Incidental Detection of Parathyroid Adenoma on Somatostatin Receptor PET/CT and Incremental Role of ^{18}F -Fluorocholine PET/CT in MEN1 Syndrome

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Abstract

Multiple endocrine neoplasia type 1 (MEN1) syndrome is characterized by combined occurrence of tumors of endocrine glands including the parathyroid, the pancreatic islet cells, and the anterior pituitary gland. Parathyroid involvement is the most common manifestation and usually the first clinical involvement in MEN1 syndrome, followed by gastroentero-pancreatic neuroendocrine tumors (NETs). Here we present a case where the patient initially presented with metastatic gastric NET and a single parathyroid adenoma was detected incidentally on ^{68}Ga -DOTANOC PET/CT done as part of post ^{177}Lu -DOTATATE therapy (PRRT) follow-up. Further ^{18}F -fluorocholine PET/CT showed four adenomas for which the patient subsequently underwent subtotal parathyroidectomy.

Keywords ^{18}F -Fluorocholine PET/CT · MEN1 · Gastrinoma · Hyperparathyroidism · ^{177}Lu -DOTATATE therapy

Introduction

Multiple endocrine neoplasia type 1 (MEN1) syndrome is characterized by combined occurrence of tumors of endocrine glands including the parathyroid glands, the pancreatic islet cells, and the anterior pituitary. Parathyroid involvement resulting in hyperparathyroidism is the most common manifestation and usually the first clinical involvement in MEN1

syndrome, followed by gastroentero-pancreatic neuroendocrine tumors (NETs) and anterior pituitary tumors. Noninvasive imaging including ultrasonography (USG), computed tomography (CT) scan, magnetic resonance imaging (MRI), and technetium-99m sestamibi are commonly used before parathyroid surgery for localization of parathyroid adenoma. Recently, few studies have shown incremental role of ^{18}F -fluorocholine PET CT for the same.

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Case Report

Here we present the case of a 49-year-old female, who initially presented with a soft tissue mass at gastro-esophageal junction extending along lesser curvature of the stomach. She underwent esophagogastrectomy for same and the histopathology (HPE) revealed NET (WHO grade II, MIB index 10%). As a part of metastatic work-up of NET, ^{68}Ga -DOTANOC PET/CT was done 2 months after the surgery and it revealed somatostatin receptor (SSTR)-expressing nodular lesion along the greater curvature of the stomach with peripancreatic, paraduodenal lymph nodes, and hypodense lesions in liver. Serum chromogranin levels were elevated at that time. In view of the residual metastatic disease, she was given Inj. sandostatin (LAR) which resulted in slight symptomatic response and also fall in chromogranin level from 4000 to 810 ng/ml. The patient was then planned for peptide receptor radionuclide therapy, starting 9 months after the surgery and was given 3 cycles of ^{177}Lu -DOTATATE (PRRT), at 6-month intervals shown in (Fig. 1a: post ^{177}Lu -DOTATATE therapy scan (acquired 24 h after the therapy showing tracer uptake in liver and peripancreatic lesion). ^{177}Lu -DOTATATE therapy resulted in partial response (symptomatic, anatomical, and biochemical response, chromogranin level post PRRT 335 ng/ml, and serum gastrin level came down to 554 pg/ml from 1232 pg/ml). Another follow-up ^{68}Ga -DOTANOC PET/CT was done at interval of 18 months after the last PRRT which revealed stable disease with residual lesions as

shown in Fig. 1c, which shows SSTR-expressing lesions in segment II of the liver, paraduodenal and peripancreatic lymph nodes and also shows a focal increased SSTR uptake corresponding to a soft tissue nodule just posterior to the lower pole of the right lobe of thyroid suggestive of parathyroid adenoma. This suspicious parathyroid lesion was not present in previous ^{68}Ga -DOTANOC PET/CT done post surgery and 3 months after the third PRRT as shown in Fig. 1b. On suspicion of parathyroid adenoma in a known case of gastric NET, she underwent biochemical investigations which revealed elevated serum parathyroid hormone level (966 pg/ml). Causes for secondary hyperparathyroidism were ruled out. As a pre-surgery imaging protocol, the patient underwent $^{99\text{m}}\text{Tc}$ -sestamibi scan, 4D CT neck, and also ^{18}F -fluorocholine PET/CT for localization of parathyroid adenomas. Planar image of $^{99\text{m}}\text{Tc}$ -sestamibi scan revealed only one large focus of increased tracer uptake in right inferior position as shown in Fig. 2. However, SPECT/CT revealed two adenomas in right inferior position, not shown in images. 4D CT neck localized three adenomas (left superior and two at right inferior position, larger right inferior adenoma showing polar vessel sign as shown in Fig. 3). Figures 4 and 5 show MIP image and axial sections of PET and fused ^{18}F -fluorocholine PET/CT which shows four parathyroid adenomas (left superior, left inferior, two in right inferior position). These lesions were confirmed by HPE correlation. Considering multiglandular parathyroid involvement in a known case of gastric NET and on evaluating her first degree relatives (her younger son was found

Fig. 1 A 49-year-old female shows ^{177}Lu -PRRT post therapy scan (acquired 24 h after the therapy) showing tracer uptake in the liver and peripancreatic lesion (a) and ^{68}Ga -DOTANOC PET/CT MIP images (b, c) showing SSTR-expressing lesions in liver segment II (thin black arrow) and paraduodenal lymph node (thick black arrow); also noted diffuse uptake in thyroid gland and focal uptake posterior to lower pole of the right lobe of thyroid corresponding to parathyroid adenoma (small thin arrow)

Fig. 2 This patient shows ^{99m}Tc -sestamibi delayed planar image showing focal increase uptake in right inferior position suggestive of parathyroid adenoma

to have a left superior parathyroid adenoma, and elder sister was found with persistent hypercalcemia), the diagnosis of familial MEN1 syndrome was apparent. Post subtotal parathyroidectomy, the patient developed a hungry bone phenomenon (bone densitometry score was -4.8), needed calcium infusion for 2 days, and is currently asymptomatic on oral calcium and vitamin D.

Fig. 3 This patient shows 4D CT coronal image showing large right inferior parathyroid adenoma with polar vessel sign (thick white arrow)

Discussion

Diagnosis of MEN1 syndrome is established when there is occurrence of two or more primary MEN1-associated tumors, and in familial MEN1, there is a positive family history (occurrence of one of the MEN1-associated tumors in a first-degree relative of a patient with a clinical diagnosis of MEN1 or a germline MEN1 mutation is identified) [1, 2]. It may be inherited as autosomal-dominant (AD) syndrome with high penetrance such that clinical and biochemical manifestations will be present in up to 80 and 98% of patients respectively by the fifth decade or it can occur sporadically [3]. More than 1133 germline mutations and 203 somatic mutations in the MEN1 gene have been reported and most of the reported mutations are diffusely scattered throughout the 1830-bp coding region of the MEN1 gene [2]. Clinical manifestations of MEN1 syndrome vary among families due to the diversity of family-specific MEN1 gene mutations [4]. Usually, parathyroid involvement resulting in primary hyperparathyroidism is the most common feature of MEN1 that occurs in approximately 95% patients, followed by gastro-pancreatic neuroendocrine tumors (GEP-NETs) in 40–70% and anterior pituitary tumors in approximately 30–40% of MEN1 syndrome patients [5, 6]. Gastrinoma is the most common GEP-NET, while prolactinoma is the commonest pituitary adenoma. Parathyroid involvement apart from being most common manifestation is usually also the first clinical involvement in MEN1 syndrome [7]. But in our case, the patient presented initially with gastric NET, which was treated, and then in routine imaging follow-up, parathyroid involvement was detected. Parathyroid gland involvement in MEN1 syndrome unlike solitary parathyroid adenoma is usually multiglandular

Fig. 4 This patient shows MIP image of ^{18}F -fluorocholine PET/CT showing focal increased uptake at left superior, left inferior, and right inferior positions

Fig. 5 This patient shows axial sections of ^{18}F -fluorocholine PET and fused PET/CT images showing parathyroid adenomas at left superior, left inferior, and two right inferior locations (white arrows)

involvement (MGD) although asymmetric involvement is noted [8]. Noninvasive imaging including ultrasonography (USG), technetium-99m sestamibi, computed tomography (CT) scan, and magnetic resonance imaging (MRI) are being used before parathyroid surgery. Though in MEN1 syndrome the likely multiple parathyroid gland involvement makes it logical to perform a four-gland exploration at initial surgery, thus regarding role of preoperative imaging, one of the indications is to rule out presence of an ectopic adenoma which can be missed during the initial exploration as shown by Gouveia S et al. [9]. For the management of hyperparathyroidism, surgical removal of the abnormally overactive parathyroid glands is the definitive treatment, but it is controversial whether to perform subtotal (3.5 glands) or total parathyroidectomy with each approach having its advantage and disadvantages. Subtotal parathyroidectomy results in persistent or recurrent hypercalcemia within 10 to 12 years in 40–60% of patients and in hypocalcemia requiring long-term therapy with vitamin D in 10–30% of patients with MEN1 [10]. Regarding surgical approach, open bilateral neck exploration is preferred, compared to minimally invasive parathyroidectomy as done in solitary adenoma and subtotal parathyroidectomy usually recommended as initial treatment; total parathyroidectomy with autotransplantation may be considered in cases which have extensive disease at presentation [11]. In our case, the patient underwent 3.5-gland excision. $^{99\text{m}}\text{Tc}$ -sestamibi which is commonly used for parathyroid adenoma localization has few disadvantages including low sensitivity in very small parathyroid lesions (due to its poor spatial resolution), when adenoma is present in close proximity to thyroid, in MGD involvement in syndromic patients [12], and in certain adenomas with unusual washout patterns, and also in up to one-third of patients, parathyroid adenomas are sestamibi negative [13]. Recently, ^{18}F -fluorocholine (^{18}F -FCH) is being highlighted in literature for the detection of parathyroid adenomas [14]. Behera et al. have shown incremental role of ^{18}F -fluorocholine (FCH) PET/CT over $^{99\text{m}}\text{Tc}$ -sestamibi scan with ^{18}F -FCH PET/CT showing additional lesions in

patients with already positive $^{99\text{m}}\text{Tc}$ -sestamibi scans [15]. GEP NETs which can be functioning or nonfunctioning in nature associated with MEN1 syndrome have an earlier age of onset and are frequently multiple in numbers [16]. Their accurate diagnosis and management presents significant challenges especially identification of nonfunctioning pancreatic NET because absence of both a clinical syndrome and specific biochemical abnormalities result in delayed diagnosis of these tumors; hence, they are associated with a worse prognosis than other functioning tumors. For the detection of GEP-NET, endoscopic ultrasound is likely to represent the most sensitive method of detecting small pancreatic tumors, whereas somatostatin receptor scintigraphy is the most reliable method for detecting metastatic disease [17]. Several studies have shown that ^{68}Ga -DOTANOC PET/CT is more effective than ^{18}F -FDG PET and ^{18}F -DOPA PET and also compared to conventional anatomical imaging (CT and/or MRI), it is more accurate in detecting additional hepatic and/or extrahepatic metastases which can help in deciding the course of management [18]. In our patient also, postoperative ^{68}Ga -DOTANOC PET/CT was performed which showed metastatic disease in regional lymph node and in liver, and later the patient underwent ^{177}Lu -PRRT for the metastatic disease which resulted in partial response. Apart from metastatic disease in lymph node and liver, the third follow-up of ^{68}Ga -DOTANOC PET/CT showed focal uptake in soft tissue nodule posterior to lower pole of the right lobe of the thyroid gland, which raised the suspicion of parathyroid adenoma and further investigations including ^{18}F -fluorocholine PET/CT which localized four parathyroid adenomas.

Conclusion

In syndromic patients like MEN1, where multiglandular parathyroid involvement is likely, ^{18}F -fluorocholine PET/CT could incrementally and correctly identify multiple parathyroid adenomas. Also, parathyroid adenomas may be

incidentally detected on SSSTR PET/CT done for monitoring neuroendocrine tumors.

Compliance with Ethical Standards

Conflict of Interest Saurabh Arora, Nishikant Avinash Damle, Averilicia Passah, Madhav Prasad Yadav, Sanjana Ballal, Vivek Aggarwal, Yashdeep Gupta, Praveen Kumar, Madhavi Tripathi, and Chandrasekhar Bal declare that they have no conflict of interest.

Ethical Approval Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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