Multiple Endocrine Neoplasia Type IIa : A Case Report

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Abstract

The authors reported a twelve year and four-month old girl who had prolonged fever for 2 weeks. Physical examination revealed a painless enlarged thyroid gland with firm consistency. Hyperparathyroidism was suspected because of hypercalcemia, hypophosphatemia, high level of serum alkaline phosphatase, and decreased density of long bones. Thyroid scan showed a cold nodule of the left upper lobe which subsequently proved to be a medullary thyroid carcinoma by high serum thyrocalcitonin level and pathological examination. Her 24-hour urinary vanillyl mandelic acid was in the normal range, and abdominal ultrasonography demonstrated normal adrenal glands. Multiple endocrine neoplasia type IIa (MEN IIa) was diagnosed by medullary thyroid carcinoma and hyperparathyroidism. However, the fully developed syndrome is characterized by the combined occurrence of medullary thyroid carcinoma, primary hyperparathyroidism, and pheochromocytomas. This syndrome is a rare, complex, and potentially lethal disease so early recognition and family screening are very important.

In 1959, John Sipple reported a case who had hypertension and subsequently died. At autopsy, there were bilateral pheochromocytomas, a pale tan mass in each lobe of the thyroid glands and nodular enlargement of the only parathyroid gland[1]. This is now well recognized as multiple endocrine neoplasia type IIa (MEN IIa). The clinical syndrome consists of medullary thyroid carcinoma, unilateral or bilateral pheochromocytomas, and less commonly, parathyroid hyperplasia or adenomatosis[1,2]. It is inherited in an autosomal dominant pattern of transmission[2] and screening should be offered to relatives of patients with this disorder as the disease becomes clinically expressed in only about 60 per cent by age 70[3,4].

We report here a girl with MEN IIa. To our knowledge, this patient is the first reported case of a child with MEN IIa in Thailand.

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CASE REPORT

A Thai girl aged twelve years and four months was referred to the Children's Hospital because of fever for 2 weeks. She had cough, rhinorrhea and vomiting and had gone to a private hospital two weeks previously without any improvement. In addition, she lost 4 kilogram in weight during the 2 weeks. One week prior to this admission, she had a painful sacral area and looked pale. Previously, she had been diagnosed with simple goiter at Trang General Hospital and for the last 2 years the goiter had remained the same size. No one in her family looked like her. On physical examination, she looked very thin and mildly pale. There was an enlarged thyroid gland of 4x3 cm size, of firm consistency, and not tender. Her sacral area had no other signs of inflammation except for mild tenderness (Fig. 1).

Laboratory investigation revealed Hct 27%; Na 133, K 2.83 Cl 107 and CO_2 26.4 mEq/L: Ca 16.8 mg% P 1.63 mg% alkaline phosphatase 1,032 U/L (normal range 110-360). Thyroid function test was normal with T4 5.3 µg/dl (normal range 4.5-11.5 µg/dl) TSH 0.19 µIU/ml (normal range 0.35-5.2 µIU/ml). Thyroid antibodies were negative. Serum thyrocalcitonin level was high with its level of 29.6 pmole/L (normal range 4.7-14.6 pmole/L). Lumbosacral spines and long bones radiography showed increased density of superior and inferior end plate of vertebral bodies, and decreased bone density at metaphysis and diaphysis of long

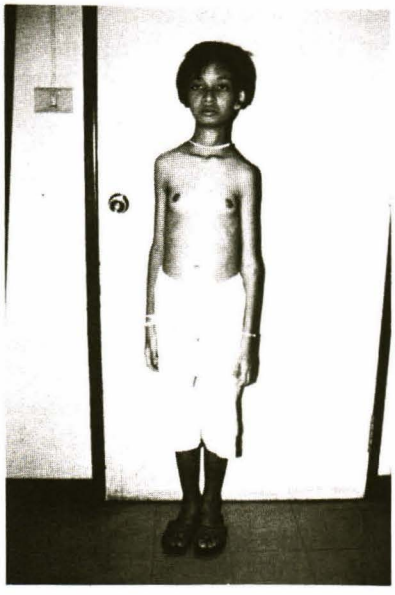

Fig. 1. The patient's appearance demonstrating thin extremities with the enlarged thyroid gland.

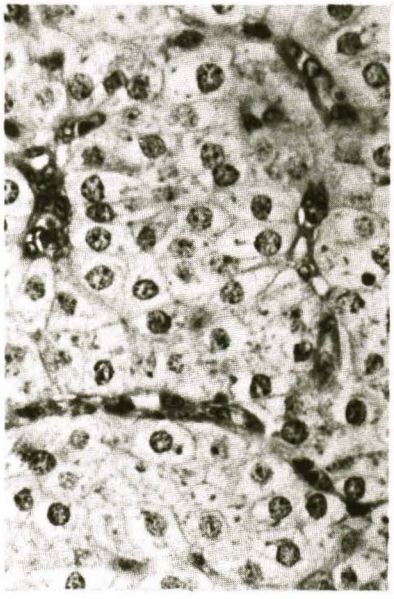

Fig. 2. H&E, x 400 Tumor cells having round or polygonal shape with rather uniform finely granular round nuclei

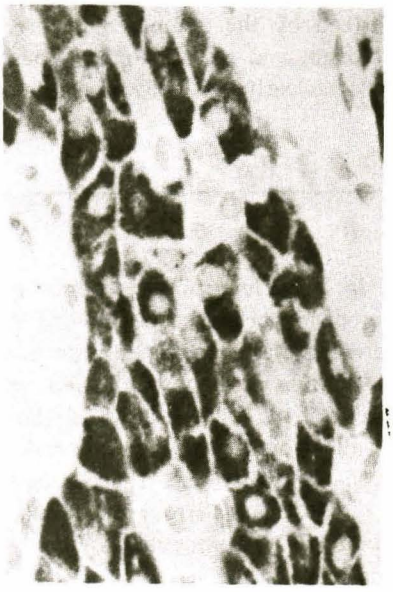

Fig. 3. Immunohistochemical staining, x 400 Immunoreaction with calcitonin.

bones. Technetium 99m thyroid scintigraphy revealed a cold nodule, solid in appearance of the left upper lobe. MIBI scan showed no definite evidence of parathyroid adenoma. The 24 hour urine for VMA was 3.1 mg/dl (normal range 1.7-70.9 mg/dl). Abdominal ultrasonography demonstrated normal adrenal glands.

She had fever for 2 days without positive finding on septic work up. Her hypercalcemia responded well by using saline diuresis and phosphate solution. Total thyroidectomy and subtotal parathyroidectomy were then performed. Pathological section revealed medullary carcinoma of the thyroid gland (Fig. 2 and Fig. 3). After the operation, she developed asymptomatic hypocalcemia and she was discharged with vitamin D, calcium gluconate and synthetic thyroid hormone. Two months later, she gained weight and her general symptoms improved. The serum calcium level and 24 hour urine for VMA of her parents and her younger brother were within normal limits.

DISCUSSION

This patient had two out of three presentations of multiple endocrine neoplasia type IIa (MEN IIa), the medullary thyroid carcinoma and hyperparathyroidism. As changes of the individual glands appear to be independent from each other, affected patients will not develop all components of the syndrome, and the time interval between development of different components may vary[2]. Therefore, the presence of an endocrine tumor known to be associated with MEN IIa should stimulate a search for other tumors in the patient. If diagnosed early, all serious features of MEN IIa are treatable and even curable.

Medullary thyroid carcinoma (MTC) is a multicentric neoplasm of parafollicular or C cell of the thyroid gland. The majority of cases of MTC reported in the literature are sporadic, (from 75% to 95%)[5-8]. Among the various forms of familial MTC, MEN IIa is the most frequent, followed by MTC-only. 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 lungs, liver, or bone most commonly occur later in the disease course [9,10]. A serum calcitonin greater than 280 pmole/L in association with an elevated carcinoembryonic antigen (CEA) level is also diagnostic for MTC[2]. Total thyroidectomy is mandatory for treatment of medullary thyroid carcinoma in this syndrome and abnormality of C cell are almost always bilateral and multicentric which are useful for distinguishing hereditary from sporadic MTC[5,8,11].

Primary hyperparathyroidism occurs in 10 per cent to 20 per cent of individuals with the mature form of the MEN IIa syndrome[12-14]. A careful review of the histology of these tumors has demonstrated occasional adenomatosis formation with a background of parathyroid hyperplasia, a finding that is analogous to that observed for C cell hyperplasia in the thyroid gland and chromaffin cell hyperplasia in the adrenal medulla[15]. Before development of hypercalcemia, the earliest indication of abnormal parathyroid function is incomplete suppression of parathyroid function by calcium infusion which implies an abnormality in set point[16]. Surgery is the treatment of choice.

The adrenal medulla in MEN IIa apparently undergoes morphologic changes that are similar to those of thyroid C cells, with diffuse or nodular hyperplasia as precursors of pheochromocytoma[17,18]. Pheochromocytomas in MEN IIa may occur unilaterally or bilaterally but are almost always unilateral and unicentric in sporadic cases [19]. The clinical features of pheochromocytoma in MEN IIa are frequently subtle, which may include intermittent headaches, palpitations, and nervousness; hypertension has become an uncommon feature[20]. Increased ratio of epinephrine to norepinephrine excretion in 24-hour urine samples are the first abnormalities noted[20,21]. Urinary vanillylmandelic acid excretion is usually normal early in the course of the disease[1]. Diagnosis is confirmed by computed tomography or magnetic resonance imaging of the abdomen. Increased [^{131}I] metaiodobenzylguanidine uptake may be observed in adenomedullary hyperplasia. Most physicians remove only adrenal glands suspected of having pheochromocytoma. If a unilateral pheochromocytoma is found, the contralateral adrenal gland is inspected at surgery and removed only if the gland is nodular or enlarged[20,22].

As we know an autosomal dominant inheritance in MEN IIa, screening test should be done in all relatives of patients. This should include pentagastrin test with serum calcitonin measurements, 12 or 24 hour urine test for epinephrine and norepinephrine and ionized serum calcium[20-24]. Recently, identification of point 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(25). However, most of these tests are not available in Thailand. So we do yearly measurements of serum calcium, serum calcitonin, and 24 hour urine for vanillylmandelic acid instead. For our patient, these parameters should be measured every 3-6 months as the early recognition of the recurrent MTC and the occurence of other tumors is necessary to improve the prognostic outcome. Death is related to either metastatic MTC or pheochromocytoma. Therefore, early diagnosis by screening family members and early recognition of the other tumors in the patient is very important.

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Multiple Endocrine Neoplasia Type IIa : รายงานผู้ป่วย

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รายงานผู้ป่วย 1 ราย เป็นเด็กหญิงไทยอายุ 12 ปี 4 เดือน มาพบแพทย์ด้วยเรื่องไข้เรื้อรัง 2 สัปดาห์ การตรวจร่างกายพบว่าต่อมธัยรอยด์โตและแข็ง ผลการตรวจธัยรอยด์สแกนพบว่ามี cold nodule ที่ left upper lobe ซึ่งจากการตรวจทางพยาธิวิทยายืนยันว่าเป็น medullary thyroid carcinoma การตรวจเลือดพบว่า serum calcium, serum alkaline phosphatase และ serum thyrocalcitonin มีค่าสูง แต่ serum phosphate มีค่าต่ำ ร่วมกับการตรวจทางรังสีวิทยาพบว่าเงากระดูกบางลง ทำให้คิดถึงภาวะ hyperparathyroidism ปริมาณ vanillyl mandelic acid ในปัสสาวะ 24 ชม. อยู่ในเกณฑ์ปกติ และการตรวจช่องท้องด้วยคลื่นเสียงความถี่สูงไม่พบความผิดปกติที่ adrenal gland ผู้ป่วยได้รับการวินิจฉัยว่าเป็นโรค multiple endocrine neoplasia type IIa (MEN IIa) ซึ่งลักษณะที่ครบถ้วนของโรคนี้ประกอบด้วย medullary thyroid carcinoma, primary hyperparathyroidism และ pheochromocytoma โรคนี้พบได้น้อยในผู้ป่วยเด็ก การตรวจหาโรคนี้ในครอบครัวผู้ป่วยมีความสำคัญมากเพราะสามารถรักษาให้หายขาดได้ถ้าได้รับการวินิจฉัยและเริ่มรักษาตั้งแต่ระยะแรกของโรค ผู้ป่วยรายนี้เป็นรายงานแรกของผู้ป่วยเด็กที่เป็น MEN IIa ในประเทศไทย

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