

Benefits of ^{11}C -methionine PET/MRI and intraoperative fluorescence in treating hyperparathyroidism

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Abstract

Multiple endocrine neoplasia 1 (MEN1) is a rare genetic syndrome characterized by the manifestation of tumors in endocrine glands most often in the parathyroid gland (PG). Treatment may involve several parathyroidectomies (PTX), especially in young patients, which increases the risk of postoperative complications. We present a 16-year-old patient with a family history of MEN1 syndrome. The patient started to show biochemical signs of hyperparathyroidism (HPT) and hypercalcemia at the age of 10. One and a half years later a PTX was successfully performed with removal of the two left PGs. However, a rise in plasma parathyroid hormone and ionized calcium was observed 4 years later. Preoperative noninvasive imaging with $^{99\text{m}}\text{Tc}$ -sestamibi scintigraphy showed no definitive parathyroid adenoma. A ^{11}C -methionine position emission tomography combined with MRI (MET-PET/MRI) was then performed and detected a focus posterior to the lower part of the right thyroid lobe. Intraoperative angiography with fluorescence and indocyanine green dye was used to assess the vascularization of the remaining PGs. The lower right PG was removed. The patient was discharged with normalized biochemical values and without postoperative complications. Recurrence of primary HPT is frequent in MEN1 patients which often necessitates repeated operations. Our case report showed that the use of advanced noninvasive preoperative imaging techniques and intraoperative fluorescent imaging are valuable tools and should be taken into consideration in selected cases to avoid postoperative complications. To our knowledge, this is the first case where MET-PET/MRI has been used to detect parathyroid pathology.

Learning points:

- MEN1 patients will develop parathyroid disease, which eventually will lead to surgical treatment with removal of the pathological glands.
- Preoperatively usage of MRI combined with PET tracers such as ^{11}C -methionine and ^{18}F -Fluorocholine are able to detect parathyroid pathology with a higher sensitivity than conventional imaging.
- Techniques using intraoperatively angiography with fluorescence and fluorescent dyes allow surgeons to verify the vascularization of each parathyroid gland.
- Optimization of noninvasive preoperative imaging techniques and intraoperative fluorescent imaging are valuable tools and should be taken into consideration when performing PTX consecutively in the same patient to avoid postoperative complications.

Introduction

Multiple endocrine neoplasia (MEN) are rare genetic syndromes, which are characterized by the manifestation of tumors in two or more specific endocrine glands in a single patient. There exist two main forms of MEN, type 1 (MEN1) and type 2 (1). In MEN1 patients, tumors mostly occur in the parathyroid glands, the pancreatic islet cells, and in the anterior pituitary (2). The syndrome can affect all age groups with an estimated prevalence of 2 per 100 000 (3) with the most common manifestation being primary hyperparathyroidism (HPT) with pathologic growth of one or more of the parathyroid glands (PG), which occurs in more than 90% of patients (1). Symptoms of HPT include abdominal pain, nausea, kidney stones, osteoporosis, depression, and tiredness. Treatment of primary HPT in MEN1 patients usually involves preoperative localization of enlarged PGs, typically with ultrasonography (US) and a ^{99m}Tc -sestamibi scintigraphy (MIBI) often combined with a single photon emission and a low-dose CT (SPECT-CT) prior to parathyroidectomy (PTX), which involves the removal of 1 or more PGs (4). The recommended surgery in MEN1 is often a subtotal PTX, where 3.5 PGs are removed. Consequently, there is a risk of developing postoperative hypoparathyroidism (hypoPT), where the remaining plasma level of parathyroid hormone (PTH) is insufficient to maintain normal plasma calcium (Ca^{2+}). HypoPT is a concern in young patients due to chronic need of daily medical supplementation and risks of long-term complications to hypoPT. It is, therefore, essential to precisely locate parathyroid pathology, especially because the necessity for more than one PTX is very likely in patients with MEN1.

Case presentation

We present a 16-year-old girl, who at the age of 10 in 2013 was tested positive for a mutation in the MEN1 gene established in her family. Laboratory findings revealed a slightly elevated plasma ionized calcium (Ca^{2+}) of 1.39 mmol/L (reference interval 1.18–1.32 mmol/L) and PTH of 5.4 pmol/L (reference interval 2.3–9.3 pmol/L). The only complaint at the time was a slight headache in the evening. After 1.5 years, the patient developed a rise in Ca^{2+} to 1.51 mmol/L and PTH to 11.3 pmol/L, and she was referred to PTX. An US raised suspicion of an adenoma in the lower left PG. No MIBI was performed in order to avoid radiation exposure, and it was decided to remove the two left PGs. PTX was performed in 2015, and intraoperative PTH monitoring (IOPTH) showed a 74%

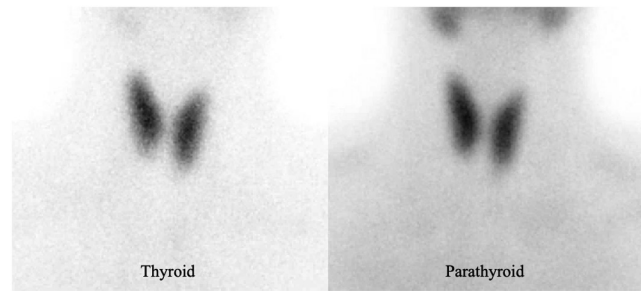


Figure 1

Planar images of the ^{99m}Tc -sestamibi-SPECT/CT showing no clear difference between thyroid scintigraphy and parathyroid scintigraphy. In addition, no adenoma was detected on the SPECT/CT (not shown).

decrease in PTH levels after the removal of the two left glands. No postoperative complications were observed and subsequent blood test revealed a decrease in Ca^{2+} to 1.33 mmol/L and PTH to 3.7 pmol/L.

An increase in Ca^{2+} was observed 4 years later and the patient was referred to a MIBI. However, no adenoma was detected (Fig. 1). Subsequently, a ^{11}C -methionine position emission tomography combined with MRI (MET-PET/MR) identified a focus posterior to the lower part of the right thyroid lobe (Fig. 2). A second PTX was performed with identification of a normal upper right PG (Fig. 3) and an adenoma in the lower right capsule of the thyroid (not presented). A small distal part of the normal PG was biopsied and marked with a clip. Vascularization of the proximal remaining part of the PG was illustrated (SPY-PHI, Stryker) with intraoperative administration of 2.5 mg Indocyanine Green (ICG) and fluorescent imaging (Fig. 4). In addition, IOPTH showed a 91% PTH decline from 13.4 pmol/L to 1.2 pmol/L. An enlarged thymus was also located on the neck and was removed with the suspicion of containing an ectopic PG, but no parathyroid tissue was detected (Fig. 5). The patient briefly experienced paresthesia in the face and right arm after the surgery and was discharged without any complications. Biochemical controls of PTH and Ca^{2+} were normal 2 weeks and 2 months postoperatively.

Discussion

Hyperfunctioning PGs can affect people of all age groups with MEN1 syndrome and are typically the first manifestation of the disease. It often occurs in the third decade of life with a lifelong penetrance of 100% and, therefore, international guidelines recommend extensive monitoring of these patients (1). Estimates have shown that approximately 17–23% develop primary HPT around the age of 20 years with one case as young as 8 years of age (2, 5).

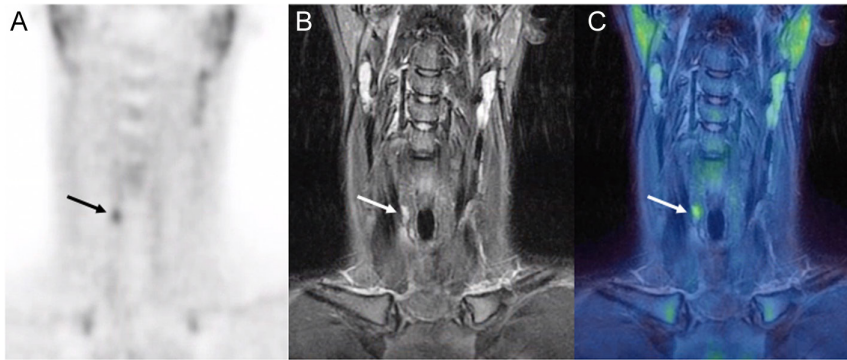


Figure 2

Frontal images of the ^{11}C -methionine PET/MRI showing a focus with high ^{11}C -methionine uptake (arrows) in the lower part of the right thyroid gland on the PET (A), MRI (B) and fusion image (C).

The treatment of HPT in MEN1 patients will ultimately lead to the surgical removal of abnormally overactive PGs. It is a compromise between leaving enough sufficient healthy parathyroid tissue to avoid permanent hypoPT and removing all the pathologic tissue to prevent persistence or recurrence of primary HPT, which occurs in 9–50% of cases depending on the primary surgical strategy (6). In our case, it was decided to initially perform a unilateral PTX with removal of the two left PGs to reduce the risk of affecting the recurrent laryngeal nerve and avoid the risk of developing hypoparathyroidism at a young age. At the time of the second surgery, the lower right PG as well as a small part of the upper right PG was removed, again to maintain sufficient healthy parathyroid tissue well-vascularized. Given the history of the patient, it was essential to provide a precise localization of PGs prior to the second PTX.

Noninvasive first-line imaging conducted prior to surgery usually includes US and MIBI. The sensitivities for US and MIBI range between 59–89% and 63–84%, respectively, which leaves a substantial amount of cases with unclear findings, necessity of more extensive surgical

exploration, and a higher risk of persistent disease after surgical treatment (7). In addition, the sensitivities are low in cases with small parathyroid lesions due to the poor spatial resolution, or when the adenoma is in close proximity to the thyroid gland, and in multi gland involvement with hyperplasia (8).

Second-line noninvasive imaging usually includes CT scans, either as a 4D CT or combined with PET tracers such as ^{11}C -methionine (MET) and ^{18}F -Fluorocholine (FCH) (9). In our hospital, MET-PET/CT is used in the case of negative or inconclusive conventional imaging studies before PTX or in the case of persisting HPT before a re-operation. There have been conflicting results regarding the usage of MET-PET/CT to localize pathological parathyroid glands in patients with primary HPT. However, newer studies have generally found a high sensitivity ranging from 77 to 91% and positive predictive values (PPV) around 93–98% (9, 10). In a situation where both the US and MIBI are negative, a study with 45 patients found a sensitivity of MET-PET/CT to be 74% and a PPV of 97% with a higher

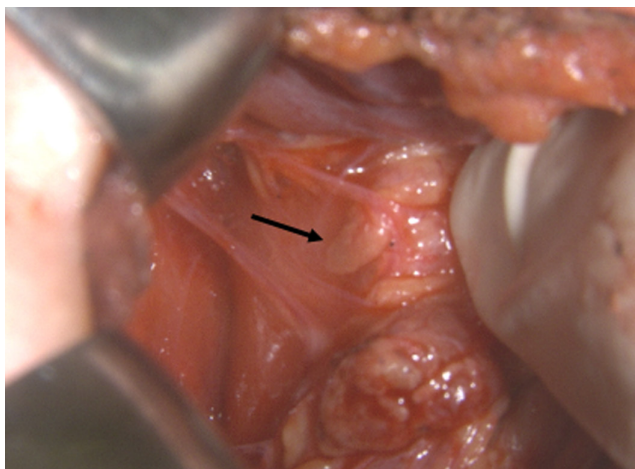


Figure 3

Right side of the neck showing a normal parathyroid gland (arrow).

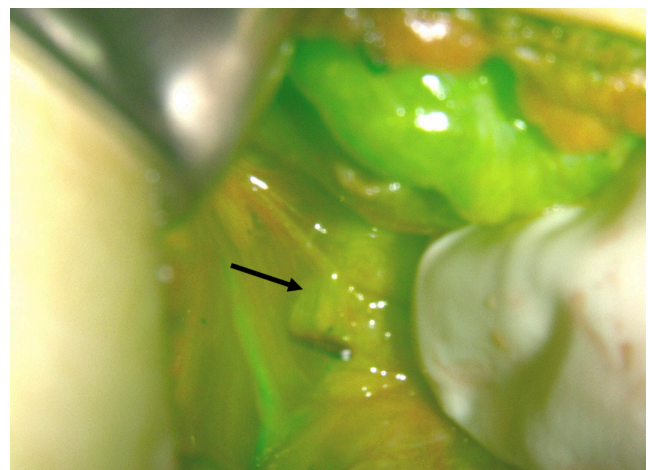


Figure 4

Usage of ICG and fluorescence with imaging of the upper right PG (arrow) marked with a clip for biopsy and future localization.

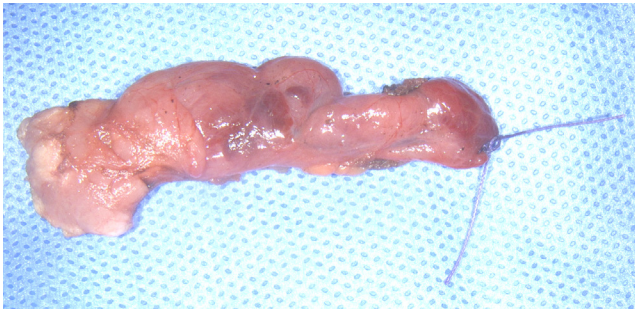


Figure 5

An enlarged right thymus was removed during the procedure with the suspicion of containing an ectopic parathyroid gland. However, no parathyroid tissue was revealed in the histologic examination.

detection rate for parathyroid adenomas (PA) compared to parathyroid hyperplasia (7). Even in the existence of a multinodular goiter or after previous neck surgery, the sensitivity and PPV values of 94% have been found including a positive correlation with the diameter and weight of the excised PGs (10). FCH-PET combined with CT and MRI has also been shown to provide high accuracy with sensitivities and PPV values above 90% (11).

Generally, these two PET tracers in combination with CT or MRI present themselves as highly sensitive methods to localize PAs even in atypical locations or in challenging anatomical positions in the neck, such as in patients with a multinodular goiter, or after unsuccessful PTX, and before a reoperation. They can provide valuable information, particularly for cases in which conventional imaging techniques have failed. Therefore, they are valuable tools and should be used in difficult cases, which will enable endocrine surgeons to successfully perform PTX. In our case, a MET-PET/MRI was performed to detect a PA after a negative MIBI. An MRI with a greater soft-tissue resolution compared with CT, in addition to a considerably lower radiation exposure, was preferred due to the case of reoperation in a young MEN1 girl. We did not find any previous published cases where MET-PET/MRI was used to detect parathyroid pathology.

Success of PTX heavily depends on surgeons' experience, and failure to identify an abnormal PG can lead to persistent HPT and unnecessary reoperations with an increased risk of damage to the recurrent laryngeal nerve. Furthermore, if normal functioning PGs are damaged or removed, development of hypocalcemia due to hypoPT can severely impact the patients' lives. So far IOPTH monitoring and post-operative plasma PTH levels have been used to verify the function of the remaining parathyroid tissue. Novel techniques using intraoperative angiography with fluorescence and fluorescent dyes are

increasingly being used in the last few years. It allows surgeons to verify the vascularization of each parathyroid gland intraoperatively (12). Autofluorescence is naturally emitted from PGs and can be detected by using near-infrared fluorescence imaging. Intensity levels have been described to be greater compared to the surrounding tissue with hyperfunctioning glands displaying a more heterogeneous and lower intensity compared to normal functioning PGs (13). ICG is a fluorescent dye that displays a high uptake in well-vascularized tissue (14). Use of either autofluorescence or fluorescence with exogenic dyes have been shown to detect PGs in more than 90% of cases, even among those with negative US and MIBI, and present themselves as valuable tools to identify and assess PGs intraoperatively (12, 13). However, only with the use of exogenic dyes as, for example, ICG can the vascularization for each PG be evaluated intraoperatively (Fig. 4).

Conclusion

Treatment of young MEN1 patients with manifestation of endocrine tumors is a very difficult task. It is crucial to perform a suitable treatment to enable them to live without symptoms for as long as possible. Therefore, optimization of noninvasive preoperative imaging techniques and intraoperative fluorescent imaging are valuable tools and should be taken into consideration when performing PTX repeatedly in the same patient to avoid postoperative complications. For the first time, we report the use of MET-PET/MRI as a valuable technique to detect parathyroid pathology in a challenging case.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written consent from the patient and the patient's parents have been obtained for publication of the submitted article and accompanying images.

Author contribution statement

The manuscript was mainly written by Thien Vinh Luong and supervised by Lars Rolighed, who also performed the surgery and provided the



fluorescence images. All listed co-authors have contributed with the scan analysis as well as proofreading of the case report.

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