

## CASE REPORT

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# Liver Metastases 9 Years after Removal of a Malignant Insulinoma Which Was Initially Considered Benign

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### ABSTRACT

**Context** Insulinomas may be regarded as potentially malignant. A long follow-up period is needed to detect any possible recurrence, even if the initial diagnosis was of a benign insulinoma.

**Case report** We present the case of a 76-year-old woman with liver metastases due to a malignant insulinoma, which had been diagnosed as benign after its complete removal 9 years earlier.

**Conclusions** This case shows the difficulty of distinguishing between benign and malignant insulinomas when there is no initial evidence of metastases. This fact poses the need to conduct a long follow-up period in order to detect any possible recurrence even if the initial diagnosis was one of a benign insulinoma.

about the need for periodic follow-up assessment for recurrence when a diagnosis of benign insulinoma is made [3]. If this tumor is resected completely, the recurrence rate is very low. One confusing factor is the fact that malignant and benign tumors are difficult to distinguish histologically and, often, the diagnosis of malignant insulinoma is made only when metastases occur. The best estimate of the incidence of malignant insulinomas is probably 4 cases per million people/year [4] which is higher than previously reported. Perhaps with the awareness that insulinoma is more frequent than suspected, the commonly reported interval of 12 to 18 months between the onset of symptoms and the confirmation of diagnosis may be shortened. We report a case of an insulinoma initially considered benign which recurred with multiple liver metastases 9 years after the initial surgery.

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### INTRODUCTION

Insulinomas are rare tumors and the majority are benign and solitary. The existing literature regarding their growth rate is controversial. Some authors [1] have characterized their course as rapidly deteriorating whereas others [2] have reported that they may be associated with long-term survival. Scant and inconclusive data account for the uncertainty

A previously healthy 76-year-old woman presented in January 1986 with a 2-year history of twice a week episodes of fasting hypoglycemia. All the tests and treatment were carried out in another hospital. Laboratory examinations revealed hypoglycemia with a fasting blood glucose level of less than 45 mg/dL (reference range: 76-110 mg/dL) and insulin levels above 100 IU/L (reference range: 2.6-24.9 IU/L) by

radioimmunoassay (RIA). Enhanced computed tomography (CT) was not able to locate either the pancreatic tumor or the possible metastasis. A laparotomy was carried out and a 2x4 cm tumor in the tail of the pancreas was found without using intraoperative ultrasound and a distal pancreatectomy was performed. The surgical limits were free and there was no residual tumor. No nuclear atypia was observed in the hematoxylin and eosin (H&E) specimens obtained and the pathology diagnosis was benign insulinoma.

After surgery, the symptoms disappeared and the patient was lost to follow-up. She remained asymptomatic until 1995 when she was admitted for the first time to our hospital with a recurrence of her original symptoms. A fasting test was performed. After 16 hours, the patient lost consciousness. A blood glucose level of less than 45 mg/dL and insulin levels (RIA) above 100 IU/L were observed. Proinsulin was not measured. The levels of vasoactive intestinal peptide, glucagon, pancreatic polypeptide, gastrin, PTH, urinary hydroxyindolacetic acid and pituitary hormones were all normal and the syndrome of multiple endocrine neoplasia was ruled out. Determination of urinary sulfonilurea was negative.

At that time, an octreotide scan found that she had a 5x5 cm mass in the pancreas and two liver metastases, consistent with an insulin-secreting carcinoma. Initial treatment with diazoxide and octreotide resulted in symptomatic remission for some weeks. During the last admission, she remained persistently hypoglycemic, requiring regular glucose infusions, despite a maximal dose of diazoxide (1,200 mg/day). She and her family refused both surgery and chemotherapy. The patient died of respiratory failure two months later. An autopsy was not performed.

## DISCUSSION

In this patient, the primary tumor was diagnosed histopathologically as a benign insulinoma; however, we observed its recurrence with liver metastases 9 years later.

The most probable explanation is a tumor recurrence. We were not able to demonstrate that this second tumor had the same origin but the existence of a second tumor-induced hypoglycemia is rather unlikely.

Danforth *et al.* [5] reported the case of a patient who survived 22 years with hepatic metastases and 31 years from the onset of symptoms from the original tumor. In that case, the patient was found to have liver metastases only 3 years after the partial pancreatectomy. To our knowledge, no data have previously been published about a recurrence more than 9 years after the removal of a malignant insulinoma which, according to the histological diagnosis, was initially considered as benign. Only Sata *et al.* reported a case of a supposedly benign insulinoma which recurred as a multiple liver metastasis 8 years after the initial resection [6].

Insulinomas have a lower malignancy rate [7] than other islet cell tumors such as gastrinomas [8] or glucagonomas [9]. It is very difficult to distinguish between malignant and benign insulinomas since endocrine carcinomas generally show mild nuclear and structural atypia. Moreover, malignant insulinomas are usually diagnosed by intrasurgical evidence of metastases in the liver, regional nodes or local invasion. However, malignant insulinomas, which are solitary and have no evidence of metastases, usually have a good prognosis.

Service *et al.* [4] followed up 196 patients with insulinomas for an average period of 20 years. Recurrences were noted from 4 to 18.5 years after the initial removal of an insulinoma. The cumulative incidence of recurrence was 6% at 10 years and 8% at 20 years after the initial surgical resection. Out of 4 patients having a malignant insulinoma with a 6 month or longer symptom-free interval after the initial removal of the tumor, two of them had recurrences at 4 and 9 years, respectively, after the initial surgical treatment. In these cases, the malignancy was detected at the beginning.

Our case and that reported by Sata *et al.* [6] indicate that even if the primary tumor is

small and histologically benign, insulinomas should be regarded as potentially malignant. Our patients did not have any evidence of metastases in the liver at diagnosis according to the results of the computed tomography although 89 % of malignant insulinomas have had metastases from the beginning.

As the patient was not hospitalized, no doctor was present at the times when the patient had an episode of these symptoms. This is the reason why we could not obtain the measurements of insulin, C-peptide and proinsulin. If we had been able to obtain these results, we could have avoided the need for a second prolonged fast. Nevertheless, the issue was discussed among the medical staff because of the ethical concern about the need of a second fasting test to make sure that the symptoms were due to an insulin-secreting tumor. Eventually, a fasting test was performed.

In light of the present case, we agree with the criteria of Falconi et al. [10] that the best approach for establishing a diagnosis of insulinoma is to perform surgery with the help of intraoperative ultrasound, preceded by only one pre-operative diagnostic imaging technique (computerized tomography or magnetic resonance imaging). Recently a study by Orlefors *et al.* [11] has demonstrated that whole body positron emission tomography (PET) with <sup>11</sup>C-5-hydroxytryptophan (5-HTP) is sensitive in the imaging of small neuroendocrine tumors, such as primary tumors, and can, in the majority of cases, significantly image more tumor lesions than somatostatin receptor scintigraphy and CT. If metastases exist, treatment with local chemotherapy (streptozocin combined with 5-fluorouracil) or even the resection of the hepatic metastases may provide significant symptomatic relief and improve survival possibilities.

It is essential that we should seek other ways of predicting the metastatic potential of insulinomas since it is not possible to do so only histopathologically. Jonkers *et al.* [12] investigated 62 sporadic insulinomas (44 benign and 18 tumors with metastases) for the identification of reliable indicators of

metastatic disease by means of comparative genomic hybridization (CGH). CGH analysis revealed that the total number of aberrations per tumor differs greatly between the benign and the malignant groups (4.2 vs. 14.1; P<0.0001). Furthermore, chromosome 6q losses and 12q, 14q and 17pq gains are strongly associated with metastatic disease.

Among patients with histopathologically benign insulinomas, recurrence is more common in patients with multiple endocrine neoplasia 1 (MEN 1) than in those without this syndrome. Therefore, regular follow-up of patients considered cured of insulinoma is important, especially for those with MEN I.

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Received November 12<sup>th</sup>, 2005 - Accepted February 1<sup>st</sup>, 2006

**Keywords** Hypoglycemia; Insulinoma; Liver Neoplasms

**Abbreviations** CGH: comparative genomic hybridization; MEN: multiple endocrine neoplasia

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