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Case Report

First Reported Case of a Pyrophosphate Kidney Stone in a Human

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Keywords
Nephrolithiasis · Hypophosphatasia · Metabolic bone disease · Genetic disease · Alkaline phosphatase

Abstract
Urolithiasis composed of pyrophosphate salts has only been reported in animals, in the form of potassium magnesium pyrophosphate. However, there have been no reports of pyrophosphate stones in humans. Hypophosphatasia is an inherited disease characterized by low alkaline phosphatase activity and elevated levels of pyrophosphate in blood and urine. Urolithiasis is a part of the hypophosphatasia phenotype. The role of elevated urine pyrophosphate levels in the formation of stones in hypophosphatasia is unknown. Here, we report a case of a 60-year-old man with recurrent urolithiasis. The patient's most recent presentation was gross hematuria and his computed tomography scan showed bilateral kidney stones. Stones were removed via retrograde intrarenal surgery. Stone analysis revealed a composition of potassium magnesium pyrophosphate. The patient also has a long history of fracturing bone disease which led to the consideration of hypophosphatasia as the cause of both his bone disease and pyrophosphate stones. Hypophosphatasia was confirmed by genetic analysis. Pyrophosphate has been of interest in the fields of mineral metabolism because of its action as a crystallization inhibitor. However, pyrophosphate at elevated concentrations in the presence of divalent cations can exceed its solubility. Nephrocalcinosis and stone disease have been described in hypophosphatasia; stones have been assumed to be calcium phosphate but no compositional analysis has been reported. This is the first report of human stones composed of pyrophosphate salts, which led to the subsequent diagnosis of hypophosphatasia in this patient.

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Introduction

Inorganic pyrophosphate (PPi) is a normal constituent of both blood and urine in humans. It functions as an inhibitor of calcium salt crystallization. In vitro studies have shown PPi capable of inhibiting both hydroxyapatite and calcium oxalate crystallization [1]. Systemic PPi levels are carefully regulated in humans. Low PPi levels are associated with soft-tissue deposition of calcium phosphate salts, particularly in the vasculature, cartilage, and kidney [2]. High PPi blood levels, such as might be seen in hypophosphatasia (HPP), can lead to inadequate mineralization of teeth and bones [3, 4]. PPi is also felt to be an important inhibitor of crystallization in the urinary tract. Multiple studies have documented lower PPi excretion in kidney stone patients than in non-stone forming people [5, 6]. Despite this important role in CaP crystal regulation, divalent cation salts of PPi are fairly insoluble and can crystallize when local levels of PPi rise, such as seen with the crystallization in joints and cartilage in calcium PPi deposition disease [7]. In this paper, we present the first reported case of a PPi urolithiasis in a human. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533442).

Case Report

The patient is a 60-year-old man presenting with gross hematuria. The patient provided written informed consent for the publication of the details of his medical case. A computed tomography scan revealed bilateral urolithiasis, multiple stones were present in the right kidney with the largest being 8 mm in diameter, and a few small stones in the left kidney, all less than 3 mm (shown in Fig. 1, left panel). The largest stone had computed tomography attenuation of 636 Hounsfield units, a value lower than usually found with calcium oxalate or calcium phosphate stones, more in the range typically reported for struvite or cystine stones [8]. No stones were noted on standard X-ray of the abdomen. The patient passed his first stone approximately 18 years earlier and had an additional 6–8 stone events in the intervening years, with only one stone requiring surgical intervention. Other pertinent medical history includes hypertension, hyperlipidemia, and a history of osteopenia of uncertain etiology, diagnosed after suffering a femoral fracture with mild trauma at age 36. He has suffered a total of three femoral fractures, as well as multiple fractures of feet, ribs, and fingers. He has no history of dental problems. He has one sibling and one child; there is no family history of bone or dental disease. He had been treated with bisphosphonates over 10 years before this recent presentation. Other therapies that had been used for his bone disease include androgen replacement and calcium supplementation. He is currently being treated with ergocalciferol.

Retrograde intrarenal surgery was performed to remove the stone burden from the right kidney (shown in Fig. 1, right panel). The stones were submitted to Litholink Corp (Itasca IL) for compositional analysis by infrared (IR) spectroscopy but did not match any compound in the spectral library. Further investigation included dissolution of stone material in 0.1 M HCl. Chemical analysis revealed the cation component to consist of magnesium and potassium. Ion chromatography/mass spectroscopy (IC/MS) was used to determine the anion component of the stone and only PPi with trace amounts of phosphate were found. Stone material was sent to a second laboratory (Herring Laboratory, Orlando FL) for analysis; IR spectroscopy was consistent with potassium magnesium pyrophosphate (KMgPPi) stones. X-ray powder diffraction revealed peaks at 2θ = 15.88°, 32.08°, 22.02°, and 18.12°, consistent with KMgPPi, though a second unidentified minor component was

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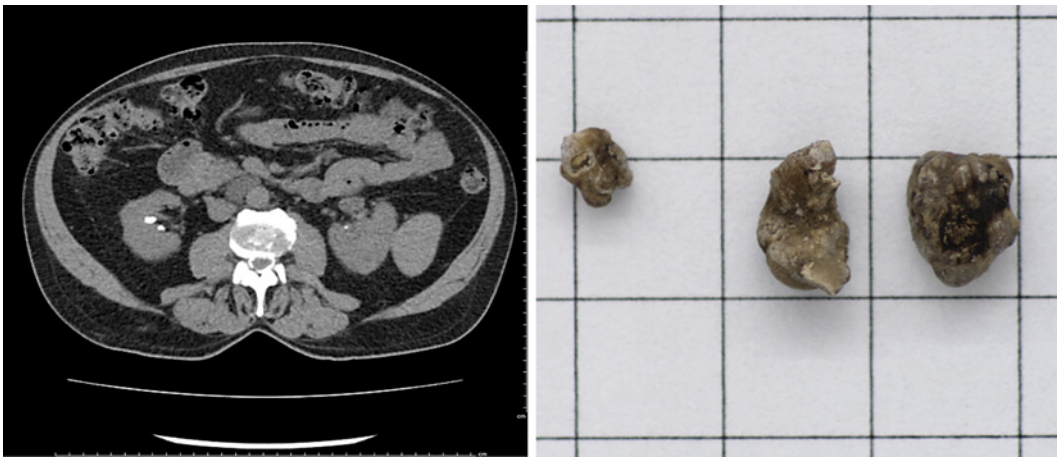

Fig. 1. Left panel: Abdominal CT scan. The largest stone in the right kidney had a radiodensity of 636 Hounsfield units. Right panel: Surgically removed kidney stones. Each square is 5 × 5 mm. CT, computed tomography.

also noted. Subsequently, feline KMgPPi stones were obtained from the Minnesota Urolith Center; the IR spectrum is presented in comparison with the patient's stone IR spectrum (shown in Fig. 2).

Pertinent laboratory tests showed a serum Ca of 2.45 mmol/L (9.8 mg/dL), 25 OH vitamin D of 107 nmol/L (43 ng/mL), and creatinine of 106 μmol/L (1.2 mg/dL). 24 h urine chemistries are listed in Table 1. Because the formation of a PPi stone would require hyperexcretion of PPi in the urine, and his history of severe metabolic bone disease, a diagnosis of HPP was considered. Review of medical records revealed serum alkaline phosphatase levels measured in the last 3 years to be in the range of 8–11 IU/L, below the reference range for the laboratory (40–130 IU/L). Urinary PPi excretion measured by IC/MS was 357 μmol/day. Prior studies of PPi excretion in patients with HPP had reported a mean urine PPi excretion of 144 ± 90 μmol/day compared to 39 ± 19 μmol/day in healthy subjects [9]. Genetic testing confirmed the diagnosis of HPP; two mutations were discovered in the *ALPL* gene. Both mutations are considered pathogenic, c.407G>A (p.Arg136His) has been associated with autosomal recessive forms of HPP while c.1240C>A (p.Leu414Met) has been reported in both autosomal dominant and recessive presentations [10].

In an effort to understand how to treat the patient's kidney stones, the effect of pH on KMgPPi solubility was studied. Feline KMgPPi stones were pulverized and 15 mg added to each test tube. 4 mL of buffer (Na Acetate/HEPES) at pH 5, 6, or 7 was added. Each pH experiment was performed in duplicate for a total of 6 tubes. The tubes were mixed continuously for 72 h at 37°C. pH was measured daily and adjusted as needed to maintain the solution at the original pH. At the end of the incubation, the tubes were centrifuged, the supernatant was harvested. The concentration of PPi in the supernatant was measured by IC/MS. As shown in Figure 3, solubility, as judged by PPi concentration, showed a pH dependence, being most soluble at pH 5.

Discussion

KMgPPi stones were first identified by Frank et al. [11], reporting five stones of a unique composition obtained from 4 cats and 1 dog. The mineral was identified by X-ray diffraction as KMgPPi pentahydrate. Subsequent surveys reported from veterinary stone laboratories have confirmed KMgPPi in animal stones, though still noted to be a rare occurrence [12]. No studies

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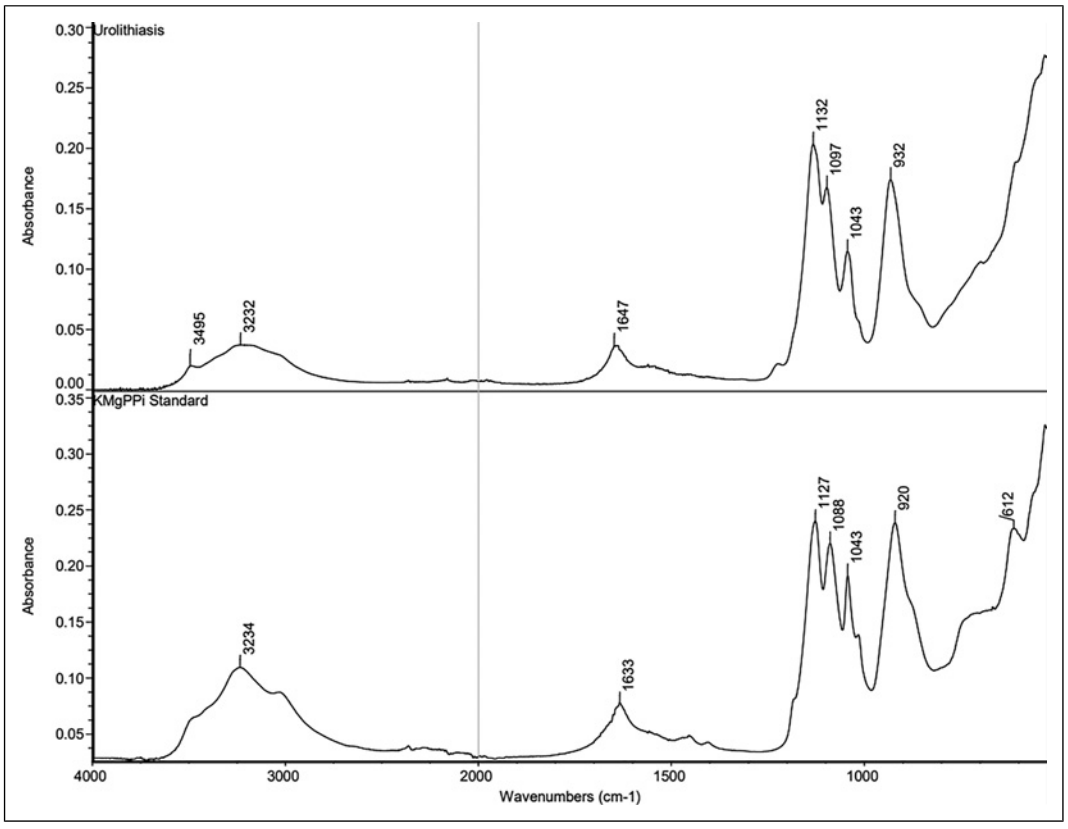

Fig. 2. Infrared spectra. Top panel is the patient's kidney stone. The bottom panel is the IR spectra of a feline potassium magnesium pyrophosphate pentahydrate stone. The vertical line at 2,000 cm^{-1} designates a change in the scaling of the *x*-axis.

Table 1. 24 h urine chemistries

	2015	2021
Volume, L/day	1.48	1.24
pH	5.70	5.55
Calcium, mmol/day	2.3	0.7
Oxalate, mmol/day	0.28	0.23
Citrate, mmol/day	<0.15	<0.15
Uric acid, mmol/day	3.3	2.4
Phosphorus, mmol/day	26.4	26.7
Creatinine, mmol/day	13.3	10.5
Potassium, mmol/day	52	55
Magnesium, mmol/day	2.9	4.6

have been published that report PPi excretion or potential bone/mineral disorders in the animals that have formed such stones. The original report found the animal stones to have a compositional formula of $K_{1.0}Mg_{1.5}(P_2O_7)_{1.0}$. Our compositional analysis of the feline stones from the Minnesota Urolith Center found similar molar ratios of $K_{1.0}Mg_{1.8}(P_2O_7)_{1.0}$. Of note, this patient's stones revealed a composition of $K_{1.0}Mg_{3.0}(P_2O_7)_{2.0}$, clearly different from the

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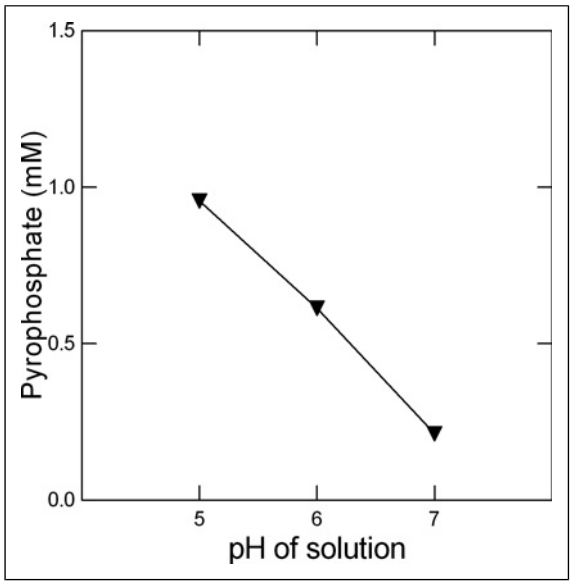

Fig. 3. Solubility of feline potassium magnesium pyrophosphate stones was determined at pH 5, 6, and 7 (*x*-axis). The *y*-axis is the pyrophosphate concentration at equilibrium at each pH. The highest pyrophosphate level at pH 5 indicates the greatest solubility.

cats. Whether this reflects a mix of a $K_{1.0}Mg_{1.5}(P_2O_7)_{1.0}$ salt with $Mg_{2.0}(P_2O_7)_{1.0}$ or whether it is a unique salt is not known. There is no human stone remaining for further analysis. The difference in molar ratios between the feline stones and human stone may help explain the extra unidentified peaks on X-ray diffraction and modest differences in peak wavelengths in the IR spectra.

Hypophosphatasia is a rare inherited disease due to mutations in the *ALPL* gene [3], which encodes tissue nonspecific alkaline phosphatase (TNAP). It can be inherited as either an autosomal recessive or dominant trait. TNAP is distributed in many tissues, particularly the liver, bone, and kidney. Its major function is the hydrolysis of phosphate groups, and it is critical in regulating blood PPi levels and the conversion of pyridoxal phosphate to pyridoxine [13]. When TNAP activity is deficient, PPi levels in the blood increase, inhibiting hydroxyapatite deposition in bone. The clinical features of HPP reflect this with osteopenia, osteomalacia, recurrent fractures, and dental abnormalities. The expression of disease has a wide range, from severe prenatal and childhood forms with a high mortality rate to mild adult forms [4]. It is assumed that the adult forms of the disease are underdiagnosed, even when clinically significant bone disease is present. The advent of enzyme replacement therapy in the form of asfotase alpha has shown great promise in early treatment trials of HPP, though most studies have focused on the pediatric forms of the disease, not the adult forms [14, 15].

Stones and nephrocalcinosis have been noted in many studies of HPP [3]. It has been assumed that the stones and NC were secondary to excess urinary excretion of calcium and phosphate due to defective bone mineralization. We have been unable to find any case reports or series that include stone composition data from patients with HPP. Whether PPi salts are common components of stones in HPP needs to be studied. There are no studies on the management of stones and nephrocalcinosis in HPP. Though the current patient has low urine citrate, it is not clear that alkali supplements to raise urine citrate would be an appropriate therapy because alkali would also raise urine pH. The solubility studies we performed showed KMgPPi to be less soluble at high urine pH. Whether enzyme replacement therapy might reduce nephrocalcinosis and stones has not been studied.

Calcium pyrophosphate (CaPPi) crystal deposition disease is a well-recognized clinical entity [7]. Chondrocalcinosis is the deposition of CaPPi in cartilage, often asymptomatic and noted as finding on routine X-rays, it is often associated with osteoarthritis. Pseudogout is a

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CaPPi crystal arthropathy which can present with acutely inflamed joints or a more chronic indolent course. Urolithiasis is not associated with CaPPi deposition disease because the PPi excess is related to local production in the affected joints; blood and urine levels of PPi are not elevated. However, CaPPi deposition disease highlights the fact that PPi salts of divalent cations are poorly soluble. Whether humans with HPP might also be at risk to produce CaPPi stones is not known. This particular patient has low urine calcium excretion, which may be why he formed KMgPPi stones rather than CaPPi. Neither his potassium nor magnesium excretion was abnormally high.

Conclusion

This is the first case report of a human kidney stone composed predominantly of PPi salts. The identification of this unusual stone led to the diagnosis of HPP, a disease known to cause high PPi levels in urine. Stone analysis laboratories should include PPi salts in their IR reference libraries.

Statement of Ethics

A formal approval for a single case report was waived by WCG Institutional Review Board. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

J.R.A. and L.Y. are employees of Litholink/Labcorp. G.A. is an employee of Louis C. Herring & Company. M.R.G., N.S.M., and J.P.L. declare no conflicts of interest.

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Author Contributions

M.R.G. was the treating physician and provided medical history and radiographs. L.Y. performed measurements of pyrophosphate and aided in design and performance of the solubility experiments. G.A. performed X-ray diffraction and confirmatory IR analysis of the kidney stone. N.S.M. provided guidance in interpretation of X-ray diffraction and IR results and interpretation of experimental results. J.P.L. provided canine pyrophosphate stones for IR studies and aided in interpretation of IR results. J.R.A. designed the solubility experiments, directed the chemical analysis of the stones and pyrophosphate measurements, and was the primary author of the manuscript. All authors contributed to the writing, review, and editing of this case report manuscript.

Data Availability Statement

All data pertaining to this study are included in the article. Further inquiries can be directed to the corresponding author.

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