The patient's charts were analyzed and the following information data was obtained to compare between groups of patients with benign and malignant disease.

- Demographic: age and gender;
- Clinical: history of signs and symptoms of hypoglycemia, body mass index (BMI), fasting time required for the occurrence of biochemical hypoglycemia, tumor growth and metastasis;
- Laboratory findings: blood glucose at the nadir glycemic and concomitant serum insulin, C-peptide, proinsulin and ketonemia.
- Preoperative topographic diagnosis: computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS) with or without biopsy.
- Histological analysis;
- Follow-up data (recurrence or metastasis disease).

The laboratory diagnosis of hyperinsulinemic hypoglycemia was established according to the following criteria: blood glucose $\leq$ 55 mg/dL, insulin $\geq$ 3μU/mL, C-peptide $\geq$ 0.6 ng/dL, proinsulin $\geq$ 5 pmol/mL and negative ketonemia (< 1 mmol/L) [3,4].

All patients were screened (clinical and laboratorial) for MEN1, and if diagnostic criteria were established, the genetic test was performed [14].

Morphological and histological analysis of tumor

The tumor size was assessed, in most patients, by direct measurement of the macroscopic tumor resection specimen. If this data was not available, tumor size was determined by CT scan, MRI and/or EUS.

The tumor classification was based on the macroscopic (size and local invasion), histological (number of mitotic figures per 10 high-power fields – HPF - or mitotic activity index) and immunohistochemical (with emphasis on Ki-67 proliferation index) analysis and graded as:

- Grade 1 or well differentiated (low grade) tumors: tumor size $\leq$ 2 cm, a mitotic count < 2 mitosis per 10 HPF, Ki-67 proliferation index $\leq$ 2%, and no local invasion, regional or distant metastasis;
- Grade 2 (intermediate grade): tumor size > 2 cm, limited to the pancreas or with minimal local extension to biliary tract or duodenum, a mitotic count of 2–20 mitosis per 10 HPF, Ki-67 index of 3–20%, with or without metastases;
- Grade 3 (high grade): local invasion of adjacent organs, a mitotic count of > 20 per 10 HPF and/or a Ki-67 index > 20%, with or without metastasis [15,16].

Assessment of disease malignancy

The tumor was classified as malignant in two situations [4]:

- Regional or distant metastatic disease (at diagnosis or during follow-up).
- Primary tumor was Grade 3.

Laboratory assays

The methods used for the determination of the various compounds studied, with the respective normal 12-h fast values were: hexokinase for blood glucose (70–100 mg/dL), electrochemiluminometric assay for insulin (2.6–24.9 μU/mL) and C-peptide (1.1–4.4 ng/mL), immunoassay for proinsulin (< 18.8 pmol/L). The capillary ketonemia was assessed by the determination of blood β-hydroxybutyrate levels using an electrochemical method (MedSense Optium meter)and levels $\geq$ 1.0 mmol/L were considered as hyperketonemia. The insulin level was previously measured by radioimmunoassay (RIA), but the method was replaced by enzyme immunoassay (EIA). In order to standardize the data, values obtained by RIA divided by two were considered the corresponding value obtained by EIA. Determination of chromogranin was done by electrochemiluminescence assay (1.9–15 ng/mL).

Statistical analysis

We compared the clinical, laboratory and radiological data of patients with benign and malignant disease. Data is presented as mean ± standard deviation, as median (25–75 percentile) or as percent frequency.

For comparing nominal variables between groups, the Chi-square or Fisher exact test was used. An unpaired *t*-test or a Mann–Whitney *U* test were performed to compare continuous variables that were approximately normally or not normally distributed, retrospectively.

A Kaplan-Meier analysis was used to estimate the survival probability over time and for each interval of time, stratified by the presence or absence of malignancy. The subjects end of follow up due to unrelated insulinoma-deaths or unknown causes were considered censored for the Kaplan-Meier curves analysis. The Log-rank test was used for comparing the survival curves.

Continuous variables were categorized by the inflection point on the receiver operating characteristic (ROC) analysis to establish the best discriminator cut-off for sensitivity and specificity. It was measured Odds Ratio (OR) and 95% confidence interval (CI) of association between these variables and malignancy. P-values < 0.05 were considered significant. All statistical analyses were performed using STATA 15.0 (StataCorp, College Station, Tex).

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