

Spinal cord compression after radiolabeled metaiodobenzylguanidine analogue therapy in advanced malignant insulinoma

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SUMMARY

Malignant insulinomas are frequently diagnosed at a late stage. Medical management is necessary to slow progression of the disease and control of hypoglycemic symptoms when cure by surgical treatment is not possible. Multimodal treatment, in these cases, has been used with variable clinical response. We describe a 68-yr-old woman who presented response failure to usual treatment and was alternatively treated with radiolabeled metaiodobenzylguanidine ([¹³¹I]-MIBG) analogue therapy with development of neurologic complications. We also present a review of the current role of [¹³¹I]-MIBG treatment in insulinomas. Arch Endocrinol Metab. 2015;59(2):186-9

INTRODUCTION

Although rare, insulinomas are the most frequent pancreatic neuroendocrine tumors with a malignant presentation in 10% of the cases (1). The incidence of insulinomas in general population is 4 cases per million a year (2) with a malignant presentation even rarer – 0.1 cases per million (3). Malignant insulinomas are frequently diagnosed at a late stage, with approximately 50% of patients already presenting metastatic disease at the time of the diagnosis (4). When distant metastases are present, the median survival time is approximately 2 years. These tumors are potentially curable if total resection is feasible, even when metastatic lesions are present. Palliative medical treatment including, chemotherapy (5), radiofrequency thermoablation (6), arterial chemoembolization (7), somatostatin analogue therapy (8,9) and diazoxide (10) are indicated to retard disease progression and control hypoglycemic symptoms when surgery is not possible. Recently, a new promising agent named everolimus, an inhibitor of mammalian target of rapamicin (mTOR), presented an improvement of progression-free disease in patients with advanced pancreatic neuroendocrine tumors, including insulinomas (11). Acute tumor growth is a rare complication that

occurs due to inflammation and edema of irradiated tissue (12,13) and to our knowledge, it has never been reported in malignant insulinomas.

We present a case of advanced malignant insulinoma in a type 2 diabetic patient with liver, lymph node and bone metastasis treated with multimodal therapy, who developed spinal cord compression after peptide receptor radiotherapy using MIBG. We also present a review of the current role of [¹³¹I]-MIBG treatment in insulinomas.

CASE PRESENTATION

A 68-year-old female presented with seven months history of tonic-clonic episodes and intermittent collapses with consciousness loss. Fasting laboratory tests revealed a glucose level of 37 mg/dL (2.05 mmol/liter), insulin of 123 mU/mL (fasting reference = 3 - 17U/mL) and C peptide of 7.0 ng/mL (fasting reference = 0.9 - 4.0 ng/mL). These tests were consistent with endogenous hyperinsulinemic hypoglycemia. Abdominal ultrasound and computed tomography (CT) demonstrated diffuse hepatic metastases and a mass in the head of the pancreas. CT guided liver biopsy revealed poorly differentiated neuroendocrine carcinoma with diffuse chromogranin A and synaptophysin staining and ki-67

index of < 2%. These findings were consistent with malignant insulinoma. Of note, her past medical history included a 10 year history of hypertension and a two year history of type 2 *diabetes mellitus* controlled with dietary changes before initiation of hypoglycemic episodes misdiagnosed as epilepsy.

The patient was initially treated with subcutaneous octreotide and frequent meals with short intervals which lead to a reduction of hypoglycemic episodes. Subsequently, diazoxide and subcutaneous octreotide were added but, despite a good hypoglycemia controlling, it had to be stopped because of important side effects, including, gallbladder stones and a severe acute cholecystitis due to octreotide. The patient kept suffering of frequent severe hypoglycemia episodes and increasing hepatic volume due to tumor dissemination. Transarterial hepatic chemoembolization was performed with good response. The patient became hypoglycemia-free for 14 months, requiring subcutaneous insulin treatment to control hyperglycemia. In the following six months there was a rapid progression of liver lesions with metastasis to lymph nodes, adrenal gland, bone metastases to spine and hip and frequent hypoglycemia episodes (about 01 per day). MIBG scintigraphy confirmed liver, pancreas and bone disease (Figure 1) and the patient was subsequently treated with one cycle of [¹³¹I]MIBG to a total administered activity of 3.7 GBq with worsening of hypoglycemia episodes starting approximately 12 hours after treatment. In an attempt to control glycemia four milligrams of intravenous dexametasone was started but after three days it had to be promptly discontinued because of severe increase of blood glucose requiring insulin therapy (Figure 2).

Bone pain suddenly worsened thirteen days after [¹³¹I]MIBG treatment followed by numbness and proximal muscular weakness of the leg rapidly progressing to paraplegia. A magnetic resonance imaging (MRI) (Figure 3) showed a metastatic involvement of the T2 to T4 levels with pathological fracture of the T2 vertebral body and a soft tissue mass invading spinal cord. Decompressive palliative laminectomy was performed four days after onset of symptoms, but the patient remained paraplegic despite the intensive physiotherapy efforts.

After [¹³¹I]MIBG treatment, the patient continued to present hypoglycemia episodes, although less frequent and severe. Everolimus was initiated with better control of hypoglycemic episodes for 32 months until patient's death due to pulmonary metastatic disease.

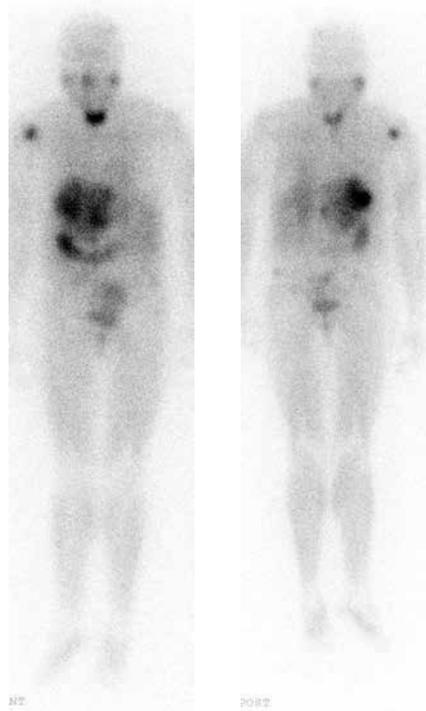


Figure 1. [¹³¹I]MIBG scan of the patient.

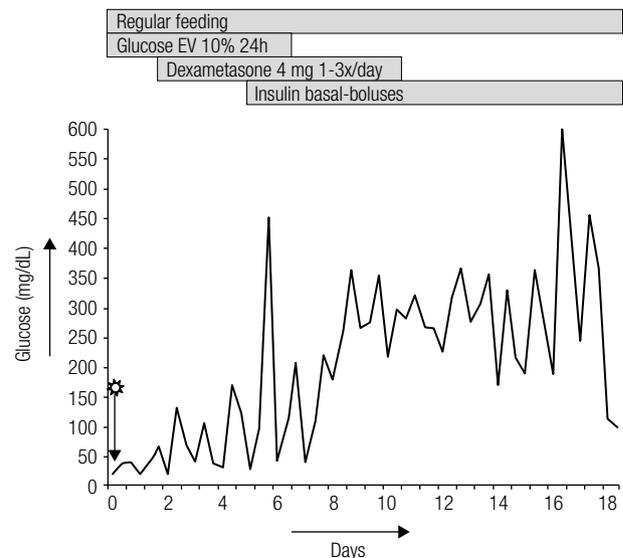


Figure 2. Timeline of treatment interventions (including [¹³¹I]MIBG marked at day 0, iv glucose, dexametasone, sc insulin) with values for blood glucose levels.

DISCUSSION

The presented case combines multiple uncommon aspects. A malignant insulinoma with liver, lymph node and bone metastases in a previous diabetic patient who was treated with multimodal therapy and developed a spinal cord compression after a peptide receptor radiotherapy using MIBG.

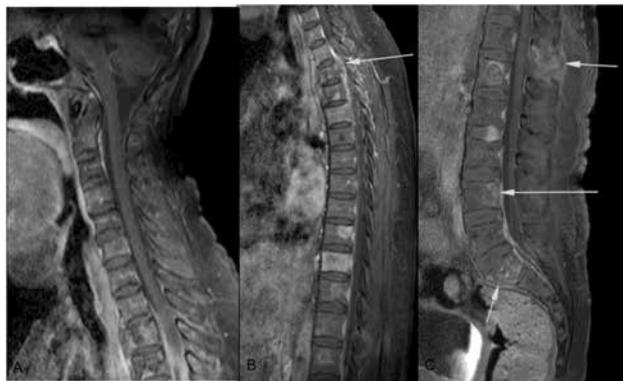


Figure 3. MRI of cervical and thoracic bone and spinal cord.

A [^{131}I]MIBG scintigraphy study was performed in our patient and showed multiple liver, bone, pancreas and lymph node uptake. [^{131}I]MIBG scintigraphy has been shown to locate neuroendocrine tumors such as pheochromocytomas, neuroblastomas, carcinoid tumors, medullary thyroid carcinoma, paraganglioma (14) but rarely insulinomas (Table 1). MIBG is a compound resembling norepinephrine that is taken up by adrenergic tissue (15). [^{131}I]MIBG targeted radiotherapy remains a highly means of management of neuroendocrine tumors of neuroectodermal origin with good responses. Octreotide and pentreotide scintigraphy are, in general, more sensitive in detecting neuroendocrine tumors than radiolabeled MIBG (15,16) in case of insulinomas. Our patient demonstrated an intense uptake of MIBG radioligand that corresponded with primary pancreatic tumor and the known metastases in the liver and lymph nodes and treatment with [^{131}I]MIBG therapy was given.

Table 1. [^{131}I]MIBG scintigraphy and treatment in insulinomas

Ref.	Total number of patients	Total number of insulinomas	MIBG uptake in insulinomas	Therapy with [^{131}I]MIBG
Von Moll and cols., 1987 (20)	57	01 (malignant)	Negative	No
Geatti and cols., 1989 (21)	01	01 (NR)	Positive	No
Tronccone and cols., 1990 (22)	158	01 (NR)	Negative	No
Zagar and cols., 1995 (23)	74	02 (malignant)	Positive	No
Kaltsas and cols., 2001 (16)	54	12 (malignant)	1/12 positive	No
Feitosa and cols., 2015	01	01 (malignant)	Positive	Yes
Our case				

NR: not reported.

Approximately 12 hours after [^{131}I]MIBG treatment there were worsening of hypoglycemia episodes requiring continuous intravenous high glucose dose, which resembled a hormonal crisis. Hormonal crisis had been reported in 1% of patients with gastroenteropancreatic neuroendocrine tumors and metastatic pheochromocytoma after [^{177}Lu]octreotate therapy (17). None of these patients had insulinomas but massive release of bioactive substances developed after first cycle of radiolabeled therapy (17). The worsening of hypoglycemias in the presented case could be due to destruction-mediated release of insulin. Similar situation can occur in thyroid after radioiodine [^{131}I] therapy. It gradually induces cell necrosis and 1 to 3% of patients may developed an acute radioiodine thyroiditis (18,19) that is characterized by a painful inflammation of the gland and is frequently associated with exacerbation of thyrotoxicosis because of destruction-mediated release of thyroid hormone. We believe that an acute cell destruction-mediated release of insulin explained what occurred with glycemia concentration in the first week of [^{131}I]MIBG therapy, and the gradually increase of glycemia in the next days could be resultant of continued tumor cell destruction.

The worsening of bone pain and subsequent spinal cord compression was explained by acute expansion of the bone lesions. Acute tissue expansion after radiolabeled therapy had been reported in very large goiter treated with radioiodine and expansion caused by inflammation and edema of irradiated tissue may be as large as 25% (12,13). No reports of this complication were found in the literature.

We could not prove the relationship of rapid expansion of spinal metastasis and cord compression with radioiodine [^{131}I]MIBG therapy because there was no previous spinal MRI to provide comparison and the bone uptake was minimal. But the sequence of events: worsening of hypoglycemias, development of hyperglycemias, worsening of bone pain and subsequent spinal cord compression makes the hypothesis of acute cell destruction and rapid tumor expansion due to tissue inflammation and edema possible.

Assuming that acute expansion of the tumor could occur due to radiation effects, we believe that special care have to be taken in advanced malignant insulinomas with suspected bone metastases when radiolabeled therapy is being considered. It is impossible to predict in whom this complication may occur and caution should always be taken. In the presented case, spinal cord com-

pression occurred after radioiodine [¹³¹I]MIBG therapy and we believe that, similar complication, could happen in other neuroendocrine tumors treated with any type of radiolabeled therapy. We recommended that a detailed study of spine should be done before peptide receptor radiotherapy, in malignant insulinomas presenting bone pain. If spinal metastases are confirmed external radiotherapy may be performed before or glucocorticoids should be used in order to prevent rapid expansion of metastases that could result in acute cord compression. Additionally, we think that radioiodine [¹³¹I]MIBG therapy, despite unusual, can be an effective alternative palliative treatment in malignant insulinoma.

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