Saudi J Kidney Dis Transpl 2012;23(1):117-121

Saudi Journal of Kidney Diseases and Transplantation

Case Report

Acute Renal Failure as an Initial Manifestation of Multiple Endocrine Neoplasia (MEN) Type 1

Reza Afshar[1], Suzan Sanavi[2], Hamid-Reza Taheri[3]

Departments of [1]Nephrology and [3]Vascular Surgery, Shahed University, Mustafa Khomeini Hospital, [2]Clinical Department, University of Social Welfare & Rehabilitation Sciences, Tehran, Iran

ABSTRACT. Multiple endocrine neoplasia (MEN) is a group of heritable syndromes characterized by aberrant growth of benign or malignant tumors in a subset of endocrine tissues. There are three major syndromes: MEN1, 2A and 2B. We describe a 60-year-old woman who initially manifested acute renal failure due to hypercalcemia and dehydration and, finally, was diagnosed as a sporadic MEN1 case.

Introduction

Multiple endocrine neoplasia type 1 (MEN1), also known as Wermer's syndrome, is an autosomal-dominant predisposition to tumors of the parathyroid glands (95%), entero-pancreatic (30–80%) and anterior pituitary (20–25%).[1] However, the clinical spectrum of this disorder has been expanded, and a number of unusual clinical manifestations with variable frequency may occur among the affected individuals. The duodenum is a common site of tumors (gastrinomas) in these patients, and carcinoid tumors (10–20%), adrenal adenomas (25–40%) and sub-cutaneous lipomas (30%) are more common than in the general population.[2] Other reported associations with MEN1 include pheochromocytoma (very rarely), angiomyolipomas and spinal cord ependymomas. The estimated prevalence of MEN1 is 2–20 per 100,000 in the general population, and approximately 10% of MEN1 mutations arise *de novo*, which are applied to sporadic.[3] MEN1 is defined as the presence of two of the three main MEN1 tumor types (parathyroid, entero-pancreatic endocrine adenomas and pituitary adenomas). Familial MEN1 is defined as an index MEN1 case with at least one relative who has one of the three main MEN1 tumors.[1] Hyperparathyroidism is the most common manifestation of MEN1, displaying almost 100% penetrance by age 40–50 years.[1] Clinically apparent pituitary adenomas develop in 15–20% of patients when sought by computed tomography (CT) or magnetic resonance imaging (MRI),[3,4] but the pathological prevalence may be over 60%.[5] The most common type of pituitary tumor in MEN1 is a pro-lactinoma. Nevertheless, growth hormone-producing, corticotropin (ACTH)-producing, gonadotroph and clinically non-func-

Correspondence to:

Dr. Suzan Sanavi,
Clinical fellow of Nephrology, Internist,
University of Social Welfare & Rehabilitation Sciences, Akhavan Center,
Valiye-Asr Ave, Tehran, Iran
E-mail: s2sanavi@yahoo.com

Table 1. Laboratory data at presentation.

Lab parameters	Patient	Normal level	Lab parameters	Patient	Normal level
Serum creatinine (mg/dL)	2*	0.5–0.9	GH after OGTT	1.9	Suppressible
BUN (mg/dL)	57*	7–20	Cortisol 8AM (mcg/dL)	16	9.4–26
Serum calcium (mg/dL)	16.8*	8.8–10.5	Calcitonin (pg/mL)	6*	0.1–5.5
Serum phosphorus (mg/dL)	2.8	2.5–4.5	Serum uric acid (mg/dL)	13.3*	2.5–5.6
Serum iPTH (pg/mL)	610*	7–82	Blood sugar (mg/dL)	78	75–110
Alkaline phosphatase (U/L)	857*	33–96	Hemoglobin (g/dL)	14.8	12–15.8
ACTH (pg/mL)	34.4	4.7–48	ESR (mm/h)	26	0–20
Prolactin (ng/mL)	21*	2–13	Urinalysis	1 granular cast	Urine analysis
Growth hormone (ng/mL)	2.4	<18	Insulin growth factor-1 (ng/mL)	173,180	94–269
T3 (ng/mL)	0.92*	0.4–1.8	Urinary vanillyl	1.2	0.5–12.5
T4 (mcg/dL)	11.5	4.5–12.5	mandelic acid (mg/d)		
TSH (mIU/L)	0.1*	0.5–5	Urinary calcium (mg/d)	626*	<300

tioning tumors can also occur.[3] Entero-pancreatic tumors become clinically apparent in 30% of the patients, but subclinical involvement is more common.[6,7] The malignant potential of entero-pancreatic tumors is now the primary life-threatening manifestation of MEN1. The most common cause of symptomatic disease is the Zollinger-Ellison (gastrinoma) syndrome (ZES), leading to multiple peptic ulcers. Approximately 60% of MEN1 patients have either the ZES or asymptomatic elevation in serum gastrin concentrations.[8] Symptomatic insulinomas also occur with moderate frequency, while VIPomas and glucagonomas are rare.

Case Report

A 60-year-old woman presented to the emergency department because of a recently elevated level of serum creatinine, nausea and vomiting. She reported a history of depression-anxiety, which was diagnosed about one year ago, and she received anti-depressant drugs for it. She mentioned also a history of dyspepsia, thyroid gland enlargement and suppressive therapy with levo-thyroxine for several years. She denied any history of hypertension, diabetes mellitus, genitourinary tract and other diseases. She complained also from chronic constipation, increased urine output and fluid intake, particularly during the past four months.

On physical examination, a 3 cm × 4 cm firm mass just below the right mandibular angle was palpated. The thyroid gland was enlarged (grade III or visible from distant) and multinodular, particularly in the right lobe. Lymph node enlargement and organomegaly were not found. Examination of other systems was unremarkable. The results of the laboratory investigations are shown in Table 1.

Acute renal failure (ARF) supportive therapy was initiated with judicious intravenous fluid replacement and diuretics associated with urine output monitoring. Then, urinary tract ultrasonography, skull radiography, MIBI parathyroid (sestamibi) scan, parathyroid hormone and calcitonin blood levels and CT scan of neck were requested. Ultrasonography (US) showed normal-sized but slightly hyperechoic kidneys compatible with acute injury. The left kidney had a simple cyst of 9.7 mm diameter in the middle part. US did not detect stones, calcifications or obstruction in the urinary system. The skull radiograph revealed osteopenia and the parathyroid scan demonstrated an active adenoma (Figure 1). Neck CT scan revealed a 3.5 cm × 2.5 cm mass just upon the right carotid artery bifurcation resembling paraganglioma (carotid body tumor), which had been confirmed by color Doppler sonography and CT angiography (after renal function improvement), thyromegaly (particularly in the right lobe) associated with multiple nodules without

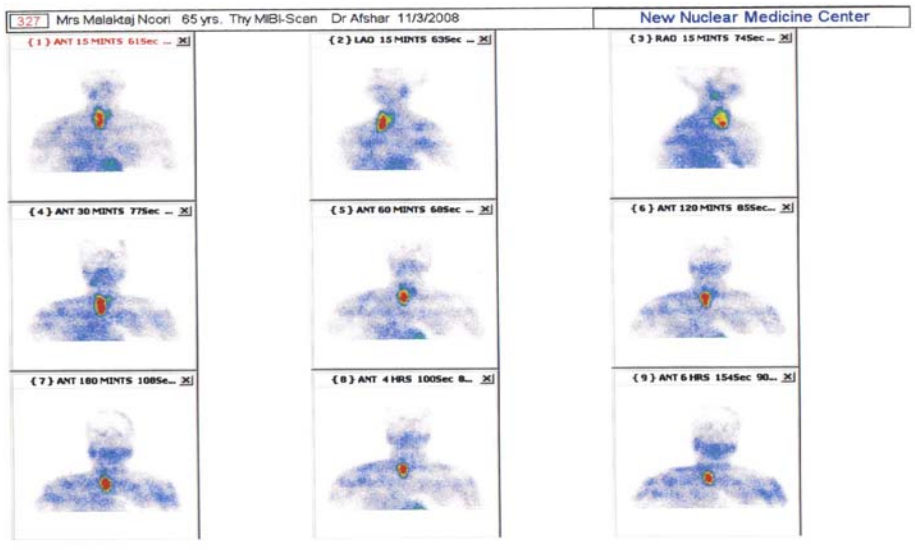

Figure 1. Sestamibi parathyroid gland scan shows an adenoma in right side.

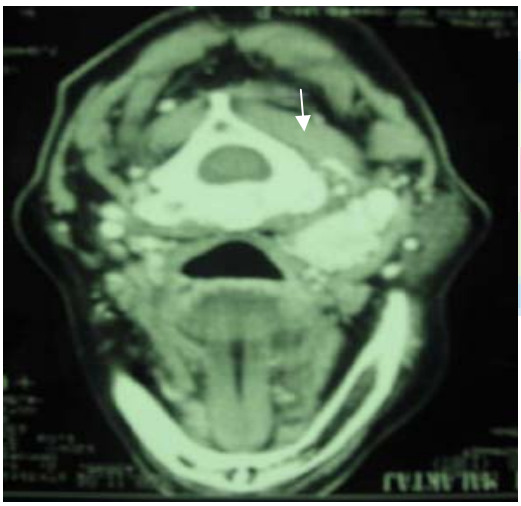

Figure 2. Neck CT scan shows thyromegaly and a mass (paraganglioma) in the right side (arrows).

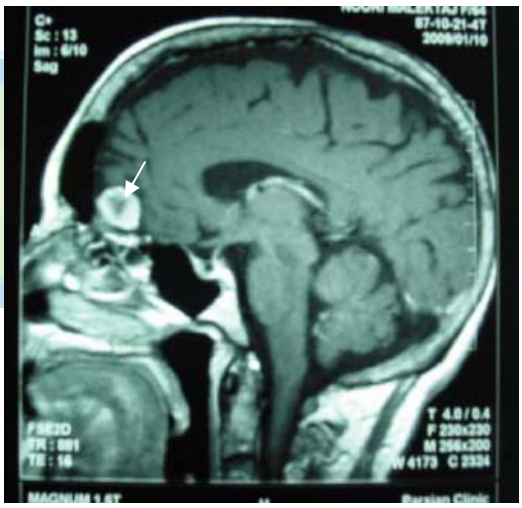

Figure 3. Brain MRI shows meningioma (arrow).

calcification besides the right parathyroid adenoma (Figure 2). Fine needle aspiration of the thyroid gland showed no malignant cells. In brain MRI, slightly enlarged pituitary gland and left subfrontal ovoid mass propounding of a meningioma (without suprasellar extension) were observed (Figure 3). Serum concentration of iPTH was elevated, which was compatible with the active parathyroid adenoma, hypercalcemia and hypophosphatemia. The thyroid function tests showed mild abnormality due to prolonged L-thyroxine therapy, and serum calcitonin level was slightly elevated that was non-specific as in various thyroid diseases. Serum creatinine, calcium and uric acid decreased to 1.12 and 5.4 mg/dL with proper hydration and diuresis. Upper gastrointestinal endoscopy was normal. Because of marked symptomatic hypercalcemia, renal dysfunction, diminished bone density in densitometry (> 2SD) and large multinodular thyroid gland with a dominant 30-mm nodule, the patient was scheduled for surgical resection of the para-

thyroid adenoma and subtotal thyroidectomy. During surgical resection, samples were sent for frozen sections to rule out malignancy, and they were negative. The pathologic report indicated parathyroid adenoma and benign hyperplastic thyroid tissue without malignancy. All pituitary hormone blood levels were within normal levels, except elevated prolactin.

Discussion

Absence of medullary thyroid carcinoma, the most common manifestation of MEN2 with approximately 100% penetrance, was excluded and the diagnosis in our patient was worked-up for MEN1.[9] The presence of two of the three main MEN1 tumor types in the patient, while no one of her family members was affected, indicated the sporadic variant of MEN1. The most important topic in this presentation is the imprudent prescription of the anti-depressant drugs for the patient by her psychiatrist with unawareness of hypercalcemia neuropsychiatric symptoms and inadequate diagnostic evaluation that resulted in a smoldering progression of hyperparathyroidism and hypercalcemia-induced ARF. A number of neuropsychiatric disturbances have been associated with hypercalcemia. The most common symptoms have been anxiety, depression and cognitive dysfunction. Improvement in some or all of these symptoms has been described after correction of the hyperparathyroidism.[10] The most important renal manifestations of hypercalcemia are nephrolithiasis, renal tubular dysfunction, particularly decreased concentrating ability, and acute and chronic renal insufficiency.[11] The development of renal insufficiency in primary hyperparathyroidism is related to the degree and duration of hypercalcemia. Mild hypercalcemia is only rarely associated with renal insufficiency. Severe elevations in the serum calcium concentrations (12–15 mg/dL) can lead to a reversible fall in the glomerular filtration rate that is mediated by direct renal vasoconstriction and natriuresis-induced volume contraction.[12] Long-standing hypercalcemia and hypercalciuria may result in the development of chronic hypercalcemic nephropathy, which may be irreversible, and continue to progress despite surgical cure of the hyperparathyroidism.[11] Calcification, degeneration and necrosis of the tubular cells leads to cell sloughing and eventual tubular atrophy and interstitial fibrosis and calcification (nephrocalcinosis), which can be detected by imaging studies and reflects severe renal parenchymal involvement.[11] It is important to remember that prompt diagnosis and proper management of hypercalcemia in our present case resulted in renal function improvement. After surgical operation, the patient was euthyroid and eucalcemic without any early or late complications detected in the follow-up evaluations.

References

1. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001; 86:56-8.
2. Glascock JM, Canty SE. Multiple endocrine neoplasia type 1: fresh perspective on clinical features and penetrance. Surg Oncol 2002;11: 143.
3. Burgess JR, Shepherd JJ, Parameswaran V, et al. Spectrum of pituitary disease in multiple endocrine neoplasia type 1 (MEN 1): clinical, biochemical, and radiological features of pituitary disease in a large MEN 1 kindred. J Clin Endocrinol Metab 1996;81:2642.
4. Verges B, Boureille F, Goudet P, et al. Pituitary disease in MEN Type I (MEN1): Data from the France-Belgium MEN1 Multicenter Study. J Clin Endocrinol Metab 2002; 87:457.
5. Padberg B, Schröder S, Capella C, et al. Multiple endocrine neoplasia type 1 (MEN1) revisited. Virchows Arch 1995;426:541.
6. Thomas-Marques L, Murat A, Delemer B, et al. Prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. Am J Gastroenterol 2006;101:266.
7. Wamsteker EJ, Gauger PG, Thompson NW, Scheiman JM. EUS Detection of Pancreatic Endocrine Tumors in Asymptomatic Patients with Type 1 Multiple Endocrine Neoplasia. Gastrointest Endosc 2003;58:531.
8. Pipeleers-Marichal M, Somers G, Willems G,

et al. Gastrinomas in the duodenums of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. N Engl J Med 1990;322:723.
9. Gagel RF, Hoff AO, Cote GJ. Medullary thyroid carcinoma. In: Werner and Ingbar's The Thyroid, 9th ed, Braverman LE, Utiger, RD (Eds), Lippincott Williams Wilkins, Philadelphia 2005;967.
10. Solomon BL, Schaaf M, Smallridge RC. Psychologic symptoms before and after parathyroid surgery. Am J Med 1994;96:101.
11. Benabe JE, Martinez-Maldonado M. Hypercalcemic nephropathy. Arch Intern Med 1978; 138:777.
12. Levi M, Ellis MA, Bert T. Control of renal hemodynamics and glomerular filtration rate in chronic hypercalcemia. Role of prostaglandins, renin-angiotensin system, and calcium. J Clin Invest 1983;71:1624.