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ORIGINAL ARTICLE

Fatal hypoglycemia in malignant pheochromocytoma: direct glucose consumption as suggested by ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography imaging

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Abstract We present a patient with metastatic pheochromocytoma, who developed progressive and fatal hypoglycemia most likely secondary to direct tumor glucose consumption that did not respond to high-dose glucose infusion, corticosteroids, or glucagon therapy. The pattern of glucose uptake on ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography, with preferential tumor glucose uptake in association with a marked reduction in normal uptake in the heart, muscles, and brain, is highly suggestive of direct consumption of glucose by the tumor rather than insulin-like growth factor-2 mediated hypoglycemia. In patients with large-volume metastatic malignancies, direct tumor glucose consumption should be considered in the differential diagnosis of hypoglycemia. Nuclear medicine imaging techniques can illustrate the pathophysiology of hypoglycemia in such cases.

Keywords Malignant pheochromocytoma · Hypoglycemia · Positron emission tomography

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Introduction

Clinically significant hypoglycemia occasionally occurs in patients with cancer. Different mechanisms can contribute to the development of hypoglycemia in these patients, including the following: (1) hepatic insufficiency, adrenal insufficiency, or hypopituitarism, resulting from destruction of the liver, adrenal glands, or pituitary gland by massive tumor infiltration or as a consequence of surgical resection or irradiation; (2) production of excessive amounts of humoral factors such as peptidic hormones or antibodies, including insulin [1], insulin-like growth factor-1 (IGF-1) [1, 2], partially processed precursors of IGF-2 (big-IGF-2) [3–5], or insulin receptor antibodies; (3) lactic acidosis-associated hypoglycemia in lymphoma patients [6]; or (4) direct glucose consumption by tumors [7].

In pheochromocytoma, catecholamine overproduction usually results in hyperglycemia; however, rare cases of hypoglycemia are reported after pheochromocytoma resection. These cases are secondary to the rebound insulin production after the inhibitory effects of catecholamine have been abrogated [8, 9]. In addition, reactive insulin production with hypertensive crisis has been reported in two pheochromocytoma cases [10, 11], and ectopic insulin production has been reported in a case of paraganglioma [12].

Among the above-mentioned causes of hypoglycemia in cancer patients, big-IGF-2 overproduction is the most common, after liver failure or endocrinopathies. The excessive secretion of big-IGF-2 inhibits growth hormone production and alters IGF-binding proteins, resulting in more bioavailable IGF-2, that in turn, reduces hepatic gluconeogenesis and increases peripheral glucose utilization, mainly in the muscles [4].

^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is

a functional/metabolic imaging method that is widely used to assess disease burden in patients with different malignancies and has proven to be a very sensitive test for evaluating disease extension in patients with malignant pheochromocytomas and paragangliomas [13, 14]. However, the use of PET/CT in assessing tumors associated with hypoglycemia is limited.

Subjects and methods

A 30-yr-old black man presented with a 1-month history of progressive abdominal and back pain. A CT scan of the abdomen and pelvis showed a 13-cm necrotic mass with calcifications, arising from the left adrenal gland. The tumor was markedly vascular, with vessels within the peripheral solid portion of the tumor and had areas of necrosis. There was evidence of liver metastases, as well as a lytic lesion in the left iliac bone that proved to be metastatic pheochromocytoma on biopsy. A CT scan of the chest was normal. The patient did not have symptoms related to catecholamine overproduction and had normal blood pressure and pulse. His physical examination was remarkable for hepatomegaly, likely secondary to tumor infiltration of the left hepatic lobe. His plasma metanephrine and catecholamine levels were within the normal ranges, but his chromogranin-A level was elevated (5,702 ng/ml; reference range, <36.4 ng/ml).

Results

A ^{123}iodine-metaiodobenzylguanidine (^{123}I-MIBG) single photon emission computed tomography (SPECT)/CT scan showed abnormal uptake in the left adrenal mass, but no abnormal uptake in either the lytic left iliac metastasis or the hepatic metastasis (Fig. 1). An ^{18}F-FDG-PET/CT scan showed a large, centrally necrotic FDG-avid left adrenal mass with abnormal metabolic activity (SUV max 15.5). Extensive hepatic metastases, involving much of the liver,

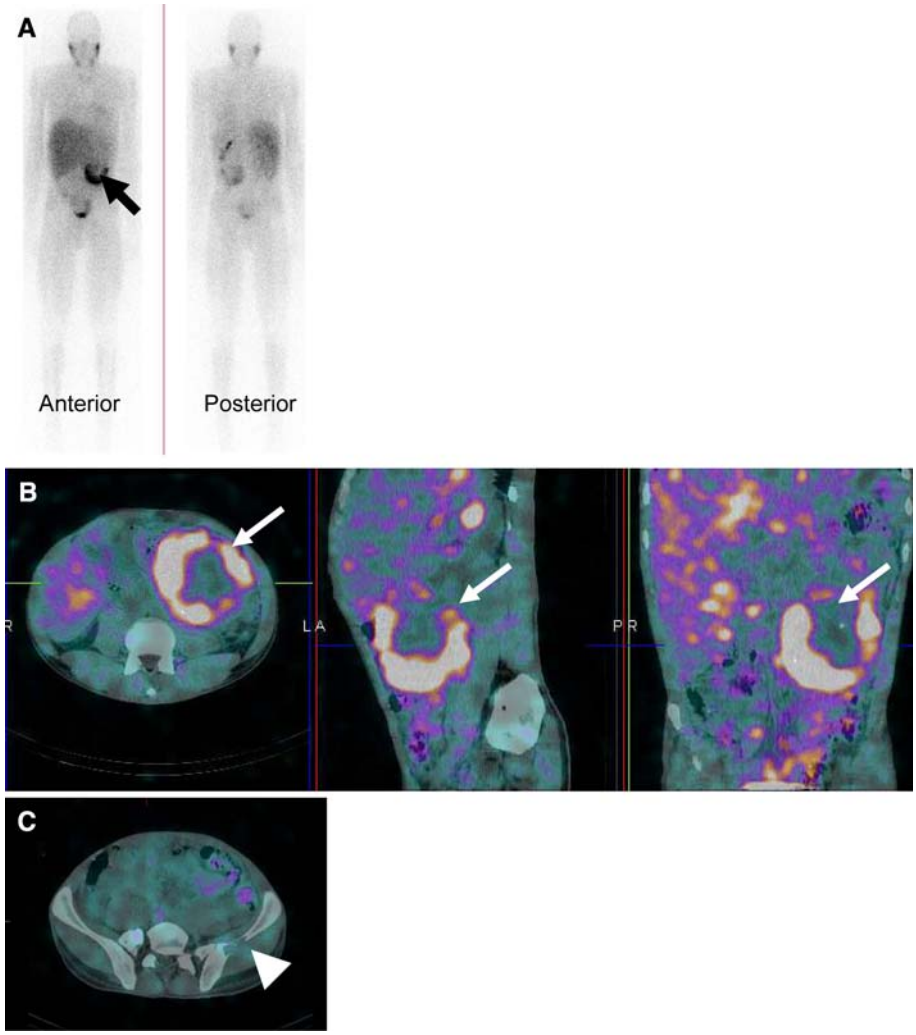

Fig. 1 ^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) single photon emission computed tomography (SPECT)/CT study. **a** Anterior and posterior whole body images were obtained 24 h after injection of the radiotracer. Abnormal uptake was seen in the inferior portion of a large left adrenal mass (*black arrow*). **b** SPECT/CT fusion images in the axial, sagittal, and coronal planes (*left*, *middle*, and *right images*, respectively) showed increased ^{123}I-MIBG uptake in a centrally necrotic left adrenal mass (*white arrows*), with relatively poor uptake in the liver with known tumor infiltration. **c** Axial SPECT/CT image of the pelvis. No ^{123}I-MIBG uptake was seen in the osteolytic left iliac bone metastasis (*white arrowhead*)

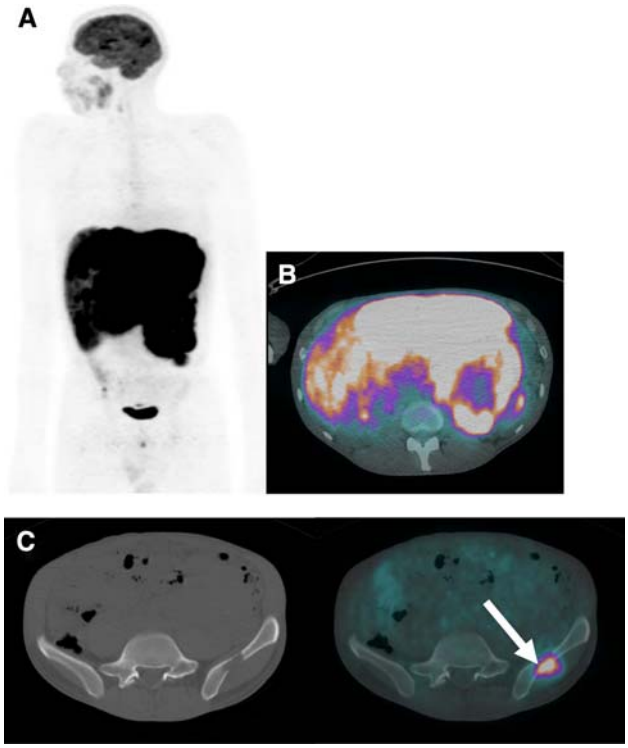

Fig. 2 ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) scan. **a** A maximum intensity projection image shows intense hypermetabolism within large tumor masses, with relatively decreased uptake in the rest of the body and the brain. **b** Fusion image of the abdomen shows intense FDG uptake in both the centrally necrotic left adrenal mass and the extensive hepatic metastasis. **c** Transaxial images of the pelvis show an osteolytic metastasis in the left iliac bone with intense FDG uptake (*white arrow*). These findings contrast with findings from the ^{123}I-MIBG SPECT/CT study

and a left iliac osseous metastasis were also seen, without evidence of other sites of disease. It is of interest to note that there was a reduction in normal FDG uptake throughout the rest of the body, most prominently in the brain (Fig. 2).

After a short period of fasting (4 h) in preparation for his PET/CT scan, the patient developed mildly symptomatic hypoglycemia (glucose level of 44 mg/dl) that responded to oral glucose. Within a few days, he started having symptoms of anxiety and excessive sweating, which were initially treated with frequent meals, until he was brought to a local emergency room after losing consciousness, with whole blood glucose of 26 mg/dl. His C-Peptide was <0.1 ng/ml (reference range, 1.1–5), insulin was undetectable, insulin antibodies were negative. IGF-1 levels were <26 ng/ml (reference range 117–329), whereas his IGF-2 level was 406 ng/ml (reference range 288–736 ng/ml). The remainder of his laboratory workup showed normal serum electrolyte, kidney function, alanine aminotransferase, and total bilirubin levels. Beta-hydroxybuterate and big-IGF-2 were not measured at the time of hypoglycemia while patient was cared for in a local hospital.

The patient received multiple injections of dextrose 50% and an intravenous infusion of concentrated dextrose at a rate of 20–30 g/h, which resulted in some clinical improvement but only kept his blood glucose level at approximately 20 mg/dl. Adding a high dose of dexamethasone and glucagon infusion did not lead to any further clinical benefit and did not normalize his blood glucose level. The patient deteriorated further and died because of rapid tumor progression and hypoglycemia.

The patient had no family history of pheochromocytoma or paraganglioma, and DNA sequence analysis of the coding regions (exons 1–8) of the B subunit of the mitochondrial complex II enzyme succinate dehydrogenase (SDHB) gene revealed no mutations. Large deletion studies of SDHB, followed by analyses of the SDHD and von Hippel-Lindau (VHL) genes, were planned, given the patient's young age at diagnosis, but could not be conducted before the patient died.

Discussion

We present a rare case of aggressive malignant pheochromocytoma in which fatal hypoglycemia resulted from direct tumor glucose consumption. To the best of our knowledge, fatal hypoglycemia has not been reported with malignant pheochromocytoma. ^{18}F-FDG-PET/CT scan was very helpful in detecting the tumor burden and explaining the etiology of the hypoglycemia.

The use of PET/CT imaging for tumors associated with hypoglycemia is limited. In this particular case, there was more extensive disease seen by ^{18}F-FDG-PET/CT than by MIBG SPECT/CT. The differences between the image patterns using these two methods may be due to the poor differentiation of this patient's tumor, which had very prominent metabolic activity, accompanied by a decrease in the uptake of MIBG [15, 16].

We believe that the hypoglycemia in our patient can be attributed to direct tumor glucose consumption as illustrated by the ^{18}F-FDG-PET/CT scan findings, in addition to a limited hepatic reserve secondary to tumor infiltration of the liver as suggested by the lack of response to glucagon which also argues against insulin or IGF mediated process [17]. This assumption is supported by the presence of FDG uptake predominantly in the tumor mass, with minimal uptake in the brain and other tissues. Competition for FDG uptake has been described in patients with bone marrow activation secondary to granulocyte macrophage colony-stimulating factor treatments [18, 19]. The uptake pattern in our patient was similar to that in a previously reported case of hypoglycemia secondary to direct glucose

consumption by metastatic malignant meningioma, where the uptake was mainly in the malignant tissues. In addition, that patient had an IGF-1/IGF-2 profile similar to our patient's profile (i.e., a normal IGF-2 level and a low IGF-1 level) [7]. These cases contrast with the uptake pattern seen in big-IGF-2 producing tumors: in one case, an ^{18}F-FDG-PET/CT scan showed a false-negative result in a tumor with big-IGF-2 mediated hypoglycemia [20], and in another report, FDG uptake in muscles reached 44% of total glucose uptake, as compared with 15% of total glucose uptake by an IGF-2-producing tumor [21]. A normal total IGF-2 does not exclude a tumor that secretes big-IGF-2, as the assay will not show if pro-IGF-2 is elevated as a fraction of total IGF-2. This precursor is less protein bound and more bioactive, and can only be demonstrated if chromatography is performed or a free IGF-2 assay is used. Unfortunately, as the patient was in outside institution, we were not able to evaluate him for pro-IGF-2. However, the ^{18}F-FDG-PET scan findings and lack of response to glucagon do not suggest hypoglycemia mediated by IGF-2 precursors.

In patients with large-volume metastatic malignancies, direct tumor glucose consumption should be considered in the differential diagnosis of hypoglycemia. ^{18}F-FDG-PET imaging is a functional study that could illustrate the pathophysiology of hypoglycemia in such cases by showing remarkable glucose uptake in the tumor with reduced physiologic uptake in other organs.

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