Bilateral Nephrolithiasis caused by Primary Hyperparathyroidism: A Case Report

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Abstract
Nephrolithiasis is one of the most common urologic condition, which is now likely to increase in time and become a burden on the health care system. Primary hyperparathyroidism (PHPT) is a disorder of calcium, phosphate, and bone metabolism due to the increase of parathyroid hormone (PTH). The incidence of PHPT is about three times higher in females than in males, approximately 66 cases per 100,000 person-years in females. This case report describes a 62-year-old woman presented with bilateral nephrolithiasis with urinary tract infection. We investigate further the cause of bilateral nephrolithiasis and hypercalcemia was detected, which then led us to diagnose primary hyperparathyroidism as the cause.

Keywords: Bilateral nephrolithiasis, primary hyperparathyroidism.

Introduction
Primary hyperparathyroidism (PHPT) is a disorder of calcium, phosphate, and bone metabolism due to the increase of parathyroid hormone (PTH).1 The incidence of PHPT is higher in females than in males. The incidence in the United States (US) is approximately 66 cases per 100,000 person-years in females and 25 cases per 100,000 person-years in males.2 The incidence is rising with advancing age.3 About 5-60% of PHPT presenting with nephrolithiasis, whether symptomatic or asymptomatic.4,5 Beside renal involvement, PHPT can manifest on bone, gastrointestinal, cardiovascular, and neuropsychiatric.1,2 Renal calcification could happen in the renal parenchyma (nephrocalcinosis), renal pelvis (nephrolithiasis), and ureter (ureterolithiasis). Stone formation occurs because of multifactorial.6 Calcium stone is the most common renal stone, comprising about 80% of renal calculi.7 About 3% of 1,190 adults who underwent evaluation for renal stones had hyperparathyroidism. Hypercalcemia that manifests in hyperparathyroidism contributes as a primary risk factor for renal stone.2

This case report describes a 62-year-old woman with bilateral nephrolithiasis. She had hypercalcemia that led us to diagnose PHPT. This
case gives us a lesson that one of the causes of renal calculi is a metabolic disease, such as primary hyperparathyroidism.

**Case Illustration**

A 62-year-old woman came to our outpatient clinic with a chief complain of flank pain since 5 days before. Her other complaints included fever, nausea, and vomiting every taking a meal or drink. The amount of urine output was lesser. Neither dysuria, hematuria, nor crystalline urine was present.

On physical examination obtained, she looked moderate-sick with vital signs tachycardia (102 bpm), temperature 37.9 °C, and flank pain. Her tongue was dried with turgor decreased. Costovertebral angle (CVA) sign and ballottement test were positive on the right side. She was diagnosed with recurrent urinary tract infection, dehydration, and dyspepsia syndrome.

The patient was given rehydration via intravenous fluid, antiemetic, antipyretic, and analgesic. For the infection, she was given the third generation of cephalosporin. From the blood evaluation, there were leukocytosis (13,300/μL, normal: 5-10x10³/μL) and decreasing renal function (urea/creatinine: 56/1.8). From urinalysis, it is obtained a cloudy urine with hematuria (3+), pyuria (leukocyte 15-20/large field of view), and positive leukocyte esterase. She was hospitalized.

In the inpatient room, abdominal ultrasound was conducted and bilateral renal calculi were detected. Further evaluation of urology CT scan was conducted and bilateral nephrolithiasis was found. From serum evaluation, there were elevated calcium level (14.5 mg/dL, normal: 8.8-10.2 mg/dL), elevated PTH level (499.30 pg/ml, normal: 15-65 pg/ml), and depressed 25-hydroxyvitamin D level (12.2).

Diagnosis of PHPT was established in this case. Consultation to urologist was recommended for percutaneous nephrolithotomy (PCNL), but she refused. In the fifth day of hospitalization, her condition got better: the fever went down, she got her appetite back, and the flank pain vanished. Her leukocyte counts and renal function returned to normal range, and from urinalysis, it shown the urine was clear without hematuria or pyuria. After the seventh day of hospitalization, she was discharged.

Then, she came to the outpatient clinic to get a neck ultrasound examination, and there was not any enlarged parathyroid gland. She still refused to get surgical treatment and did not come back to be followed up until 1.5 years. She came back again with bilateral nephrolithiasis with infection and hydronephrosis. Surgical treatment was again recommended to her, but she still refused to get the treatment. So, she just got supportive and symptomatic treatment while being hospitalized and got discharged after her condition got better.

**Discussion**

All patients with renal calculi should undergo further evaluation to know the risk factors of stone formation, urinalysis, and stone analysis. We could analyze the risk factors from a urinalysis, including UTI, proteinuria, and stone components. All renal calculi patients should be evaluated for the components of the stone. Biochemical evaluation could help us identify specific disorders, such as primary hyperthyroidism. In this case, the patient had recurrent nephrolithiasis. The risk of recurrent nephrolithiasis in a year is 15% of the cases and in 10 years is up to 50% of the cases. Especially in patients with recurrent bilateral nephrolithiasis or nephrocalcinosis, it should be suspected for any systemic disorder, including metabolism disorder.

In this case, hypercalcemia and elevated parathyroid hormone were present in plasma. These conditions supported the diagnosis of PHPT. In PHPT, calcium level in plasma is elevated about 1 mg/dL above the upper limit of the normal range and the PTH is elevated about 2 times of upper limit of the normal range. Whereas, phosphate serum level is low or low-normal. Approximately 2-8% of nephrolithiasis is caused by PHPT. Out of patients with asymptomatic PHPT, 21-55% manifest renal calcification.
Elevated calcium excretion via renal caused by PHPT is an important risk factor for nephrolithiasis.\textsuperscript{12} PTH will stimulate bone resorption, releasing calcium and phosphate to circulation, and activate 1-alpha-hydroxylase enzyme in renal proximal tubules, which in turn converts 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D-3 (calcitriol) which promotes reabsorption of calcium and phosphate in intestines.\textsuperscript{14} Accordingly, it has been suggested that synthesis of calcitriol may be higher in younger patients with higher renal mass than elderly patients, thereby causing a higher intestinal calcium absorption with a more pronounced hypercalciuria and a higher risk of renal stones.\textsuperscript{12} Besides, PTH also increases calcium reabsorption and decreases phosphate reabsorption in renal. Overall, these actions of PTH increase calcium concentration in circulation which in turn increase the renal excretion of calcium.\textsuperscript{14} It should be noted that PTH actions are modulated by calcium-sensing receptor (CaSR), magnesium (Mg), and other cations that activate CaSR.\textsuperscript{12,14} The polymorphism of gene which codes CaSR can be a risk factor for renal calculi in PHPT.\textsuperscript{12} The patient, in this case, addition to hypercalcemia, had signs of dehydration and UTI which enhanced the risk for nephrolithiasis.\textsuperscript{7}

Further evaluation that should be done is imaging of parathyroid gland. In this case, the patient underwent an ultrasound evaluation of the neck, but abnormality was not found. Ultrasound is a non-invasive and cheapest examination that can visualize parathyroid tissue and allows concomitant evaluation of thyroid pathology. It has a sensitivity range from 42-82% and specificity of approximately 90%. Other imaging modalities that could be done are Sestamibi scan, neck and mediastinum CT scan, or arteriography.\textsuperscript{14} In this case, advanced imaging evaluation was not conducted because the patient refused to undergo surgical treatment. No abnormality was found from ultrasound evaluation. Nonetheless, the diagnosis of primary hyperparathyroidism is based on biochemical findings and is not affected by the result of imaging studies.

The American Association of Endocrine Surgeons Guidelines strongly recommend parathyroidectomy as definite treatment of symptomatic PHPT (high-quality evidence), when calcium serum level is more than 1mg/dL above upper limit of normal range with or without objective symptoms (low-quality evidence), and of the patients who are diagnosed when 50 years old or above with or without objective or subjective symptoms (moderate-quality evidence).\textsuperscript{15} In this case, the patient had strong indications for undergoing surgical treatment, but she refused. Medical treatments that could be given to patients having no indication for or refusing surgical treatment are supplementation of vitamin D to maintain vitamin D level within the normal range, bisphosphonate to increase bone mass density, and calcimimetics to lower calcium serum level.\textsuperscript{14}

**Conclusion**

Primary hyperparathyroidism is an endocrine problem with various clinical presentation, one of which is nephrolithiasis. Patients diagnosed with nephrolithiasis, especially recurrent bilateral nephrolithiasis, has to be further explored about the cause of the stone formation, particularly metabolic disorders. By knowing the underlying disease, the patients could be treated promptly, thereby nephrolithiasis will not occur again nor other complications.

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