RCR RADIOLOGY CASE REPORTS

Case Report

Molecular imaging of a glucagonoma with ^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE PET/CT imaging: A case report and review of the literature

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ABSTRACT

A 35-year-old man presented with significant weight loss of 30 kg over the previous 6 months, with newly diagnosed diabetes. Routine laboratory tests were normal, except for markedly elevated blood glucose. Computed tomography (CT) of the abdomen revealed a large severely enhanced mass replacing most of the pancreas and liver metastatic nodules and multiple paraaortic lymph node metastases, ^{18}F-fluorodeoxygluocse positron emission tomography/computed tomography (^{18}F-FDG PET/CT) was performed and revealed mild FDG uptake in the pancreatic mass, as well as mild uptake in the liver and lymph node metastases. A biopsy of the liver metastasis was consistent glucagonoma that was confirmed with markedly elevated serum glucagon level. Subsequently, ^{68}Ga-DOTATATE PET/CT was performed for better tumor characterization and for assessment of the tumors' response to therapy, ^{68}Ga-DOTATATE scan revealed intense uptake in the pancreatic mass, liver metastases, and paraaortic lymph node metastases. The patient responded well to peptide receptor radionuclide therapy. This case highlights the role of both ^{68}Ga-DOTATATE and [18]FDG-PET/CT in the diagnosis and management of a glucagonoma. ^{68}Ga-DOTATATE is the tracer of choice for well-differentiated glucagonoma and offers very high diagnostic accuracy as compared with that of cross-sectional and other functional imaging and enables correct patient selection for peptide receptor radionuclide therapy.

Case presentation

A 35-year-old man presented with a history of significant weight loss of 30 kg in the last 6 months, with newly diagnosed diabetes and uncontrolled skin itching and erythema. Numerous patches of erythematous areas, with irregular borders, vesicles, and crust formation were visible on the skin of his lower limbs, abdomen, and both thighs. Routine laboratory tests, including a complete blood count and blood chemistry, were normal. The patient's renal function and his liver function were also normal. Serum glucose was 6.4 mmol/L. A computed tomography (CT) scan of his chest,

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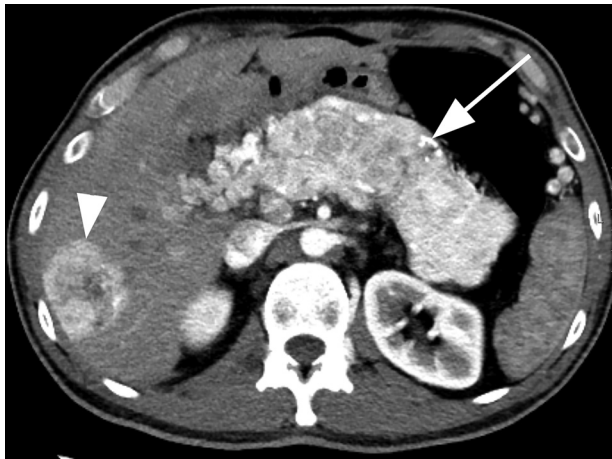E-mail address: ahm35799@hotmail.com (A. Fathala).

Fig. 1 – Axial contrast enhanced computed tomography (CT) of the abdomen at the level of the pancreas during the arterial phase showed a largely and markedly enhanced mass replacing most of the pancreas (arrow) and a well-enhanced liver metastatic nodule (arrow head)
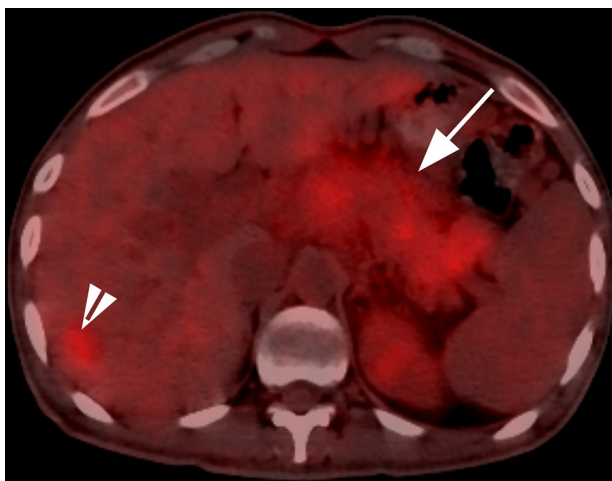

Fig. 2 – Axial image of ^{18}F-FDG PET/CT at the same level as the CT image showed mild FDG uptake in the pancreatic mass (arrow) and liver metastasis (arrow head)

Fig. 3 – (A) Coronal fused ^{68}Ga-DOTATATE and (B) selected axial fused image of ^{68}Ga-DOTATATE demonstrates uptake of ^{68}Ga-DOTATATE in both the primary pancreatic tumor (arrow) and liver metastatic nodules (arrow head). Note the markedly intense uptake of ^{68}Ga-DOTATATE as compared to the FDG uptake in Fig. 2.

abdomen, and pelvis showed a hypervascular mass replacing most of the pancreas, with severe diffuse pancreatic enlargement, in addition to multiple liver lesions in the right lobe and left para-aortic lymph nodes (Fig. 1). For further staging, ^{18}F- fluorodeoxygluocse positron emission tomography/computed tomography (FDG PET/CT) was performed. It showed mild to moderate heterogeneous activity in the pancreatic mass, with mild FDG uptake in 2 liver lesions, a pattern suggestive of metastasis (Fig. 2). A biopsy of one of the liver lesions confirmed a metastatic grade 2 neuroendocrine tumor (NET) (mitotic index = 1, Ki-67 index of 10%). Further workup revealed a markedly elevated serum glucagon level of 2500 pg/ml (normal = 80 pg/ml) and an elevated chromogranin level of 4600 ng/ml (93 ng/ml). Subsequently, ^{68}Ga-DOTATATE was performed and revealed an intense Ga-avid large
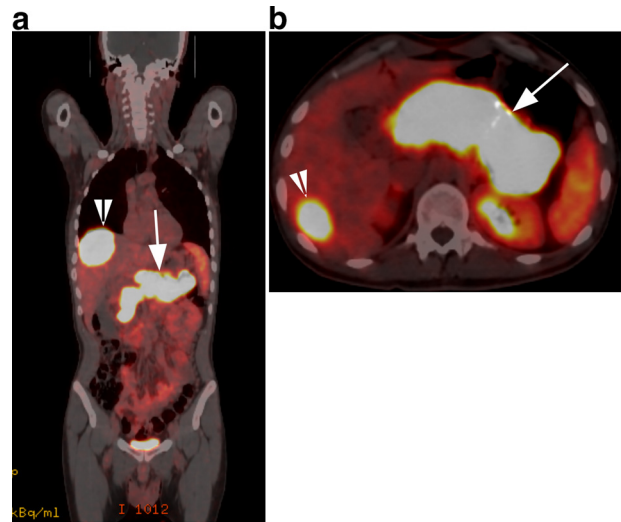
pancreatic mass replacing the pancreatic head, body, and tail consistent with a glucagonoma, in addition to multiple Ga-avid lesions in the liver and per-pancreatic foci consistent with liver and nodal metastasis, respectively, with no additional distant metastases (Fig. 3). The patient was prescribed a short-acting subcutaneous octreotide for a few days and then shifted to a long-acting intramuscular octreotide, with multiple antidiabetic medications, including liraglutide, gliclazide, and metformin. This regimen led to good control of his blood glucose. After approximately 4 weeks of octreotide therapy, the erythematous skin changes had mostly resolved, with weight gain of 3 kg. The surgical consultation recommended tumor-shrinking therapy with locoregional peptide receptor radionuclide therapy (PRRT) before surgical excision of both pancreatic and liver metastases.

Discussion

A glucagonoma is a rare (0.01-0.1/million population/year) but often malignant (50%-80%) tumor, and most cases are overlooked and present at a late stage with metastasis. The typical presentation includes skin changes (i.e., necrolytic migratory erythema [NME]), impaired glucose tolerance or new onset diabetes mellitus, weight loss, a general catabolic state, and a high thromboembolic risk [1]. Generally, NME begins with small, itchy, erythematous patches, with irregular borders. These propagate and form central erosions, with crusts. After healing, hyperpigmentation is observed. Although NME may not be present in all glucagonoma patients at the time of the initial diagnosis, up to 67%-90% of glucagonoma patients will develop NME, NME usually affects the lower limbs, thighs, abdomen, and perioral area [2]. In all cases, the glucagonoma

originates within the pancreas. The diagnosis is based on the fasting glucagon level as measured by a radioimmunoassay. The normal range is usually < 150 pg/ml. typically, glucagonoma patients have a glucagon level of more than 500 pg/ml. Some glucagonoma may co-produce other hormones, such as gastrin, vasoactive intestinal polypeptide, insulin, and/or adrenocorticotropic hormone. Other disorders that cause hyperglucagonemia include prolonged fasting hypoglycemia, Cushing's syndrome, and hepatic failure. However, in such cases, the glucagon level is < 500 pg/ml.

Cross-sectional imaging of glucagonoma

On CT, typically, a glucagonoma presents as a more or less homogenous isodense mass in the precontrast phase. After contrast injection, during the arterial phase, the glucagonoma is homogenously hyperdense and clearly enhanced as compared with adjacent parenchyma. During the portal phase, it appears hyperdense or isodense due to vascularization. On magnetic resonance imaging, a glucagonoma has low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, with better visualization using fat suppression techniques. Metastasis from a glucagonoma tends to resemble imaging features observed in primary tumors and usually shows contrast enhancement after contrast injection. For depiction of pancreatic NETs (P-NETs), contrast enhanced MRI has sensitivity of 53%-79%, whereas contrast-enhanced CT has sensitivity of 50%-73% [2–4].

Molecular imaging of glucagonoma

The majorities (70%) of P-NETs are characterized by the presence of somatostatin receptors (SSRs) along the cell membrane, and functional imaging using a somatostatin analog can detect the neoplasm [5,6]. However, insulinoma and poorly differentiated NETs are not characterized by SSRs and are not well detected by somatostatin analog scan imaging. Somatostatin receptor scintigraphy (SRS), also known as an Octreoscan, is based on the high affinity of synthetic somatostatin analogs for tissue, such as glucagonoma, that express SSRs. Ooctreotide was the first commercially available somatostatin analog. SRS provides functional information and enables correct patient selection for therapy. However, SRS has several limitations, including nonspecific uptake in inflammatory tissue, poor intrinsic resolution, and poor uptake by poorly differentiated tumors [8]. It also does not provide anatomic or surgical information [7].

A new somatostatin analog labeled with ^{68}Ga has significantly increased sensitivity in NET imaging. As compared with single photon emission computed tomography imaging, PET imaging with ^{68}Ga-DOTA peptides has several advantages. These include wide availability, easy synthesis, lower cost, and prediction of the response to therapy. In addition, ^{68}Ga-DOTA peptides can be used for tumor detection, staging, and targeted treatment selection. A major advantage of ^{68}Ga-DOTA peptides is that on-site cyclotron is not required, as ^{68}Ga can be eluted from a commercially available

generator [8].Gabrielle et al. described 84 cases with biologically proven NETs investigated with conventional imaging methods, such as CT, US, and SRS, and demonstrated that Ga-DOTATOC PET/CT detected a higher number of true positive lesions [9]. The sensitivity and specificity of Ga-DOTATATE for the detection for NETs was reported to be 90% and 82%, respectively [10]. The main limitations of DOTA-peptides are their inability to detect tumors with low SSR expression, undifferentiated tumors, and adrenal lesions, which are a frequent site of physiological ^{68}Ga-DOTA uptake [11].

NETs are associated with amine precursor uptake decarboxylase cells. This association makes NETs ^{18}F-Dihydroxyalanine (DOPA) avid, and ^{18}F-DOPA PET offers higher sensitivity than either SRS or CT alone (100%, 92%, and 87%, respectively) [12]. ^{18}F-DOPA PET also provides more relevant information for the clinical management of patients who have an unclear clinical presentation or inconclusive findings on other imaging modalities [13]. Although ^{18}F-DPA has been suggested as a useful tool for NET imaging, it is not widely employed at present, mainly as a consequence of limited commercial availability and difficult synthesis. The most widely used PET radiopharmaceutical in daily clinical practice is F-FDG, an analogue of glucose with replacement of the oxygen in the C-2 position with fluorine -18. As tumoral cells have high glucose metabolism, they exhibit FDG uptake. Slow-growing NETs are generally well differentiated and show little or no FDG uptake due to low metabolic activity. In contrast, poorly differentiated NETs exhibit intense FDG uptake as a result of high metabolic activity and are well depicted. Thus, FDG PET/CT can play a role in distinguishing both well- and poorly differentiated NETs [3]. Previous research reported that high-grade and poorly differentiated NETs showed greater FDG uptake, whereas low-grade and well-differentiated tumors showed greater Ga-DOTATATE uptake [14]. Another study reported that the overall sensitivity of F-FDG PET for the detection of NETs was 58% and that the sensitivity of FDG was higher (80%) in NETs with a proliferation index of more than 2%. The sensitivity increased to 92% for NETs with a proliferation index more than 15% [15].

In conclusion, the present case highlights the role of both ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT in the diagnosis and management of a patient with glucagonoma replaced most of the panaceas, with both liver and lymph node metastases. The primary tumor and metastases showed mild to moderate FDG uptake, with intense ^{68}Ga-DOTATATE uptake. In this study, we used ^{68}Ga-DOTATATE, as this is the tracer of choice for well-differentiated glucagonoma and offers very high diagnostic accuracy as compared with that of cross-sectional and other functional imaging and enables correct patient selection for PRRT therapy. However, FGD PET has an important role to play in the management of patients with poorly differentiated, aggressive, and high-grade tumors because it has high sensitivity and high prognostic value.

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