Calcium Phosphate Stone Morphology Can Reliably Predict Distal Renal Tubular Acidosis

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Abbreviations and Acronyms

dRTA = distal renal tubular acidosis

MSK = medullary sponge kidney

SEM = scanning electron microscope

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Purpose: Calcium stones represent 85% to 90% of all urinary calculi, including various crystalline compositions and etiological conditions. Calcium phosphate accounts for 10% to 15% of cases. These stones are mainly related to 3 groups of risk factors, including calcium or phosphate metabolism disturbance, renal acidification defects and urinary tract infection. Identifying the stone etiology often requires extensive metabolic evaluation. We assessed whether stone analysis including morphological typing in addition to stone composition could be a valuable help for diagnosis.

Materials and Methods: Of 60,564 stones analyzed by morphological examination and infrared spectroscopy at our laboratory 6,439 (10.6%) were mainly composed of carbapatite. Of these stone 1,093 patients were included in study who had an available etiological diagnosis and stones containing at least 70% of calcium phosphate without struvite.

Results: Of the 1,093 calcium phosphate stones 12.8% showed a peculiar morphology termed IVa2, characterized by a smooth aspect and a glazed brown-yellow appearance with tiny cracks. IVa2 morphology was observed in 96.1% of stones associated with inherited distal renal tubular acidosis. In contrast, the other stones of similar composition but different morphology were related to distal renal tubular acidosis in only 3.9% of cases. In addition, IVa2 stones were found in 65% of calcium phosphate stone formers associated with Sjögren syndrome and in 35% of calcium phosphate stones in patients with medullary sponge kidney. These 2 conditions are related to a mild to moderate distal acidification defect.

Conclusions: Identifying IVa2 stone morphology is clinically relevant because it should prompt clinicians to search for complete or incomplete distal acidosis and initiate specific therapy to decrease recurrence.

Key Words: kidney; nephrolithiasis; calcium phosphate; acidosis, renal tubular; diagnosis

NEPHROLITHIASIS is a common disease affecting more than 10% of the population in Western countries with a high recurrence rate. The annual cost in the United States was $2 billion in 2000 and it is increasing with time.[1] The causes are diverse, including dietary disequilibrium, urinary tract

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infection and metabolic disorders related to acquired or genetic diseases. Although stone classifications commonly distinguish only few chemical compounds, namely calcium, uric acid, cystine and infection stones, physical analysis may identify a wide variety of components. More than 100 mineral or organic compounds have been identified to date.[2] In industrialized countries and in an increasing number of developing countries so-called calcium stones account for about 90% of all urinary calculi with calcium oxalate the most frequent chemical species.[3–5]

However, calcium stones can be divided into subgroups according to the main crystalline phase, which is often a strong marker of a specific urine composition.[6] Of the calcium phosphate stones those of carbapatite (crystallized carbonated hydroxyapatite) may result from urinary tract infection or metabolic factors such as hypercalciuria, phosphate leak or tubular acidification defects.

Although rare, some genetic or acquired diseases may be responsible for severe forms of urolithiasis associated with nephrocalcinosis and end stage renal failure, especially when the diagnosis is delayed. For example, in primary hyperoxaluria cases stone morphology and not composition could help with the diagnosis.[7] Thus, stone morphology appears to be a convenient, straightforward and useful examination to diagnose this rare but severe pathological condition while stone composition alone does not lead to the diagnosis.

Based on this background we hypothesized that other varieties of stones could benefit from morphological examination. An example would be calcium phosphate stones, which account for 10% to 15% of all calculi and result from urinary tract infections and/or different metabolic disorders such as idiopathic hypercalciuria, hyperparathyroidism, phosphate leak, tubular acidosis or an excessive alkali load.[8,9]

The advantage of adding a stone morphology examination to infrared analysis is to provide a rapid, inexpensive orientation to specific pathological conditions that could not be readily identified when extensive metabolic investigations are not systematically performed. For example, in our experience the identification of typical IVa2 morphology led to the diagnosis of poorly symptomatic Sjögren syndrome with incomplete dRTA.

We sought to provide evidence that in addition to infrared spectroscopy, determining stone morphology is a key step in the diagnostic procedure of stone analysis that may identify sometimes unexpected metabolic or monogenic related stone diseases.

PATIENTS AND METHODS

Of 60,564 stones analyzed by morphological examination and infrared spectroscopy at our laboratory 6,439 (10.6%) were mainly composed of calcium phosphate (more than 50% of the stone mass), including carbapatite, brushite, octacalcium phosphate pentahydrate, amorphous carbonated calcium phosphate or whitlockite. Of the stones 5,181 were mainly composed of carbapatite, representing 80.5% of calcium phosphate stones and 8.5% of the whole series. Stones containing any proportion of struvite, which more specifically indicates urinary tract infection with ureolytic microorganisms, were excluded from analysis. Because calcium phosphate may be associated with a high proportion of calcium oxalate in a number of cases and, thus, be related to various metabolic conditions, we selected only stones containing an unambiguously high proportion of calcium phosphate, namely 70% of the whole stone content on infrared spectroscopy. Finally, we included in study only calculi associated with a detailed etiological diagnosis provided by physicians, which was available for 1,093 patients.

Of the relevant diagnoses dRTA was diagnosed first based on low serum bicarbonate, moderately low arterial pH (excluding pulmonary alkalosis), low urine ammonium, urine pH greater than 6.5 and in some cases a bicarbonate load test. In addition, when measured, urine citrate was low in the absence of urinary tract infection, commonly less than 0.7 mmol per 24 hours. The diagnosis of inherited dRTA was proven by DNA sequencing of the Cl^-/HCO_3^- exchanger gene (*SLC4A1*) or the H^+ adenosine triphosphatase gene (*ATP6V0A4* or *ATP6V1B1*). MSK was diagnosed by computerized tomodensitometry or excretory urogram. Sjögren disease was diagnosed by at least 4 classic criteria, including a salivary gland biopsy based Chisholm score of greater than 3 and autoimmunity.

Morphological Examination and Infrared Analysis

Each calculus was studied using a stereomicroscope to define morphological type and structural characteristics as previously described.[9] This also enabled the selection of representative parts of the stone for infrared analysis, such as the nucleus, the inner and external layers, and the surface.[10] Spectra were recorded by a Spectrospin Vector 22 Fourier transform infrared spectrometer (Bruker, Karlsruhe, Germany). Figure 1, *a* shows the typical spectra of carbapatite stones.

SEM and Statistics

A SUPRA 55-VP type environmental SEM (Carl Zeiss, Oberkochen, Germany) was used to observe the microstructure. This field effect gun microscope operates at 0.5 to 30 kV. High resolution observations were made using 2 secondary electron detectors, including an in-lens secondary electron detector and an Everhart-Thornley secondary electron detector. An important feature of the environmental SEM compared to a conventional SEM is that nonconductive materials can be imaged without a conductive coating, which permits direct observation with no damage to the sample.

The Fisher exact test was used for statistical comparison between groups. Statistical analysis was done with NCSS™ software.

RESULTS

While the infrared spectra of carbapatite stones were similar, the stones showed 2 morphological