Case Report

Multiple Endocrine Neoplasia Type IIa Associated with Cushing's Syndrome

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Abstract

Multiple Endocrine Neoplasia type IIa (MEN IIa) is an autosomal dominant syndrome characterized by pheochromocytoma, medullary thyroid carcinoma and hyperparathyroidism. Pheochromocytoma occurs in approximately 50% of patients with MEN IIa. This tumor has the capacity to produce ACTH ectopically and manifests as the Cushing syndrome, although it is very rare. We report a 26-year-old woman patient with severe muscle weakness, skin lesions in extremities, hypertension, and new onset diabetes whose laboratory findings included hypokalemia, metabolic alkalosis, high serum level of cortisol, metanephrine, normetanephrine, calcitonin and bilateral adrenal mass in computed tomography as the first clinical manifestations of an ACTH-secreting pheochromocytoma. In the patients with hypertension, new onset diabetes and hypokalemia, the Cushing syndrome and pheochromocytoma should always be ruled out.

Keywords: Cushing syndrome, multiple endocrine neoplasia, medullary thyroid carcinoma

Cite this article as: Borzouei S, Mousavi Bahar SHA, Fereydouni MA, Salimbahrami SA, Taghipour M. Multiple Endocrine Neoplasia Type IIa Associated with Cushing's Syndrome. *Arch Iran Med*. 2014; **17(6):** 451 – 454.

Introduction

Multiple endocrine neoplasm type 2a (MEN IIa) is a combination of pheochromocytoma, medullary thyroid carcinoma (MTC) and hyperparathyroidism which has autosomal dominant inheritance. Mutation of proto-oncogene (RET) has been detected in most of patients suffering from it. Half of patients with RET gene mutation up to 50 years of age and about 70% of them up to 70 years of age present manifestations of the disease. MTC is the most common manifestation of this dysfunction and is usually present in the second or third decades of life in 100% of patients. Pheochromocytoma presents in about 30%–50% of patients and is bilateral in more than half of them. Presentation of pheochromocytoma can be associated with MTC synchronously or after a few years.[1–3]

Hyperparathyroidism occurs in 15%–20% of patients in the third or fourth decades of life.[4] In the majority of patients, it is clinically silent.[3]

Here, we describe a 26 year old woman with clinical manifestations of ectopic Cushing's syndrome, bilateral pheochromocytoma and medullary thyroid carcinoma with MEN IIa diagnosis.

Case report

A 26-year female homemaker from Hamedan, Iran was admitted to our service with complaints of fatigue, malaise, severe numbness in the limbs and progressive muscle weakness since three months ago. She had lost 7–8 Kg of weight without anorexia. Another complaint was skin lesions that were worsening progressively. She had frequent headaches with hospital admission and was being treated with NSAIDs. She had been suffering from constipation for the last 3 years and used laxatives. Her last menstrual period was 6 months ago.

She reported a history of thyroid surgery with unremarkable results and was taking levothyroxine since three years ago. There was a history of HTN and thyroid disorders in several members of her family.

On physical examination, the patient was thin and had a puffy face. The vital signs were as follows: temperature 37.5°C, respiratory rate 17/min, pulse rate 114/min, blood pressure 170/100 mmHg. There were diffuse papulae, hyperpigmentation, erythematouse lesions and livedo reticularis in the upper and lower limbs, especially in the plantar and palmar areas but without petechiae, ecchymoses or purple striae (Figure 1).

She had a puffy face without moon face or plethora. On funduscopic exam, there was diffuse arterial narrowing with normal disc and macula. The thyroid lobes were palpable and with one nodule 10×10 mm with firm texture in the RT lobe. The heart was tachycardic. Muscle wasting was present with diffuse erythematous lesions and livedo reticularis in the limbs and little gangrene on fingertips. The hands and feet were cold and peripheral pulses were severely weak.

Muscle force was $\frac{2-3}{5}$ in the proximal limbs and $\frac{4}{5}$ in the distal limbs. There was not neurologic deficit.

On electrocardiography, sinus tachycardia and inverted T were seen. On echocardiography, diffuse HK was found except in the base and mid-posterior wall, and mild Iv DIA dysfunction with EF = 30%–35%.

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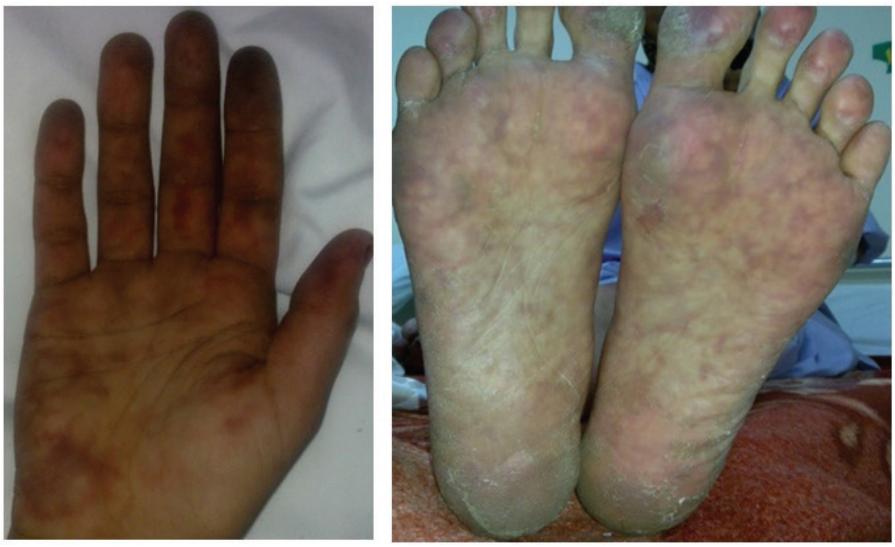

Figure 1. diffuse papule, hyper pigmentation erythematouse lesion and lividoveticulris in the palmar and the plantar areas.

Table 1. Laboratory tests.

FBS: 341 mg/dL	BetaHCG: Neg
Total Cholesterol: 601 mg/dL	FSH: 2.3
TG: 925 mg/dL	LH: 0.7
Na: 138 meq/L	TSH: 0.1(0.4–6)
K: 2.3 meq/L	T4: 48.39 (Normal: 44–181)
CBC: Normal	T3: 0.38 (Normal: 1.3–3.1)
PT,PTT,INR: Normal	LFT: Normal

Table 2. Laboratory data before and after adrenalectomy.

	Base line	Day 3 low Dose Dex	Day 3 high Dose Dex	Post-OP	Normal-value
Cortisol	142	135	—	1.2	12.25 mcg/dL
UFC	*>2000	2324	2570	—	50–190micg/day
ACTH	*180.72				7.2–63pg/mL
VMA	55.8			6.8	Up to 13.6 mg/day
Metanephrine	*1540			342	<350 micgr/day
norMetanephrine	*10840			820	Upto 600
Aldosterone	220				25.315 pg/mL
PRA	55				4.4–46.1 micIu/mL
Calcitonin	*122				Up to 14 mg/mL
TSH	0.1			4.28	0.4–6miu/mL
T4	48.39			95.39	66–81nmol/L
T3	0.3			1.92	1.3–3.1nmol/L

The ABG finding showed metabolic alkalosis. The clinical and paraclinical data showed secondary hypertension. Differential diagnosis included: glucocorticoid excess and pheochromocytoma. Additional laboratory tests and imaging were done (Tables 1 and 2).

Abdominal CT scanrevealed bilateral adrenal enlargement with a round mass of 22 mm in the right adrenal and a homogeneous, round mass of 35 mm in the left adrenal (Figure 2).

Pathological examination of the tumor demonstrated a typical pheochromocytoma of the adrenal gland with the classic Zellballen pattern (Figure 3).

The patient was diagnosed with ectopic Cushing syndrome due to pheochromocytoma. On the 20th day of hospitalization, she underwent bilateral adrenalectomy. Subsequently, all her skin lesions were improved (Figure 4).

Laboratory data after adrenalectomy were done (Table 2). After adrenalectomy, she was bedridden several days and treated with prednisolone and fludrocortisone acetate. She was discharged after one week.

After three months, she was referred with chief complaint of a thyroid mass. On physical examination, she had a thyroid nodule. She underwent Fine Needle Aspiration that revealed nodular goiter.

Based on bilateral adrenalectomy and her family history of thyroid cancer suspected of MEN IIa, she underwent total thyroidectomy.

Pathological examination of the thyroid tumor demonstrated Thyroid Medullary Carcinoma with associated amyloid deposition appearing on hematoxylin and eosin staining (Figure 5).

Considering her thyroid medullary carcinoma and pheochromocytoma, we checked for RET proto-oncogene which was positive, and thus a definitive diagnosis of MEN2A was established.

On follow-up 6 months later, her clinical condition had remained stable and while treated with levothyroxine, pednisolone and fludrocortisone acetate.

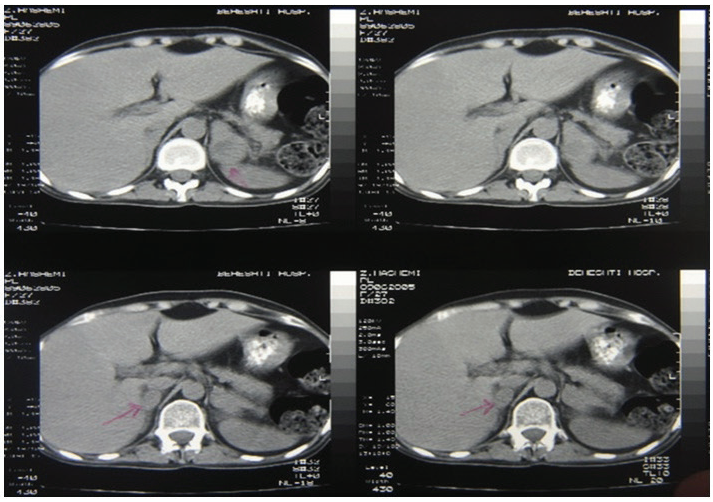

Figure 2. CT showing the bilateral adrenal enlargement with round masses in right and left adrenal.

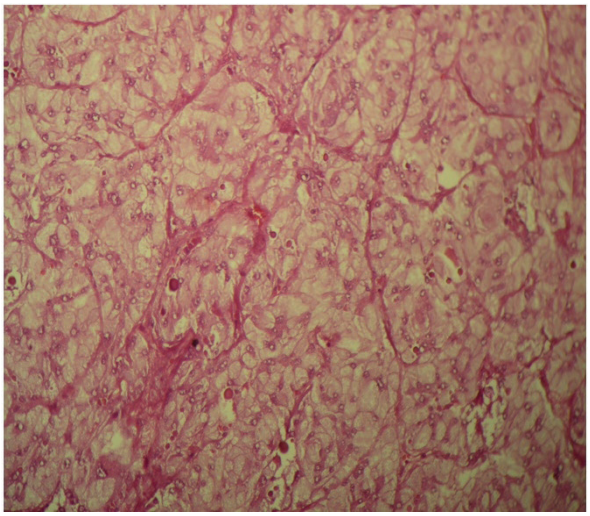

Figure 3. The classic Zellballen pattern in Pheochromocytoma.

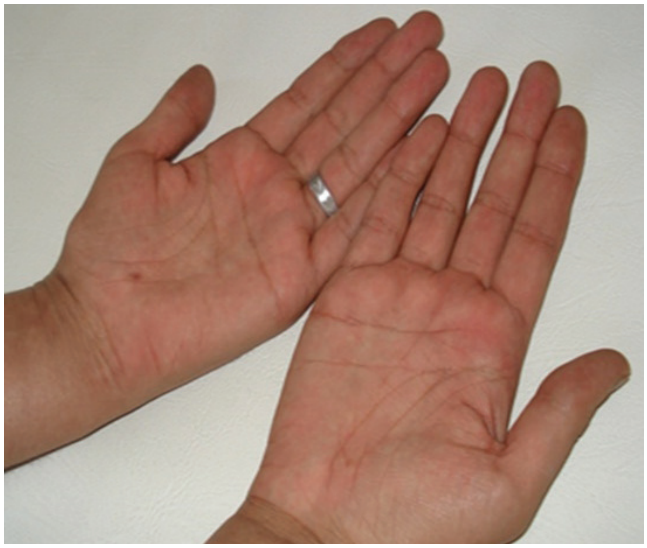

Figure 4. After surgery, patient skin lesions was improved.

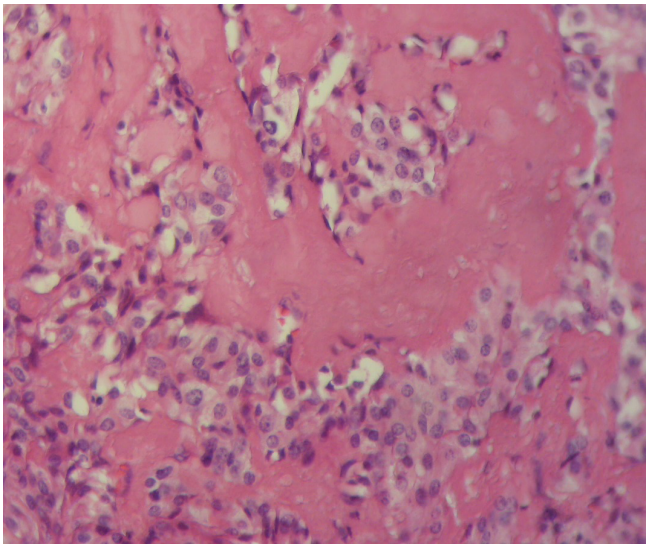

Figure 5. Thyroid Medullary Carcinoma with associated amyloid deposition appearing on H and E stained.sections as acellular eosinophilic appearing material.

Discussion

Clinical and paraclinical data in this patient included: hypertension, diabetes and recent hyperlipidemia, clear muscle weakness, hypokalemia, metabolic alkalosis and secondary amenorrhea which firstly suggest hypercortisolism. High levels of cortisol and also corticotropine with severe hypokalemia are usually in favor of an ectopic Cushing`s Syndrome which accounts for approximately 5%–10% of Cushing's causes.[5]

On the other hand, episodes of headache, recurrent palpitations with weak, unpalpable pulses plus severe hypertensive crisis and skin lesions strongly suggest another cause of secondary HTN, the most important of which is pheochromocytoma.

Lab data and imaging together suggested bilateral pheochromocytoma and ectopic Cushing`s Syndrome. Despite lack of prominent phenotype in favor of Cushing for this patient, the source of ectopic excretion of ACTH is pheochromocytoma masses and of course Cushing`s Syndrome caused by this mass is quite rare.

Sources of ectopic excretion of ACTH include small cell carcinoma of the lung in 50% of cases, other endocrine tumors such as bronchi and thymus carcinoids and rarely GI carcinoids, and also some neoplasms like medullary thyroid carcinoma (5%) and pheochromocytoma (5%).[6–8]

Pheochromocytoma is a rare tumor which excretes catecholamine. Its incidence is 2–8 cases in every 1 million persons per year and in 1% of cases, the manifestation is secondary HTN.[9]

Only about 15% of patients with MEN II present with pheochromocytoma as the first symptom and 25% of them have MTC synchronization.[1]

One remarkable point in this patient is skin lesions as the chief complaint, a vasomotor manifestations due to high excretion of metanephrine and nor-metanephrine in pheochromocytomaalthough, it can be a sign of other endocrinopathies like hyperthyroidism, medullary thyroid carcinoma and carcinoma of the pancreas.[10]

Pheochromocytoma can be associated with skin manifestations and flushing phenomenon including, macular rash, erythrocyanosis, and even necrosis in extremities.

In our patient, after adrenalectomy and before thyroidectomy, the levels of catecholamines were decreased and all lesions improved which is strongly in favor of pheochromocytoma.

Cardiac signs, like severe insufficiency and ventricular dysfunction, are other findings in this patient. Unspecific changes in rhythms and conduction system of the heart may occur in patients with pheochromocytoma, and its cause is myocardial stimulation with high levels of catecholamines in the plasma.

High levels of norepinephrine may have toxic effects on the myocardium because of decreased coronary blood supply.

Epinephrine is 10 times stronger than norepinephrine, and epinephrine secreting pheochromocytoma is usually silent and has a high rate of mortality due to cardiogenic shock.[12]

In our patient, level of normetanephrine, a metabolite of norepinephrine, is very high and signs of ischemia and severe heart insufficiency improved after the operation and decrease of levels of catecholamines.

This patient presented a collection of unusual manifestations of pheochromocytoma as part of MEN IIa syndrome who was saved with proper and timely diagnostic and curative approach.

The patient had no clinical or laboratory findings of hyperparathyroidism, although hyperparathyroidism occurrs in 15%–20% of patients and is clinically silent in the majority of patients.[3]

It must be noted that after a diagnosis of MEN IIa, study of proto-oncogene of RET is necessary in all patients and in cases with positive results, genetic study in the family members is also necessary.

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