Thiazide Therapy and Severe Hypercalcemia in a Patient With Hyperparathyroidism

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THIAZIDE DIURETICS can precipitate hypercalcemia in patients predisposed to this condition, such as those with primary hyperparathyroidism,[1,2] and can transiently elevate serum calcium levels in normal subjects.[3] Mild to moderate hypercalcemia has developed in patients receiving this type of medication. We describe the case of a patient who presented with severe hypercalcemia, electrocardiographic changes suggesting acute myocardial ischemia, and renal insufficiency following the institution of antihypertensive therapy with a combination of hydrochlorothiazide and triamterene. Symptomatically, the patient had a remarkable tolerance for severe hypercalcemia. In other respects, the case illustrates the typical manifestations of hypercalcemia involving multiple organ systems.

Report of a Case

The patient, a 61-year-old Iranian man, was brought to the emergency department by his family because of an inability to walk and was found to have a serum calcium level of 4.52 mmol per liter (18.1 mg per dl). Four months before admission, the patient immigrated to the United States. During a screening examination, he was told that he had hypertension and a large heart, and a regimen of methyldopa and digoxin was started. At a refugee health clinic ten weeks before admission, his calcium level was noted to be 2.69 mmol per liter (10.8 mg per dl), and he was referred to the hospital outpatient department for further evaluation. He was seen six weeks before admission, still hypertensive. The methyldopa dosage was increased, and the digoxin therapy was discontinued. Serum chemistry tests at that time revealed a calcium level of 2.72 mmol per liter (10.9 mg per dl), phosphate 0.45 mmol per liter (1.4 mg per dl), urea nitrogen 4.64 mmol per liter (13 mg per dl), and creatinine 106 μmol per liter (1.2 mg per dl). The patient was seen by a different provider 10 days before admission, at which time his medical records could not be located. The methyldopa therapy was discontinued, and a regimen of hydrochlorothiazide-triamterene (25 mg of hydrochlorothiazide and 50 mg of triamterene per day) was started. The patient became increasingly weak and, according to his family, somewhat confused. He began to have pain in the knees and ankles during this period.

On the day of admission, the patient's joint pain was severe enough to interfere with ambulation. In the emergency department, he complained only of constipation. His serum calcium level, as mentioned, was 4.52 mmol per liter, with a phosphate level of 1.42 mmol per liter (4.4 mg per dl). Hematologic studies showed a hemoglobin of 10.7 mmol per liter (17.2 grams per dl), hematocrit of 0.52, and a leukocyte count of 10.6×10^9 per liter. Serum chemistry tests showed a sodium level of 131 mmol per liter, potassium 3.2 mmol per liter, chloride 88 mmol per liter, bicarbonate 24 mmol per liter, urea nitrogen 22.1 mmol per liter (62 mg per dl), creatinine 336 μmol per liter (3.8 mg per dl), and glucose 11.8 mmol per liter (213 mg per dl). The uric acid level was 363 μmol per liter (6.1 mg per dl). Urinalysis showed a specific gravity of 1.010, a pH of 5, 1+ protein but no glucose or ketones, and no bacteria or cellular elements. The chest x-ray film showed a calcified nodule in the upper lobe of the left lung versus a calcified end of rib. The electrocardiogram (Figure 1-A) showed a mild sinus tachycardia with first-degree atrioventricular block, a QT interval that was short for the rate, and an early peaking T wave mimicking ST-segment elevation in leads V_2 through V_5.

The patient was admitted to the medical intensive care unit and started on a program of vigorous intravenous hydration and furosemide, together with etidronate, 1,600 mg orally per day for three days. The combination diuretic agent was stopped, and the patient's hypertension was controlled with nifedipine. After an initial rise to 5.06 mmol per liter (20.3 mg per dl), his calcium level fell to 3.64 mmol per liter (14.6 mg per dl) over the next three days. There was no initial improvement in his renal function. The electrocardiogram (Figure 1-B) continued to show a short QT interval with lessening of the ST-segment elevation. There was no enzymatic evidence for a myocardial infarction.

Plain abdominal x-ray films showed normal-sized kidneys and no abnormal calcifications. He subsequently had a normal abdominal computed tomographic (CT) scan. A chest CT scan showed minimal scarring in the left upper lobe of the lung with no abnormal calcifications, no mediastinal widening, and no hilar adenopathy. Skin tests for tuberculosis and coccidioidomycosis were negative with positive controls. A bone scan showed increased uptake in both knees and ankles consistent with osteoarthritis; in addition, a broad band of increased uptake with indistinct borders was noted in the occipitoparietal region of the skull. Skull films were normal. The results of serum and urine protein electrophoresis studies were normal. Thyroid function test values were normal.

On the fourth hospital day, the patient was given plicamycin (previously called mithramycin), 25 μg per kg of body weight by vein over eight hours. The serum calcium level decreased to 2.7 mmol per liter (10.8 mg per dl) the following morning. Over the next four days, the calcium concentrations varied between 2.74 and 3.02 mmol per liter (11 and 12.1 mg per dl) while the patient was placed on a regimen of oral hydration and furosemide. The phosphate value remained within the normal range. There was modest improvement in renal function. Pain in the knees and ankles worsened and interfered with ambulation; pain, swelling, and decreased range of motion of the wrists began on the seventh hospital day. Knee and ankle films showed chondrocalcino-

(Strong P, Jewell S, Rinker J, Hoch D, Crapo L: Thiazide therapy and severe hypercalcemia in a patient with hyperparathyroidism. West J Med 1991 Mar; 154:338-340)

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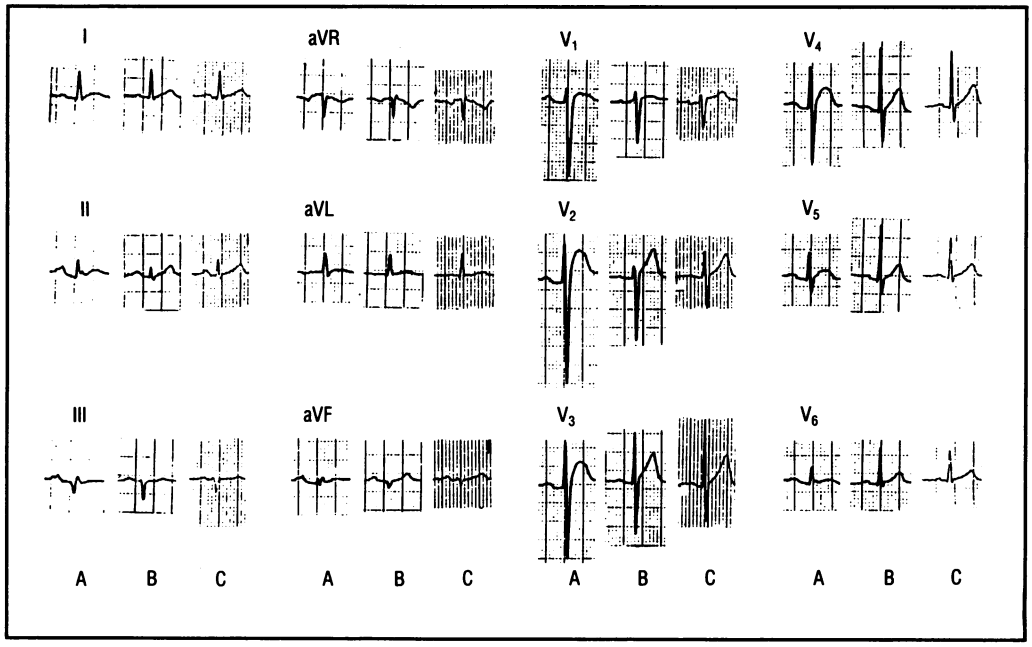

Figure 1.—A, The strips are from an electrocardiogram (ECG) taken on admission, when a serum calcium level was 4.52 mmol per liter (18.1 mg per dl). **B,** The ECG was taken 6 days later, when the calcium level was 2.6 mmol per liter (10.6 mg per dl). **C,** Four months after admission, the patient had a normal calcium value.

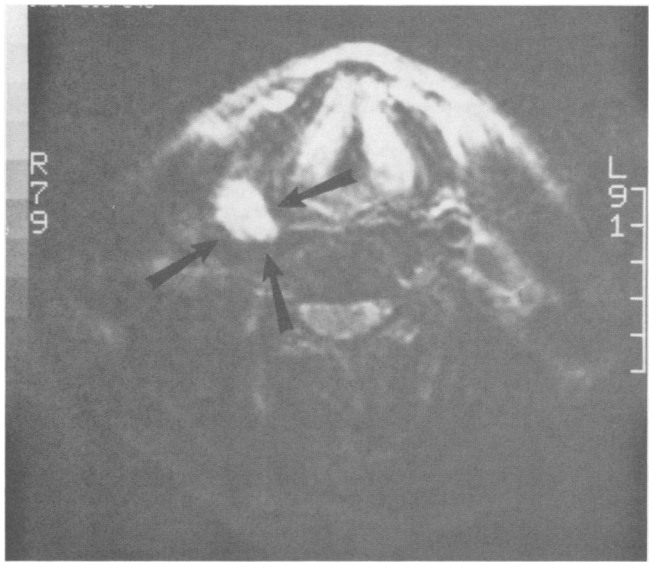

Figure 2.—An axial T2-weighted (TE = 80, TR = 2,800) magnetic resonance image of the neck shows high signal emanating from a large parathyroid adenoma **(arrows).**

sis, and there were small bilateral knee effusions. Wrist films were normal. A small amount of fluid removed from the left knee revealed minimal inflammation and no crystals.

On the tenth hospital day, the parathyroid hormone level, determined by immunoradiometric assay, was reported to be 1,040 ng per dl (upper limit of normal <65). The surgery service was consulted. Preoperative magnetic resonance imaging of the neck revealed a 2-cm mass adjacent to the thyroid gland consistent with a parathyroid lesion (Figure 2). At the operation, a 2- by 3-cm parathyroid adenoma was removed. After the operation, the patient's calcium level remained within the normal range; renal function steadily improved, with a serum creatinine level of 177 μmol per liter (2 mg per dl) before discharge; ambulation became less painful. The patient was discharged on the 18th hospital day.

Discussion

The three most common causes of hypercalcemia are hyperparathyroidism, accounting for 70% of cases in asymptomatic outpatients[4] and perhaps 20% of inpatient cases[5]; tumors, accounting for approximately 50% of inpatient cases[5]; and vitamin D-mediated conditions, such as hypervitaminosis D and sarcoidosis. Less common causes, accounting for fewer than 25% of cases, include other granulomatous diseases, immobilization, thyrotoxicosis, the milk-alkali syndrome, Addison's disease, vitamin A intoxication, the acquired immunodeficiency syndrome, Paget's disease, parenteral nutrition, rhabdomyolysis, and drug use—most notably thiazides, but also lithium,[6] theophylline,[7] and aspirin.[8]

Thiazides are thought to cause persistent hypercalcemia only in the presence of certain underlying conditions. Thiazide therapy for more than a few weeks' duration enhances distal tubular calcium reabsorption in the kidney, which results in hypocalciuria. In normal subjects, able to respond with appropriate, effective decreases in parathyroid hormone secretion, at most a transient mild increase in serum calcium levels can be observed. In patients for whom increased urinary calcium excretion plays a more important role in calcium homeostasis, persistent hypercalcemia can occur. It has been suggested that immobilization, Paget's disease, high-dose vitamin D therapy, and hyperparathyroidism can predispose patients to thiazide-induced hypercalcemia in this way.[9] Of these, only hyperparathyroidism has been clearly documented to have this effect.[10] In previously reported cases, mild to moderate hypercalcemia (2.7 to 3.5 mmol per liter [11 to 14 mg per dl]) was observed.

While the patient in this report was known to be taking a thiazide-containing diuretic, the nature of the predisposing condition was not initially clear. On admission, the normal serum phosphate value, the markedly elevated serum calcium level, the (questionable) left upper lobe nodule on a chest film, and the mild proteinuria seemed most suggestive of malignancy. The low phosphate level a month before

admission, however, was a major clue to the diagnosis of hyperparathyroidism, confirmed during the subsequent evaluation.

Severe hypercalcemia can cause electrocardiographic abnormalities. Arrhythmias and QT interval shortening are typical. There is another report of a patient who had extreme hypercalcemia—serum calcium level of 21.8 mg per dl—with ST-segment elevations in the precordial leads as seen in the present case.[11] The mechanism of this effect is unknown.

This is the most severe case of thiazide-induced hypercalcemia that we have seen reported. Shortly after admission, the patient had a strikingly elevated parathyroid hormone level. We speculate that before the thiazide therapy was instituted, the patient was near the limit of his ability to compensate for his extreme parathyroid autonomy, and the diuretic precipitated a dramatic decompensation. Other factors probably contributed to this patient's pronounced hypercalcemia, however.

Studies in animals have shown that potassium-sparing diuretics (including triamterene) decrease the ratio of calcium to sodium clearance in the kidney.[12] Amiloride, in particular, has an effect that is additive to that of chlorothiazide (suggesting an independent mechanism of action). This patient was taking a combination hydrochlorothiazide-triamterene diuretic. While we know of no studies that specifically show an additive effect of triamterene or that document a clinically important effect of potassium-sparing diuretics on calcium in humans, this may have contributed to the marked hypercalcemia noted here.

The relationship between serum calcium levels and the kidneys is complex. Hypercalcemia can impair renal function by several mechanisms.[13,14] Calcium is thought to have a direct vasoconstrictive effect on renal vasculature capable of reducing the glomerular filtration rate. Calcium has been shown to alter electrical forces in the renal ultrafiltration barrier, also contributing to a decreased glomerular filtration rate. Calcium inhibits the sodium-potassium adenosine triphosphatase level in the distal renal tubules, which can cause decreased active salt resorption and volume depletion. It also reduces renal cyclic adenosine monophosphate activity, which can cause decreased antidiuretic hormone activity and nephrogenic diabetes insipidus. Conversely, extracellular volume depletion aggravates hypercalcemia. The resulting increased renal avidity for sodium is thought to increase calcium reabsorption in the proximal renal tubules.[15] While we know of no studies specifically documenting this effect, the potential exists for a vicious cycle that may also have contributed to the pronounced hypercalcemia in this case.

In conclusion, this patient had a preexisting parathyroid adenoma and mild hypercalcemia and received combination antihypertensive therapy with hydrochlorothiazide-triamterene. After several weeks, severe hypercalcemia developed that required intensive management. This illustrates the possible danger that thiazide therapy poses to patients with hyperparathyroidism and possibly several other hypercalcemic conditions. It suggests that screening patients for hypercalcemia before initiating thiazide treatment may be indicated.

REFERENCES

1. Klimiuk PS, Davies M, Adams PH: Primary hyperparathyroidism and thiazide diuretics. Postgrad Med J 1981; 57:80-83

2. Parfitt AM: Chlorothiazide-induced hypercalcemia in juvenile osteoporosis and hyperparathyroidism. N Engl J Med 1969; 281:55-59

3. Duarte CG, Winnacker JL, Becker KL, Pace A: Thiazide-induced hypercalcemia. N Engl J Med 1971; 284:828-830

4. Palmér M, Jakobsson S, Akerström G, Lunghall S: Prevalence of hypercalcemia in a health survey: A 14-year follow-up of serum calcium values. Eur J Clin Invest 1988; 18:39-46

5. Dent DM, Miller JL, Klaff L, Barron J: The incidence and causes of hypercalcemia. Postgrad Med J 1987; 63:745-750

6. Mallette LE, Eichhorn E: Effect of lithium carbonate on human calcium metabolism. Arch Intern Med 1986; 146:770-776

7. McPherson ML, Prince SR, Atamer ER, Maxwell DB, Ross-Clunis H, Estep HL: Theophylline-induced hypercalcemia. Ann Intern Med 1986; 105:52-54

8. Re IR: Transient hypercalcemia following overdoses of soluble aspirin tablets. Aust NZ Med J 1985; 15:364

9. Field MJ, Lawrence JR: Complications of thiazide diuretic therapy: An update. Med J Aust 1986; 144:641-644

10. Christensson T, Hellström K, Wengle B: Hypercalcemia and primary hyperparathyroidism—Prevalence in patients receiving thiazides as detected in a health screen. Arch Intern Med 1977; 137:1138-1142

11. Douglas PS, Carmichael KA, Palevsky PM: Extreme hypercalcemia and electrocardiographic changes. Am J Cardiol 1984; 54:674-675

12. Costanzo LS, Weiner IM: Relationship between clearances of Ca and Na: Effects of distal diuretics and PTH. Am J Physiol 1976; 230:67-73

13. Benabe JE, Martinez-Maldonado M: Hypercalcemic nephropathy. Arch Intern Med 1978; 138:777-779

14. Fellner SK, Spargo BH: Nephrotic syndrome from hypercalcemia in a patient with primary hyperparathyroidism. Am J Med 1987; 83:355-358

15. Garrick R, Goldfarb S: Differential diagnosis and pathophysiologic effects of hypercalcemia. Am J Kidney Dis 1989; 13:160-163