ROLES OF NUCLEAR MEDICINE IMAGINGS IN DIAGNOSIS MULTIPLE ENDOCRINE NEOPLASIA TYPE 2a : A CASE REPORT

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ABSTRACT

Multiple endocrine neoplasia type 2a (MEN 2a) is rare, with complex disorders. MEN 2a is characterized by medullary thyroid carcinoma in combination with pheochromocytoma and hyperparathyroidism. We report a case of 48-year-old woman who had a severe hypertension. Physical examination revealed a painless enlarged thyroid gland and palpable abdominal mass. Hyperparathyroidism was diagnosed by elevated serum calcium level and parathyroid hormone level. ^{99m}Tc-pertechnetate thyroid scinitigraphy showed 2 hypofunctioning nodules at both thyroid lobes but both nodules were hot on ^{131}I MIBG imaging. ^{131}I MIBG imaging also revealed intense uptake at both enlarged adrenal glands. Medullary thyroid carcinoma and pheochromocytomas were subsequently proved by pathologic sections. Double phase ^{99m} Tc sestamibi parathyroid scintigraphy showed intense uptake at the right side of lower neck, suggesting parathyroid adenoma or hyperplasia. In conclusion,nuclear medicine imaging is very useful in the diagnosis of MEN 2a.

Key Words : multiple endocrine neoplasia , MEN 2a , nuclear medicine imaging, ^{131}I -MIBG

INTRODUCTION

The multiple endocrine neo-plasia (MEN) is a rare disease. It is divided into two categories: MEN type 1 and MEN type 2. The MEN type 2 is further divided into MEN 2a and MEN 2b. The association of medullary thyroid carcinoma with unilateral or bilateral pheochromocytomas and less common with parathyroid hyperplasia or adenomatosis is termed MEN 2a.[1,2]

We report a woman with MEN 2a. The presented case illustrates the important role of nuclear medicine in the diagnosis of endocrine neoplasms associated with MEN 2a.

CASE REPORT

A 42-year-old-woman was refered to Chulalongkorn Memorial hospital because of a severe hypertension. She had loss of weight (approximately 11 kg. in 2 months), palpitation, sweating, headache, tremor of hands and exhaustion for 7 months. One month prior to admission, her headache and palpitation became more severe with high blood pressure. On admission, her BP was 230/150 mm Hg, heart rate was 108/min and she looked chronically ill. On physical examination, thyroid gland was enlarged with nodular surface, firm consistency. A mass at left side of abdomen was found by bi-manual palpation.

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Laboratory findings showed increased levels of serum calcium (12.1 mg/dl), CEA (202 ng/ml), PTH (79.47 pg/dl), calcitonin (2511.77 pg/ml) and urine VMA (22.54 microgram/24 hrs). Thyroid function test was within normal limit. Ultrasonography of thyroid gland showed multinodular goiter with a few propable degenerated nodules. ^{99m}Tc-pertechnetate thyroid scintigraphy revealed enlargement of thyroid gland with two hypofunctioning thyroid nodules (figure 1). Double-phase ^{99m}Tc-sestamibi parathyroid scintigraphy suggested an adenoma or hyperplastic parathyroid gland (figure 2).^{99m} Tc-MDP bone scintigraphy revealed no metabolic bony disease but demonstrated abnormal radiotracer uptake at thyroid gland (figure 3). MRI of whole abdomen showed well-marginated mixed solid and partly cystic bilateral adrenal masses with heterogenous enhancement. Whole body imaging with ^{131}I-metaiodoben-zylgaunidine (MIBG) showed two focal areas of high activity at thyroid gland and enlargement of both adrenal glands (figure 4).

Bilateral adrenalectomy was done, the tumor in the left and right adrenal glands weighed 265 gm. and 70 gm. respectively. The histopathologic finding was bilateral pheochromocytomas. Total thyroidectomy and subtotal parathyroidectomy with implantation of the parathyroid glands into the left forearm were subsequently performed. Pathological section revealed medullary carcinoma of thyroid gland with foci of calcification. Surgical finding of parathyroidectomy shows enlargement of the right upper parathyroid gland but the right lower parathyroid gland cannot be identified. The other parathyroid glands on the left side are normal.

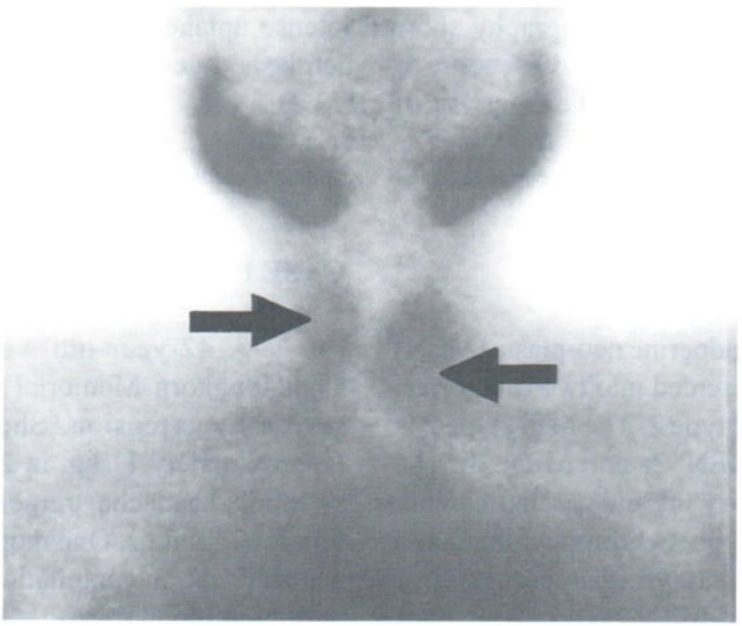

Fig. 1. ^{99m}Tc-pertechnetate thyroid scintigraphy shows 2 hypofunctioning thyroid nodules (arrows) at both thyroid lobes.

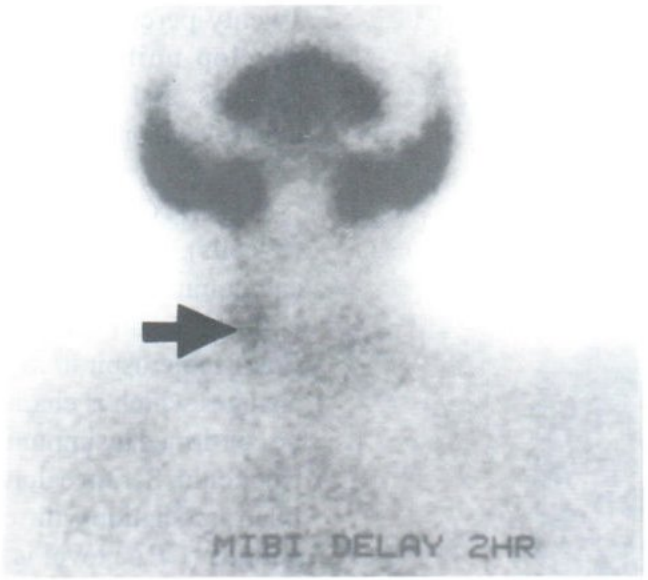

Fig. 2. Double-phase ^{99m}Tc-MIBI parathyroid scintigraphy ; The delayed 2 –hour after injection image shows intense uptake of radiotracer at the right side of lower neck (arrow).

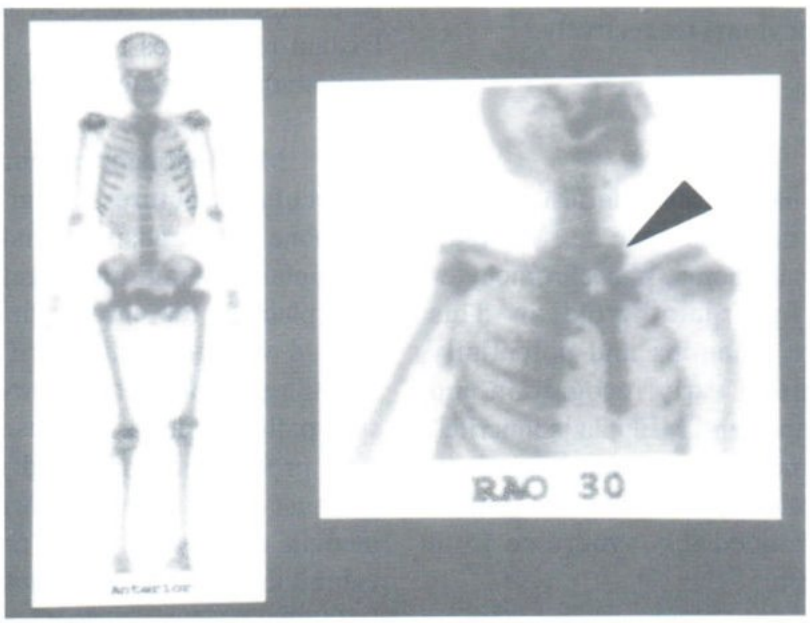

Fig. 3. ^{99m}Tc-MDP bone scintigraphy reveals normal radiotracer uptake throughout whole body skeleton but abnormal radiotracer uptake is noted at thyroid gland (arrow).

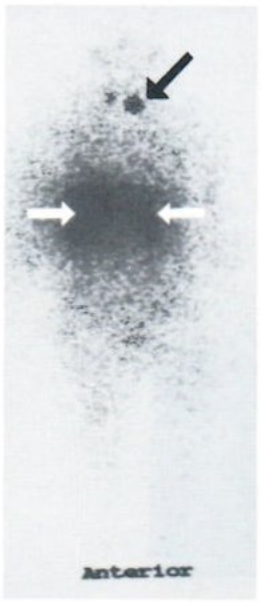

Fig. 4. Whole body ^{131}I-MIBG scintigraphy shows two focal areas of intense uptake at thyroid gland (black arrow) and both enlarged adrenal glands (white arrows), which were subsequently proved to be medullary thyroid carcinoma and pheochromocytoma respectively.

DISCUSSION

The patient had a triad manifestations of multiple endocrine neoplasia type 2a (MEN2a): medullary thyroid carcinoma, pheochromocytomas and primary hyperparathyroidism. This syndrome is a rare, complex and potentially lethal disorder, so that early recognition and diagnosis is very important. MEN 2a is inherited by an autosomal dominant mode of transmission.[2] However, many patients, including the patient reported here developed this syndrome from spontaneous mutation.

The most common manifestation and, indeed ,the hallmark of MEN 2a is hyperplasia of thyroidal C-cells, which progresses through several intermediate stages until finally developing into medullary thyroid carcinoma (MTC). Twenty percent to 50% of affected individuals develop unilateral or bilateral pheochromocytomas, and 10% to 20% develop parathyroid hyperplasia or multiple parathyroid adenoma.[3,4]

MTC originates from para-follicular cell (C-cells), which synthesize, store, and secrete calcitonin.[2] The clinical presentation is usually a unilateal or bilateral nodules or thyroid mass. A fine needle aspiration typically shows cytologic changes which is characteristic for MTC and can be confirmed by immunocytochemical staining for calcitonin. Serum calcitonin greater than 1000 pg/ml in association with elevated carcinoembryonic antigen (CEA) level is also used for diagnosis of MTC. In particular, determination of the serum calcitonin value stimulated by intravenous pentagastrin or calcium infusion is the prefered screening test for patient who is at risk for MTC.

Metastases to cervical or mediastinal lymph nodes are found in one half of the patients with a palpable enlarged MTC at initial presentation. Distant metastases to lung, liver, or bone most commonly occur later in the disease course .[5,6]

Metaiodobenzylgaunidine (MIBG) has molecular structure similar to the adrenergic hormone neurotransmitter, norepinephrine (NE). The uptake, storage and release of NE and MIBG take place in the chromaffin granules.[7] MIBG labeled with radioiodine (^{131} I or ^{123} I) can be used to image pheo-chromocytoma and other sym-patho-medulla neoplasm.[8] ^{131}I-MIBG also may protray primary[9] and metastatic MTC.[10] Because the embryonic orgin of the adrenal medulla and thyroid C-cell are similar, both may exhibit the capacity to sequester ^{131} I-MIBG.

Sensitivity of MIBG for diagnosis MTC is about 30%,but its specificity is high.[11-12] Clarke et al [11] compared the uptake of ^{99m}Tc(V) DMSA, ^{131}I-MIBG and ^{99m}Tc-MDP in patients with MTC and showed that ^{99m}Tc(V) DMSA was the most

sensitive agent for detecting sites of MTC. ^{99m}Tc-MDP is useful for evaluation of bony metastases and extraoxeous metastases in MTC.[13] Total thyroidectomy is mandatory for treatment of MTC, however, pheo-chromocytomas should be removed before thyroid surgery.[14]

MTC = Medullary Thyroid Carcinoma

The adrenal medulla in MEN2a apparently undergoes morphologic changes that are similar to those of the thyroid C-cells with diffuse or nodular hyperplasia as precursors of pheochromocytoma.[15] The early clinical features of pheochromocytoma in MEN 2a are inter- mittent headache, palpitation and nervousness ; hypertension is uncommon.[16] Increased urinary excretion of epinep-hrine and an increased ratio of epinephrine to norepinephrine excretion in 24-hr. urine sample are the first abnormalities noted.[17] In most patients with pheochromocytoma, the increase in urine metabolites such as urine VMA is considerable, often to more than three times of the normal range.[18] The specificity and sensitivity of urine VMA is 80-100% and 70-90% respectively.[19-20]

The diagnosis of pheochomocytoma is further confirmed by computed tomography (CT), magnetic resonance imaging (MRI), ^{131}I-MIBG scan. Scanning with ^{131}I-MIBG is useful for confirming the presence of functioning intra-adrenal chromaffin tissue and the exclusion of the rare extra- adrenal pheochromocytoma.[21,22] In the study of Quint LE et al,[23] MIBG scanning had a sensitivity of 100% (20/20). The sensitivity of MRI was 90% (18/20), and CT scaning was 70% (14/20). Scanning with CT is relatively insensitive in detecting extra- adrenal pheochromocytomas elsewhere in the abdomen or the chest, while MIBG scan is outstandingly sensitive in localizing pheochromocytomas in both areas.[24]

If a unilateral pheochromocytoma is found, the contralateral adrenal gland is inspected at surgery and removed only if the gland is nodular or enlarged.[25] This selective approach may prevent or postpone the necessity for glucocorticoid and mineralocorticoid replacement. Because of the 50% likelihood that nonaffected adrenal glands will develop a pheochromocytoma within 10 years, some advocate bilateral adrenalectomy at the time of first operation.[26]

Primary hyperparathyroidism is confirmed by elevated serum calcium level with an inappropriately elevated serum parathyroid hormone level.[27] Bone scintigraphy may show slight generalized increased activity with high bone to soft tissue ratio but rarely more obvious metabolic features and twenty-four–hour whole body imaging is more sensitive.[28] Because most cases of primary hyperparathyroidism are mild and asymptomatic, the high generalized uptake is not a consistent finding and the bone scan should not be used for diagnosis. In clinical practice, the detection of hyperparathyroidism is most likely occurred when a bone scan is performed as part of the investigation of hypercalcemia.[29]

An experienced surgeon will render a high cure rate (greater than 95%) in surgery for sporadic hyperparathyroidism even without preoperative steps to localize the abnormal parathyroids.[30] Success is harder to achieve in MEN, because all parathyroid tissue must be located. Preoperative localization imaging of intrathyroid parathyroid glands or extraparathyroid gland is needed before surgery.[31] Double phases ^{99m}Tc-sestamibi (MIBI) has been reported to significantly increase the reliability of scintigraphic localization of hyperfunctioning parathyroid tissue.[32-33] The mechanism is different biokinetic handling in thyroid and parathyroid tissue. The difference in uptake may be explained by the number of mitochondria in the cells where adenoma and hyperplastic gland have in large number.[34] Chiu et al [35] suggested that ^{99m}Tc-sestamibi is sequestered in the cytoplasm and

mitochondria. Joseph et al[36] showed sensitivity of double phases ^{99m}Tc-sestamibi in the detection of adenoma and hyperplastic gland to be 80% and 60% respectively. Hyperplasia is more difficult to be evaluated because of varying criteria for positive diagnosis. Strict criteria was defined that four parathyroid glands were detected scintigraphically. Loose criteria define a positive result that more than one parathyroid glands were demonstrated in the scan. Rodriquez et al[37] reported that dual phases MIBI sensitivity is greater than ultrasonography and CT, but similar sensitivity and greater specificity for MIBI, as compared with MRI. MRI has a high cost and low specificity.

Limitation of double-phases technique is related to the presence of parathyroid adenoma with a rapid ^{99m}Tc-sestamibi wash-out, similar to that of thyroid tissue; this condition can cause false-negative scintigraphic result.[38] Another limitation is related to thyroid nodules which can be ^{99m}Tc-sestamibi avid regardless of whether they are benign or malignant. Such nodules may trap and retain the tracer for a prolonged time, as do parathyroid adenoma, causing false-positive result.[39]

As we know an autosomal dominant inheritance in MEN2a, screening test should be done in all relatives of the patient. Identification of point of mutation of the RET proto-oncogene now makes it possible to identify gene carriers with 100 per cent accuracy in families with a proven mutation.[40]

In conclusion, patient with the MEN2a syndrome manifest a spectrum of endocrinologic abnormalities. Radio-nuclide imaging is useful in the detection of MTC, pheochromocytomas and, primary hyperparathyroidism. Death is related to either metastatic MTC or pheochro-mocytoma. Therefore, early diagnosis and recognition of the tumors in the patient is very important.

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