Article published online: 2022-05-18

Case report

Metabolic Bone Disease in the Context of Metastatic Neuroendocrine Tumor: Differentiation from Skeletal Metastasis, the Molecular PET–CT Imaging Features, and Exploring the Possible Etiopathologies Including Parathyroid Adenoma (MEN1) and Paraneoplastic Humoral Hypercalcemia of Malignancy Due to PTHrP Hypersecretion

Rohit Ranade, Sandip Basu

Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital, Annexe, Mumbai, Maharashtra, India

Abstract

Three cases of metabolic bone disease in the setting of metastatic neuroendocrine tumor (NET) are illustrated with associated etiopathologies. One of these cases harbored mixed lesions in the form of vertebral metastasis (biopsy proven) while the other skeletal lesions were caused due to metabolic bone disease related to multiple parathyroid adenomas. While the metastatic lesion was positive on 68Ga-DOTATATE positron emission tomography–computed tomography (PET–CT), the lesions of metabolic bone disease were negative and the 18F-fluoride PET–CT demonstrated the features of metabolic bone scan. Similar picture of metabolic bone disease [18-sodium fluoride (18NaF)/68Ga-DOTATATE mismatch] was documented in the other two patients, while fluorodeoxyglucose (FDG)-PET–CT was variably positive, primarily showing tracer uptake in the metabolic skeletal lesions of the patient with hypersecretion of parathyroid hormone-related protein (PTHrP) by the underlying tumor. Discordance between 18NaF PET–CT and 68Ga-DOTATATE PET–CT serves as a good marker for identification of metabolic bone disease and diagnosing such a clinical entity. In a patient of NET with metabolic bone disease and hypercalcemia, thus, two causes need to be considered: (i) Coexisting parathyroid adenoma in multiple endocrine neoplasia type I (MEN-I) syndrome and (ii) humoral hypercalcemia of malignancy (HHM) related to hypersecretion of PTHrP by the tumor. The correct diagnosis of metabolic bone disease in metastatic NET can alter the management substantially. Interestingly, peptide receptor radionuclide therapy (PRRT) can emerge as a very promising treatment modality in patients of metabolic bone disease caused by HHM in the setting of NET.

Keywords: Bone metastasis, humoral hypercalcemia of malignancy, metabolic bone disease, metastatic neuroendocrine tumor, multiple endocrine neoplasia type I syndrome, peptide receptor radionuclide therapy, 68Ga-DOTATATE positron emission tomography–computed tomography, 18F-fluoride PET–CT

Address for correspondence:
Dr. Sandip Basu, Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital, Annexe, Jerbai Wadia Road, Parel, Mumbai - 400 012, Maharashtra, India.
E-mail: drsanb@yahoo.com

Access this article online

Quick Response Code:

Website: www.wjnm.org

DOI: 10.4103/1450-1147.172307

How to cite this article: Ranade R, Basu S. Metabolic bone disease in the context of metastatic neuroendocrine tumor: differentiation from skeletal metastasis, the molecular PET-CT imaging features, and exploring the possible etiopathologies including parathyroid adenoma (MEN1) and paraneoplastic humoral hypercalcemia of malignancy due to PTHrp hypersecretion. World J Nucl Med 2017;16:62-7.

Introduction

Neuroendocrine tumors (NETs) are rare tumors that are slow growing and considered less aggressive than cancers arising from exocrine glands. They may be localized or metastatic at presentation. The most common site of metastasis is liver.[1] Extrahepatic metastasis along with a high proliferation index are considered important poor prognostic factors during the assessment of NETs.[2] The prevalence of bone metastasis in NETs ranges from 7% to 15%.[3,4] Metabolic bone disease is another important entity that could be observed in association with NETs either in cases of coexisting parathyroid adenomas as a part of multiple endocrine neoplasia type I (MEN-I) syndrome (or Wermer's syndrome) or due to paraneoplastic syndrome caused due to hypersecretion of parathyroid hormone-related protein (PTHrP) by the tumor. Hence, in a patient of bone lesions in NET it is important to determine whether the bony lesions are metastasis or sequel of the underlying metabolic bone disease as both disease prognosis and the line of further management differs from each other. In this report, we present three cases of NET where the underlying pathology causing bony lesions was metabolic bone disease due to different etiologies.

Case Reports

Case I

A 50-year-old male initially presented with severe abdominal pain that was of acute onset and associated with vomiting. Contrast-enhanced computed tomography (CECT) of the abdomen demonstrated heterogeneously enhancing soft tissue density lesion along the posterolateral aspect of left lobe of thyroid with right supraclavicular lymphadenopathy, mostly arising from parathyroid. Also necrotizing pancreatitis with walled off necrosis was diagnosed with CT severity index of 8. Multiple lytic lesions were noted involving right third rib, bilateral iliac bones, and bilateral sacral ala suspecting them to be brown tumors secondary to parathyroid pathology. 99m-technetium (Tc) sestamibi (99m-Tc-MIBI) scan [Figure 1a] was undertaken for the evaluation of the parathyroid pathology that showed tracer avid foci in multiple parathyroid glands and was indicative of multiglandular parathyroid disease. Fine-needle aspiration cytology (FNAC) from both right and left parathyroid lesions was concluded as parathyroid adenomas. Evaluation of multiple biochemical markers demonstrated elevated parathyroid hormone (PTH), serum gastrin, and serum chromogranin A levels [Table 1]. In addition, he had elevated serum calcium levels with low vitamin D3 levels [Table 1].

Suspecting it to be a part of MEN-I syndrome, the patient underwent upper gastrointestinal endoscopy that revealed multiple duodenal nodules. Biopsy from these revealed it as an intermediate grade NET with Mib-1 index of 12%. Brain magnetic resonance imaging (MRI) was negative for any pituitary pathology. 18-NaF positron emission tomography–computed tomography (PET–CT) [Figure 1b] showed diffusely increased tracer uptake in the entire skeleton with both the kidneys being not visualized. The skull showed prominent tracer uptake with CT showing marked thickening of the skull bones. 68Ga-DOTATATE PET–CT [Figure 1b] showed solitary somatostatin receptor (SSTR) positive liver lesion and a

Table 1: Serum biochemical markers of patient 1

Biochemical parameter	Value	Normal range
Serum PTH (pre-operative)	1389	14-72 mg/dL
Baseline serum calcium	12.9	8.5-10.5 mg%
Baseline serum vitamin D3	6.49	30.00-100.00 ng/mL
Serum chromogranin A	45,394.7	<98 ng/mL
Serum gastrin	6,202	13-115 pg/mL
Serum PTH (postoperative)	309.5	14-72 mg/dL

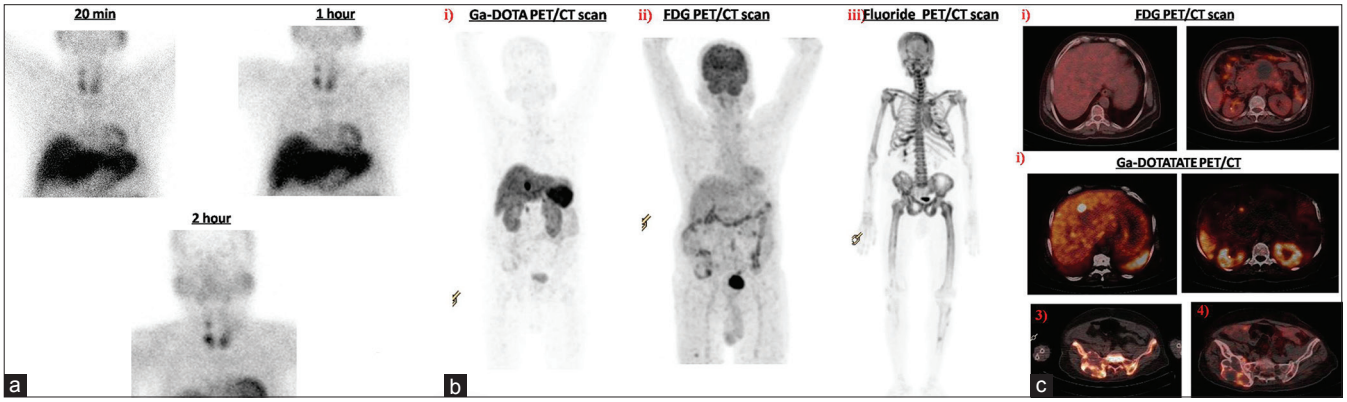

Figure 1: (a) 99m-Tc Sestamibi (99m-Tc-MIBI) parathyroid scintigraphy showing tracer avid foci in multiple parathyroid gland indicative of multi-glandular parathyroid disease. (b and c) 68-Ga-DOTATATE PET CT (Fig 1bi and 1c) showing solitary SSTR positive liver lesion and a peri-pancreatic node. The skeletal lesions do not any evidence of SSTR expression. 18-NaF PET-CT (1b iii) showing diffusely increased tracer uptake in the entire skeleton with faintly visualized kidneys bilaterally akin to superscan, while FDG-PET (1b ii and 1c) does not show any uptake in the skeletal lesions

peripancreatic node. The skeletal lesions did not show any SSTR expression. The patient was finally diagnosed as a suspected case of MEN-I syndrome with parathyroid adenoma and duodenal NET with liver metastasis. The necrotizing pancreatitis was attributed to the elevated serum calcium levels.

The patient underwent excision of both upper and lower left parathyroid and right lower parathyroid. The final HPR showed left parathyroid lesion showing features of parathyroid carcinoma whereas the right parathyroid lesion showed features of parathyroid adenoma. Postoperatively, the patient was evaluated for peptide receptor radionuclide therapy (PRRT), which was deferred as in view of compromised renal function. In the further course, the patient had recurrence of elevated PTH levels [refer Table 1]. Follow-up 99m-Tc-MIBI parathyroid scan this time showed focal tracer concentration at right inferior parathyroid location suspicious for right parathyroid adenoma and is now being considered for resurgery for the right parathyroid adenoma but is currently deferred due to uncontrolled diabetes. In the meantime, he had undergone one cycle of transarterial chemoembolization (TACE) for the liver lesion. Follow-up 68Ga-DOTATATE PET–CT showed no change [Figure 1c]. The patient is being now contemplated for radiofrequency ablation (RFA) of the liver lesion and is on medical management of diabetes as a part of fitness for resurgery.

Case II

A 47-year-old female initially presented with complaints of backache. MRI of the dorsal spine showed multiple foci of altered marrow signal intensity involving multiple dorsal vertebrae with the largest lesion in D6 vertebrae. Biopsy from this lesion showed metastatic deposit of NET of intermediate grade (unknown primary) with Mib-1 index of 15%. CT scan of chest and abdomen showed an anterior mediastinal lesion, prevascular lymph node, and a lytic lesion in the left half of D6 vertebrae. As one skeletal lesion was a proven metastatic lesion, all other skeletal lesions were assumed by the attending oncologist to be metastatic. Subsequently, the patient was labeled to have NET of unknown primary with multiple skeletal metastases. She had elevated serum chromogranin A level, elevated serum calcium, and low vitamin D3 levels [Table 2]. She received palliative radio therapy (RT) to dorsal spine with monthly injection of long-acting octreotide (30 mg). A total of seven such monthly injections were taken by the patient before presenting them to us.

There was documentation of a significant fall in the serum chromogranin A level [Table 2], but there was no resolution of the backache that had actually worsened over a period of time. A follow-up CT scan showed no change with persistence of all the lesions. The MRI showed multiple lesions in the dorsolumbar vertebrae, sternum, bilateral pelvic bones, and bilateral femora. 68Ga-DOTATATE PET–CT [Figure 2a and b] was undertaken, which showed one single SSTR expressing lesion in the D6 vertebrae that was of Krenning score 2. The other skeletal lesions or the anterior mediastinal lesion did not show any SSTR expression on the scan. 18NaF fluoride PET–CT showed diffusely increased tracer uptake in the entire skeleton with both the kidneys

Table 2: Serum biochemical markers of patient 2

Biochemical parameter	Value	Normal range
Serum PTH (preoperative)	667.6	14-72 mg/dL
Baseline serum calcium	11.9	8.5-10.5 mg%
Baseline serum vitamin D3	11.2	30.00-100.00 ng/mL
Serum chromogranin A (baseline)	1,635	<100 ng/mL
Serum chromogranin A (post seven injection of sandostatin)	149.59	<100 ng/mL

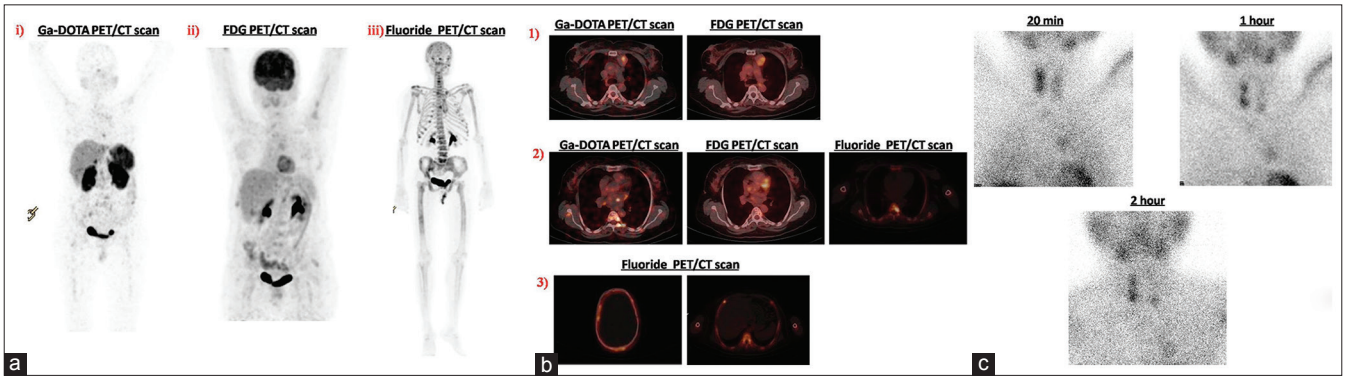

Figure 2: (a and b) 68-Ga-DOTATATE PET CT (Fig 2ai and 2b) showing single SSTR expressing lesion in the D6 vertebrae of Krenning score 2. The other skeletal lesions or the anterior mediastinal lesion do not show any SSTR expression on the scan. 18NaF fluoride PET-CT (Fig 2aiii and 2b) showing diffusely increased tracer uptake in the skeleton, with prominent tracer uptake in the skull with evidence of costochondral beading all suggesting the features of metabolic bone disease. Also a single osteoblastic lesion involving the D6 vertebrae is noted in the fused transaxial image. (c) 99mTc-MIBI parathyroid scan demonstrating multiple tracer avid foci in delayed scan in multiple parathyroid glands indicative of multi-glandular parathyroid disease

not visualized. The skull showed prominent tracer uptake with the evidence of costochondral beading all suggesting the features of metabolic bone disease. Also a single osteoblastic lesion involving the D6 vertebrae was noted. Due to the scan suspicion of metabolic bone disease, a serum PTH level was undertaken which was found to be substantially elevated [Table 2]. 99mTc-MIBI parathyroid scan [Figure 2c] demonstrated tracer avid foci in multiple parathyroid glands indicative of multiglandular parathyroid disease. Ultrasonography (USG) neck showed two suspicious lesions: One in the right superior gland and one in the right inferior gland that were suspicious for parathyroid adenomas. MRI of the brain was done to rule out any pituitary lesion that was negative for the same. The patient was finally diagnosed as a case of suspected MEN-I syndrome having parathyroid adenoma and thymic carcinoid with a solitary metastatic D6 vertebral lesion. She is now being planned for surgical removal of the parathyroid adenomas.

Case III

A 49-year-old male initially presented with watery diarrhea and increased fatigue. USG abdomen demonstrated multiple hypoechoic liver lesions. Fluorodeoxyglucose (FDG) PET–CT study [Figure 3a] showed multiple low grade FDG uptake in the liver lesions and a FDG avid lesion arising from the distal body of pancreas and multiple sclerotic low grade FDG avid skeletal lesions. 68Ga-DOTATATE PET–CT scan [Figure 3a] showed multiple SSTR avid liver lesions and a SSTR positive pancreatic body lesion. The skeletal lesions showed no SSTR expression. The patient had elevated serum chromogranin A level, elevated serum calcium, and low vitamin D3 levels [Table 3]. 18F-NaF PET–CT [Figure 3a] was done that showed diffusely increased tracer uptake in the entire skeleton and both the kidneys not being visualized. The skull showed prominent tracer uptake with observation of costochondral beading. He was evaluated for parathyroid disease but the CT neck was normal and PTH level was undetectable. A suspicion of the differential diagnosis in this patient was raised and worked up to rule out hypercalcemia as a paraneoplastic manifestation. PTHrP was done that was found to be elevated [Table 3], hence the etiopathogenesis of the hypercalcemia was confirmed. The patient was finally diagnosed to have humoral hypercalcemia of malignancy (HHM) due to PTHrP secretion from the primary pancreatic NET.

Table 3: Serum biochemical markers of patient 3

Biochemical parameter	Value	Normal range
Serum PTH	0	14-72 mg/dL
Baseline serum calcium	12.7	8.5-10.5 mg%
Baseline serum vitamin D3	12.45	30.00-100.00 ng/mL
Baseline serum chromogranin A level	720.53	<98 ng/mL
Baseline PTHrP	52.6	14-27 pg/mL
Post first cycle PRRT serum calcium	9.4	8.5-10.5 mg%
Post first cycle PRRT serum vitamin D3	21.1	30.00-100.00 ng/mL

The patient was initially put on monthly long-acting octreotide injections. But even after 18 months, there was no improvement in the symptoms as well as the biochemical values, hence he was referred for PRRT. The patient has been treated subsequently with two cycles of PRRT with 177Lu-DOTATATE with the cumulative dose being 324 mCi (1.19 GBq) and also with three cycles of capecitabine and temozolomide in between the two cycles. He showed complete resolution of all the symptoms with reduction in the serum chromogranin A and serum calcium level with increase in the vitamin D3 levels. Patient is now on follow-up and due for the third cycle of PRRT.

Discussion

NETs are relatively rare tumors but the rate of incidence is gradually increasing, with a 2.7% increase in the number

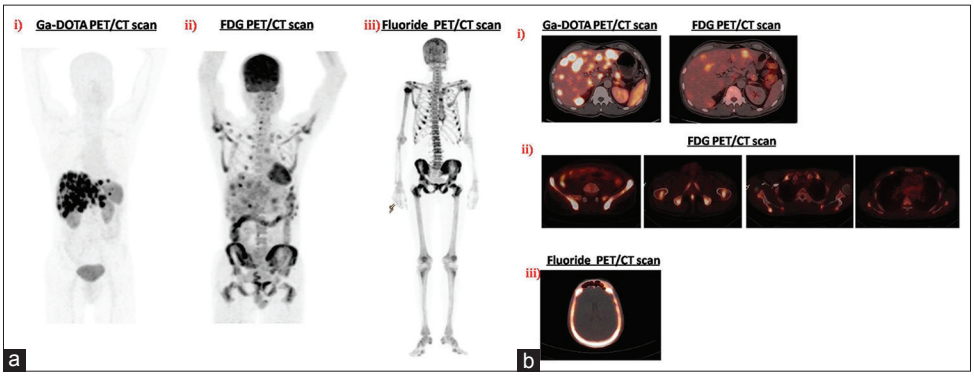

Figure 3: (a and b) 68-Ga-DOTATATE PET-CT scan (Fig 3ai and 3bi)showing multiple SSTR avid liver lesions and a SSTR positive pancreatic body lesion. The skeletal lesions show no SSTR expression. FDG PET-CT study (Fig 3aii and 3bii) showing multiple low grade FDG uptake in the liver lesions and a FDG avid lesion arising from the distal body of pancreas and multiple low grade sclerotic skeletal lesions which are FDG avid.18F-NaF PET-CT (Fig 3aiii and 3biii) show diffusely increased tracer uptake in the entire skeleton and non visualization of the kidneys bilaterally consistent with superscan features. The skull showed prominent tracer uptake with observation of costochondral beading

of cases according to the SEER database analyzing the cases from 1973 to 2003. This may be due to the better surveillance and increased sensitivity and specificity of the diagnostic modalities. The most common site of metastasis is liver. Skeletal metastases are well known in cases of NETs. The incidence of bone metastasis is about 7–15% and are generally multiple.[4] They are more commonly seen along with liver metastasis and are only rarely seen isolated. They are usually associated with a poor prognosis[5] and their presence is a contraindication for surgery.[6] Both osteoblastic as well as osteolytic metastases can be found in patients of NET but they are predominantly osteoblastic.[6] The major symptoms in these groups of patients are (i) pain at the site of metastasis and (ii) pathological fractures.

Metabolic bone disease in the setting of NET is a rare but possible association. It is mainly due to underlying abnormalities in the calcium metabolism. Hypercalcemia in cases of NET can occur due to two causes: (i) In the setting of coexisting parathyroid adenoma in MEN-I syndrome and (ii) HHM. MEN-I syndrome is said to have primarily three components as follows: (i) Parathyroid tumors, (ii) pituitary adenomas, and (iii) gastroenteropancreatic tumors. If any patient has two of the above three tumors he is diagnosed to be a case of MEN-I syndrome. About 95% of the cases of MEN-I syndrome have parathyroid pathology.[7]

In the described three case series, case I was diagnosed as MEN-I syndrome with parathyroid adenoma and duodenal polyp also having metabolic bone disease due to elevated PTH levels. In this patient, initial evaluation diagnosed the parathyroid adenoma. It is important to identify metabolic bone disease when one evaluates NET patients with skeletal complaints: NET patients, in the setting of syndromic variant, are at high risk of skeletal complications due to elevated PTH related to parathyroid adenoma, which is noted in high incidence in MEN-I syndrome. Case II was a diagnosed case of metastatic NET with possible thymic primary with skeletal metastasis. But this patient was refractory to the treatment [external beam radiation therapy (EBRT) and somatostatin analogs]. Further evaluation showed that the patient had associated metabolic bone disease due to underlying parathyroid pathology. Thus, the patient was finally diagnosed as a case of thymic NET and a solitary vertebral metastasis coupled with MEN-I syndrome (multiple parathyroid adenomas leading to metabolic bone disease), which substantially altered the line of management for this patient. This indicates that a high degree of suspicion is necessary when one encounters patients of NET with skeletal symptoms refractory to routine treatments and should be evaluated for ruling out any metabolic bone disease. Any skeletal lesion on imaging should not be always considered metastatic but could be due to associated metabolic bone disease. A coexisting picture of metabolic bone disease with metastatic skeletal lesions is also rarely possible as seen in case II. The importance of appropriate identification for proper treatment is invaluable.

Neuroendocrine tumors are known to secrete biologically active peptides and amines that produce distinct clinical symptoms.[8] HHM is a paraneoplastic syndrome occurring due to hypersecretion of parathyroid hormone-related protein (PTHrP) by the underlying tumor. HHM due to PTHrP had been described first by Broadus *et al*. in 1988[9] in three sub-groups. It is most commonly seen in cases of carcinoma breast and carcinoma lung. HHM in cases of NET has also been reported. It has been reported in cases of pheochromocytoma[10] and carcinoid,[11] but are most commonly seen in cases of pancreatic NET.[12] A case III patient was labeled to have HHM from the pancreatic primary and thus was proven to have metabolic bone disease rather than skeletal metastasis. Treatment with somatostatin analogs was not useful, and hence he was subsequently treated with 177Lu-DOTATATE based PRRT. The patient symptomatically improved with a fall in serum calcium and rise in vitamin D3 levels. Thus, PRRT proves a promising treatment for HHM secondary to NET resistant to conventional treatments.

As seen in aforementioned three cases, there were a discordance seen on the 18-NaF PET–CT and 68Ga-DOTATATE PET–CT in the metabolic skeletal lesions which is theoretically predicted. This may serve as a clue for identifying metabolic bone disease in the setting of NET.

Conclusion

Metabolic bone disease in the setting of N NET needs to be identified early as detecting its presence alters the management and these patients have much better prognosis than those with skeletal metastasis. Also discordance seen on 18-NaF PET–CT and 68Ga-DOTATATE PET–CT serves as a good marker for such a clinical entity. The entity of metabolic bone disease may coexist with skeletal metastasis. Interestingly, PRRT serves as a very promising treatment modality in cases of metabolic bone disease due to HHM secondary to the primary NET.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of intrest.

References

1. Bodei L, Mueller-Brand J, Baum RP, Pavel ME, Hörsch D, O'Dorisio MS, *et al*. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013;40:800-16.
2. Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, *et al*. Prognostic factors and survival in endocrine tumor patients: Comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer 2005;12:1083-92.
3. Leboulleux S, Dromain C, Vataire AL, Malka D, Aupérin A, Lumbroso J, *et al*. Prediction and diagnosis of bone metastases in well-differentiated gastro-entero-pancreatic endocrine cancer: A prospective comparison of whole body magnetic resonance imaging and somatostatin receptor scintigraphy. J Clin Endocrinol Metab 2008;93:3021-8.
4. Kos-Kudła B, O'Toole D, Falconi M, Gross D, Klöppel G, Sundin A, *et al*.; Palma de Mallorca Consensus Conference Participants. ENETS consensus guidelines for the management of bone and lung metastases from neuroendocrine tumors. Neuroendocrinology 2010;91:341-50.
5. Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, *et al*. Prognostic factors and survival in endocrine tumor patient: Comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer 2005;12:1083-92.
6. Gupta S, Johnson MM, Murthy R, Ahrar K, Wallace MJ, Madoff DC, *et al*. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: Variables affecting response rates and survival. Cancer 2005;104:1590-602.
7. Thakker RV. Multiple endocrine neoplasia type 1 (MEN1). In: Robertson RP, Thakker RV, editors. Translational Endocrinology and Metabolism. Vol. 2. Chevy Chase, MD: The Endocrine Society; 2011. p. 13.
8. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 2004;25:458-511.
9. Broadus AE, Mangin M, Ikeda K, Insogna KL, Weir EC, Burtis WJ, *et al*. Humoral hypercalcemia of cancer. Identification of a novel parathyroid hormone-like peptide. N Engl J Med 1988;319:556-63.
10. Kimura S, Nishimura Y, Yamaguchi K, Nagasaki K, Shimada K, Uchida H. A case of pheochromocytoma producing parathyroid hormone-related protein and presenting with hypercalcemia. J Clin Endocrinol Metab 1990;70:1559-63.
11. Siyam F, Abdullah O, Gardner M, Brietzke S, Sowers J. A case of carcinoid tumor-associated hypercalcemia. Cardiorenal Med 2012;2:52-6.
12. Kanakis G, Kaltsas G, Granberg D, Grimelius L, Papaioannou D, Tsolakis AV, *et al*. Unusual complication of a pancreatic neuroendocrine tumor presenting with malignant hypercalcemia. J Clin Endocrinol Metab 2012;97:E627-31.