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Case Report

Renal Papillary Necrosis Associated With Normocalcemic Primary Hyperparathyroidism

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ABSTRACT

Objectives: Renal papillary necrosis (RPN) occurring in primary hyperparathyroidism (PHPT) has not been reported. We present a 50-year-old woman who manifested RPN associated with hypercalciuria and normocalcemic PHPT.
Methods: The diagnosis of RPN was based on imaging studies (ultrasound and computed tomography [CT] scan). PHPT was diagnosed with high parathyroid hormone (PTH) and high/normal serum calcium.
Results: A 38-year-old woman was evaluated for hypercalcemia (serum calcium, 11.8 mg/dL; ionized calcium, 6.3 mg/dL; phosphorus, 1.8 mg/dL; intact PTH, 98 pg/mL; and 24-hour urine calcium, 543 mg). Renal ultrasound showed no nephrocalcinosis or nephrolithiasis. A parathyroid scan revealed a left parathyroid adenoma. The patient underwent parathyroidectomy, and she became normocalcemic with normal serum PTH levels postoperatively. One year later, she was diagnosed with a left-sided bronchial carcinoid tumor. Following surgery, a surveillance gallium[68] positron emission tomography/CT scan performed 2 years later was negative for metastases. Twelve years later (aged 50 years), she presented for follow-up and reported no symptoms of hypercalcemia, fractures, nephrolithiasis, history of pyelo-nephritis, diabetes mellitus, analgesic drug use, or hypertension. Her serum calcium level was 9.1 mg/dL, PTH level was 82 pg/mL, 25-OH vitamin D level was 34 ng/mL, and 24-hour urine calcium level was 410 mg. However, renal ultrasound showed bilateral RPN that was confirmed by a CT scan.
Conclusion: RPN may be associated with hypercalciuria and normocalcemic PHPT. Additional studies with a large number of patients are needed.

Introduction

Primary hyperparathyroidism (PHPT) due to the autonomous secretion of parathyroid hormone (PTH) is considered the most common cause of hypercalcemia in ambulatory patients. The clinical features of PHPT have changed over time, from symptomatic disease, with bone pain, fractures, nephrolithiasis, and muscle weakness, to mainly asymptomatic patients. Commonly described renal manifestations in PHPT include hypercalciuria, nephrolithiasis, nephrocalcinosis, chronic renal insufficiency, and renal tubular dysfunction.[1–5] Here, we report a 50-year-old woman who manifested renal papillary necrosis (RPN) associated with hypercalciuria and normocalcemic PHPT 12 years after surgical resection of a parathyroid adenoma and apparent cure.

A literature search was conducted using the PubMed and Google Scholar databases for diagnosis and management of RPN and normocalcemic hyperparathyroidism.

The diagnosis of RPN was based on imaging studies (ultrasound and computed tomography [CT] scan). Laboratory testing was performed to diagnose PHPT. A dual-energy X-ray absorptiometry (DXA) scan was performed using a Discovery DXA System (Hologic). A UroRisk Diagnostic Profile was performed by Quest Diagnostics.

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A 38-year-old Caucasian woman was seen for evaluation of PHPT. She had no family history of fractures, renal stones, or

Table 1
Results of UroRisk Diagnostic Profile

Laboratory tests	Laboratory results (24 h)	Reference values
Urine volume (mL)	2575	600-1600
Calcium (mg)	410	100-250
Creatinine (mg)	927	800-1300
Sodium (mmol)	131	39-258
Phosphorus (mg)	765	400-1300
Uric acid (mg)	408	250-750
Potassium (mmol)	39.7	25-125
Chloride (mmol)	121	110-250
Citrate (mg)	901	320-1240
Magnesium (mg)	129	12-293
Sulfate (mg)	23	0-30
Cystine (mg)	9.9	24-184

The UroRisk diagnostic profile was performed by Quest Diagnostics.
Additional 24-hour urine calcium values were as follows: volume, 2130-2790 mL; calcium, 370-511 mg; creatinine, 892-993 mg; and calculated calcium excretion, 6.1 mg/kg (normal <3.5 mg/kg).

Table 2
Results of the DXA Scan Performed When the Patient Was 50 Years-Old

Location	T-score	Z-score
Lumbar spine	0.7	1.0
Total hip	0.1	0.5
Femoral neck	0.9	1.3
Distal one third of the radius	0.5	1.3

The bone mineral density was determined using a Discovery DXA System (Hologic).

symptoms of hypercalcemia. At this time, the laboratory values were as follows: serum calcium, 11.8 mg/dL (range, 10.9-12.1; normal, 8.4-10.2); ionized calcium, 6.3 mg/dL (range, 6.1-6.8; normal, 4.8-5.6); phosphorus, 1.8 mg/dL (range, 1.4-2.0; normal, 2.5-4.5); intact PTH, 98 pg/mL (range 92-131; normal, 15-65), and 24-hour urine calcium, 543 mg/dL (range, 476-568; normal < 3.5 mg/kg). A parathyroid sestamibi scan revealed a left superior parathyroid adenoma. Renal ultrasound showed no evidence of nephrocalcinosis or nephrolithiasis. Immediately following parathyroid adenoma resection, serum PTH level dropped to 12 pg/mL, and the patient became eucalcemic with normal serum PTH and normal 24-hour urine calcium levels. Histology confirmed parathyroid adenoma with no evidence of hyperplasia. One year postoperatively, she was diagnosed with a left-sided bronchial carcinoid tumor, and this was successfully resected. Serial computed axial tomography of the chest and gallium[68] positron emission tomography/CT scan results were negative for metastasis. The pituitary evaluation was normal, and a DXA scan was not performed at this time. The patient remained eucalcemic, with normal serum PTH and normal 24-hour urine calcium levels for the next 10 years. During this 10-year period, the laboratory values were as follows: serum calcium, 9.3 mg/dL (range, 8.9-9.7); phosphorus, 3.2 mg/dL (range, 3.1-4.3); PTH, 42 pg/mL (range, 32-58 pg/mL); and 24-hour urine calcium, 134 mg (range, 118-189). However, the patient did not undergo any laboratory tests for the next 2 years. She had no history of hypertension, analgesic drug abuse, urinary tract infections, or diabetes mellitus. Twelve years later, at the age of 50 years, a follow-up laboratory panel showed a serum calcium level of 9.1 mg/dL, phosphorus level of 3.8 mg/dL, PTH level of 82 pg/mL, 25-OH vitamin D level of 34 ng/mL (normal, 30-50), and 1,25(OH)$_2$ D level of 38 pg/mL (normal, 21-65). A neck ultrasound showed two 7-mm lesions inferior to the right thyroid lobe, likely representing parathyroid adenomas, and these lesions were not seen in the scan. However, the parathyroid scan showed an uptake in the left upper pole, suggesting a possible parathyroid adenoma. A UroRisk diagnostic profile was normal, except for 24-hour urine calcium level of 410 mg (Table 1). A DXA scan (Hologic) was also normal (Table 2). Renal ultrasound showed bilateral RPN, and this diagnosis was confirmed by a CT scan (Fig. A and B). Urinalysis showed microalbuminuria with no red blood cells or casts. A repeat urine microalbumin test's result was negative. A glucose tolerance test's and sickle cell screen's results were normal.

Discussion

In PHPT, high levels of PTH lead to increased renal absorption of calcium, hypercalciuria, phosphaturia, and increased synthesis of 1,25(OH)$_2$ D. This disorder is also associated with increased resorption of bone and increased intestinal calcium absorption. The classical clinical manifestations of PHPT include osteoporosis, increased risk of fractures, and renal manifestations, such as hypercalciuria, nephrolithiasis, nephrocalcinosis, chronic renal insufficiency, and renal tubular dysfunction.[1–5]

Multiple endocrine neoplasm 1 (MEN-1) is characterized by benign or malignant tumors of the parathyroid glands, pancreatic cells, and pituitary gland and is rarely associated with carcinoid tumors. In contrast with the normal midgut and hindgut organ, most carcinoid tumors in MEN-1 are of foregut origin, and approximately 30% of patients with them have bronchial carcinoids. Most patients with carcinoid tumors and hyperparathyroidism have parathyroid hyperplasia or multiple parathyroid adenomas.[6–10] Our patient had a history of bronchial carcinoid tumors occurring in association with PHPT. She had no family history of MEN-1, her pituitary functions were normal, and she had a negative screening test result for the MEN1 gene. However, the recurrence of hyperparathyroidism, although normocalcemic, raises the possibility of MEN-1. Eller-Vainicher et al[9] studied patients with PHPT to identify clinical or biochemical features predictive of MEN-1. These investigators reported that patients with MEN-1 and PHPT had lower serum phosphorus and PTH levels and lower bone density scores at the lumbar spine and femur neck than sporadic PHPT patients. They concluded that serum PTH levels in the normal range plus an age <50 years old were strongly associated with MEN-1. Although our patient was aged 50 years, she had elevated serum PTH levels and also had normal bone mineral density. It should be noted that it is difficult to apply the criteria of these investigators to an individual patient. However, it is possible that our patient has a new MEN-1 mutation that is not identified by the present testing methods.

Normocalcemic PHPT is a variant of hyperparathyroidism characterized by persistently normal serum calcium levels, high PTH, and normal serum 25-OH vitamin D status.[11–13] Tuna et al[11] studied patients with normocalcemic PHPT and found no significant differences in terms of age, gender, hypertension, low bone mineral density, and nephrolithiasis and concluded that normocalcemic PHPT had hyperparathyroid-related complications similar to hypercalcemic PHPT. Schini et al[12] studied 11 patients with normocalcemic PHPT and noted that only 4 had persistently normal serum calcium levels, whereas the remaining 7 had intermittently elevated serum calcium levels. In normocalcemic PHPT, multiglandular disease may be more common, as seen in our patient. A neck ultrasound performed at our institution showed two 7-mm lesions inferior to the right thyroid lobe, likely representing parathyroid adenomas, and these lesions were not seen in the scan. Although the scan localized in the left upper pole, it is possible that an adenoma developed in postsurgical remnant tissues 12 years later. Small cohorts of patients with normocalcemic PHPT responded similarly to those with hypercalcemic PHPT with regard to the medical and surgical approaches.[13] Our patient presently has normocalcemic PHPT and hypercalciuria. Although she was offered surgery, she preferred continued follow-ups.
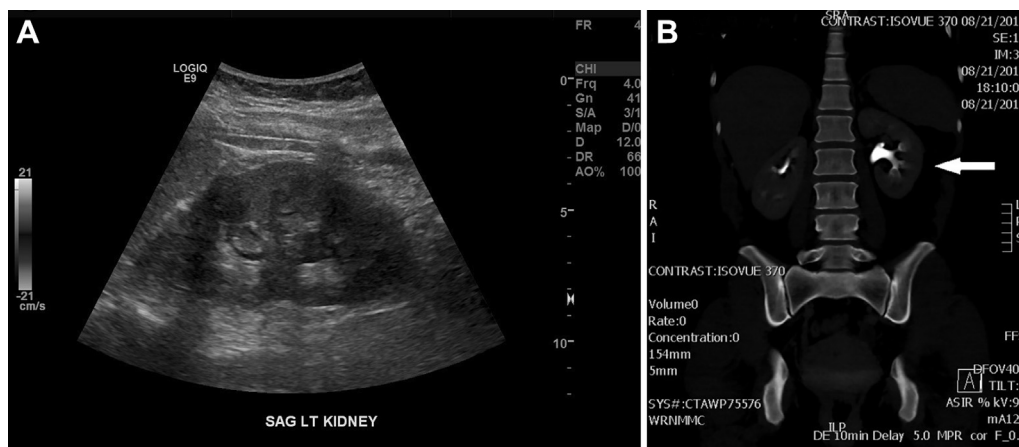
Fig. *A*, Renal ultrasound showed bilateral renal papillary necrosis. *B*, Computed tomography scan confirming renal papillary necrosis (arrow).

RPN is considered a sequela to ischemia occurring in the renal papillae and medulla. The ischemia may be caused by several factors. The vasculature supplying the renal medulla can become compressed, attenuated, or impaired from other associated diseases, such as diabetes mellitus, urinary tract obstruction, and analgesic nephropathy.[14—16]. RPN is usually a bilateral process, as is expected in systemic diseases. RPN may occur unilaterally when the predisposing factor is an infection or obstruction. Nearly 90% of cases occur in individuals aged 40 years or older.[3] Other causes of RPN include sickle cell hemoglobinopathy, analgesic nephropathy, and other factors. RPN may be characterized by periods when the patient is completely asymptomatic but may present with gross hematuria with or without flank pain, often mimicking renal colic. Our patient had no history of analgesic drug use, including nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors, chemotherapy, or systemic diseases causing RPN. Diabetes mellitus was ruled out by a normal glucose tolerance test and hemoglobin A1C level. She had a negative sickle cell screening. Additionally, she had no history of hematuria, renal colic, or urinary tract infections. Thus, it was concluded that in our patient, there was an association between normocalcemic PHPT with hypercalciuria and RPN. In our patient, it is interesting to note that results from the initial ultrasound of the kidneys were normal, although radiologic imaging done 12 years later showed RPN when the patient had normocalcemic PHPT with hypercalciuria. Although nephrocalcinosis and nephrolithiasis are known to occur in PHPT, our patient did not demonstrate these on radiologic imaging. In nephrocalcinosis, calcium phosphate deposits may occur in the renal tubules and or renal parenchyma, and in the early stages, microscopic deposition of calcium oxalate or phosphate may not be visible on radiologic imaging. Additionally, it is unclear whether calcium deposition can cause renal ischemia. It is also possible that these could be unassociated. Generally, in patients with PHPT and normal baseline renal imaging, follow-up studies are not often performed, and hence, RPN may be underdiagnosed in these patients.

Thiazides are used to treat idiopathic hypercalciuria; however, these drugs were avoided in PHPT owing to concern for exacerbating hypercalcemia. Recent studies have shown the beneficial effects of thiazide in PHPT.[17—20] Tsvetov et al[17] studied 72 patients with inoperable PHPT and showed that hydrochlorothiazide was effective in controlling hypercalciuria and also lowered serum PTH levels. Although serum calcium levels remained normal during thiazide treatment, it was recommended to monitor for hypercalcemia. Stein et al[18] also concluded that thiazide treatment lowered serum PTH in patients with PHPT. However, Rejnmark et al[19] demonstrated that thiazide increased serum PTH levels in patients with PHPT, whereas Riss et al[20] concluded that during thiazide administration, serum PTH levels did not show any changes. It is also recommended that serum 25-OH vitamin D is repleted in all patients to a minimum level of 20 ng/mL.[2] Thiazide administration may lower urine citrate levels, which may increase the risk for calcium oxalate nephrolithiasis.[19,20] A UroRisk Diagnostic Profile confirmed hypercalciuria occurring in association with RPN in our patient. However, the urine citrate level was normal. The patient was counseled regarding thiazide treatment, but she refused the treatment.

Conclusion

In conclusion, we reported a patient with RPN occurring in association with normocalcemic PHPT and hypercalciuria. Additional studies involving a large number of patients are needed.

Disclosure

The authors have no multiplicity of interest to disclose. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of the Navy, Department of Defense, or the U.S. Government.

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