

Nephrocalcinosis: re-defined in the era of endourology

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Abstract Nephrocalcinosis generally refers to the presence of calcium salts within renal tissue, but this term is also used radiologically in diagnostic imaging in disease states that also produce renal stones, so that it is not always clear whether it is tissue calcifications or urinary calculi that give rise to the characteristic appearance of the kidney on x-ray or computed tomography (CT). Recent advances in endoscopic imaging now allow the visual distinction between stones and papillary nephrocalcinosis, and intra-renal endoscopy can also verify the complete removal of

urinary stones, so that subsequent radiographic appearance can be confidently attributed to nephrocalcinosis. This report shows exemplary cases of primary hyperparathyroidism, type I distal renal tubular acidosis, medullary sponge kidney, and common calcium oxalate stone formation. In the first three cases—all being conditions commonly associated with nephrocalcinosis—it is shown that the majority of calcifications seen by radiograph may actually be stones. In common calcium oxalate stones formers, it is shown that Randall's plaque can appear as a small calculus on CT scan, even when calyces are known to be completely clear of stones. In the current era with the use of non-contrast CT for the diagnosis of nephrolithiasis, the finding of calcifications in close association with the renal papillae is common. Distinguishing nephrolithiasis from nephrocalcinosis requires direct visual inspection of the papillae and so the diagnosis of nephrocalcinosis is essentially an endoscopic, not radiologic, diagnosis.

Keywords Kidney calculi · Nephrocalcinosis · Medullary sponge · Renal tubular acidosis · Hyperparathyroidism

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Introduction

Nephrocalcinosis as currently utilized in the world literature has various meanings and implications. On a pathologic basis the term refers to the presence of calcium salts within renal tissue. We are more interested in the term as it refers to radiographically apparent calcium deposits that overlie the renal substance, particularly the renal proper and corticomedullary regions. Albright et al. [1] who coined the term nephrocalcinosis first reported radiographically demonstrable diffuse renal calcification in patients with primary hyperparathyroidism in 1934. Since

Table 1 Conditions associated with nephrocalcinosis

Common	Less common
Primary hyperparathyroidism	Phosphate and vitamin D in X-linked hypophosphatemic rickets
Type 1 (distal) RTA	Hyperphosphatasia
Medullary sponge kidney	Sarcoidosis
Furosemide therapy (neonatal)	Tuberculosis
	Vitamin D intoxication
	Hypomagnesemia
	Bartter's syndrome
	Glycogen storage disease 1
	Prolonged immobilization
	Idiopathic hypercalciuria
	Oculocerebral syndrome
	Hyperoxaluria
	Cushing's syndrome
	Hypothyroidism
	Acetazolamide
	Cerebrotendinous xanthomatosis
	Dent's disease

that time the most common clinical conditions associated with nephrocalcinosis have been primary hyperparathyroidism, medullary sponge kidney disease (MSKD), and Type 1 or distal renal tubular acidosis (RTA) (Table 1) [2–4].

Although the calcifications associated with the aforementioned conditions are easily seen on standardized radiographs, these diseases are all typically associated with renal calculi as well, and distinguishing nephrocalcinosis from renal calculi can be problematic. Further complicating the diagnostic limits of radiographic evaluation in the modern era of CT based technology for stone identification, the finding of minute calcium deposits overlying the renal substance also presents a challenge in distinguishing nephrocalcinosis from small renal stones which commonly originate as calcium oxalate overgrowth on Randall's plaque [5].

Fortunately, the steady advancement in endourologic technology and techniques presents a solution to the conundrum—is it stone or is it nephrocalcinosis? Insight gained into this clinically important distinction is the purpose of the current report.

Materials and methods

Patients with extensive renal parenchymal calcification who underwent percutaneous nephrolithotomy (PCNL) were retrospectively reviewed from our institutional review board (IRB) approved database. These patients also

underwent renal endoscopic mapping and papillary biopsy as part of another IRB approved protocol investigating Randall's plaque. We present four representative cases of pre-operative and post-operative radiographic imaging along with endoscopic findings and metabolic characterization. The disease states explored include: primary hyperparathyroidism, MSKD, and distal RTA. We also include a case of CT findings of Randall's plaque in a common calcium oxalate stone former.

Results

The following four cases are meant to serve as illustrative examples for exploring the definition of nephrocalcinosis in the common disease states of primary hyperparathyroidism, distal RTA, and MSKD, as well as revisiting the concept of nephrocalcinosis in the CT era in the common calcium oxalate stone former.

Case 1: primary hyperparathyroidism

In the case of primary hyperparathyroidism, nephrocalcinosis is thought to result as a consequence of hypercalcemia and hypercalciuria [6]. Figure 1 represents the pre-operative KUB in a patient with primary hyperparathyroidism. Note the presence of bilateral partial staghorn calculi and what was interpreted radiographically to be nephrocalcinosis in the lower pole of the left kidney. Figure 2a is an endoscopic image of this area demonstrating that these calcifications were actually surgically removable stones. Figure 2b depicts a relatively normal-appearing papilla in the upper pole of the left kidney in this patient with hyperparathyroidism. Figure 3 is a post-operative KUB following bilateral PCNL in the same patient which demonstrates complete surgical removal of all calcifications. This case illustrates the difficulty in judging nephrocalcinosis by radiography alone. Stone analysis in this patient



Fig. 1 Pre-operative KUB in patient with primary hyperparathyroidism. Arrows indicate regions that appear to be nephrocalcinosis

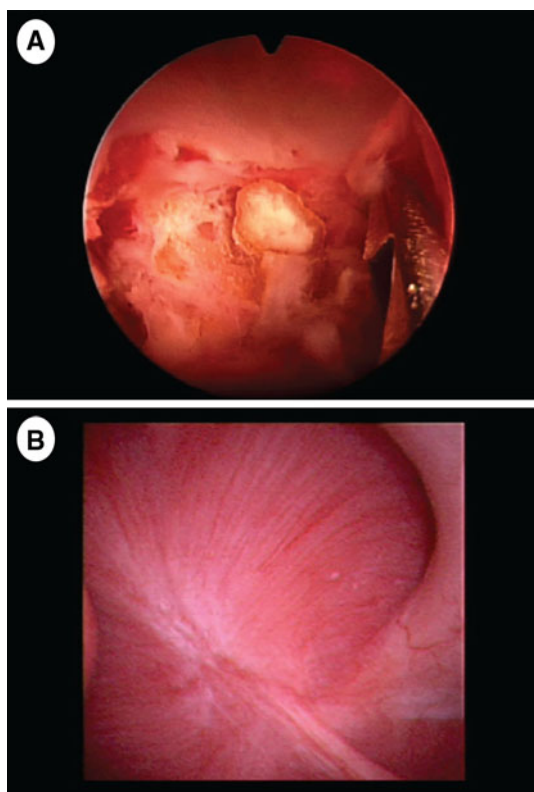


Fig. 2 **a** Endoscopic image of left lower pole calcifications in patient with primary hyperparathyroidism. **b** Endoscopic view of relatively normal papilla in the upper pole of the left kidney in the same patient



Fig. 3 Post-operative KUB following bilateral PCNL in this patient with primary hyperparathyroidism demonstrating complete removal of all renal calcifications

revealed a mixture of calcium phosphate and calcium oxalate from both kidneys (right 42% HA, 58% COM, left 73% HA, 27% COM) as is commonly found in primary hyperparathyroidism.



Fig. 4 Pre-operative KUB in patient with Type 1 distal RTA

Case 2: type 1 distal RTA

In the case of Type 1 distal RTA, there is either an inherited or acquired inability to maintain a hydrogen ion gradient in the distal nephron, resulting in abnormal acid–base metabolism. Systemic and/or intracellular acidosis leads to increased citrate reabsorption in the proximal tubule and thus reduced urinary citrate excretion. The end result of these metabolic derangements is inappropriately alkaline pH in the presence of low plasma bicarbonate and hypocitraturia which combined with hypercalciuria leads to nephrocalcinosis and calcium phosphate nephrolithiasis in these patients.

Figure 4 represents the pre-operative KUB in a patient with inherited distal RTA. Note the coarse, well-rounded calcifications overlying both kidneys which were judged radiographically to represent primarily medullary nephrocalcinosis. At the time of PCNL, this patient was found to have a large calyceal stone burden with very little nephrocalcinosis. Figure 5a depicts a representative endoscopic view of one of the calyces in this patient. Note the large calyceal stone, and following removal (Fig. 5b), the finely stippled scattered calcifications remaining. The postoperative KUB is shown in Fig. 6. There has been a dramatic reduction in the calcifications overlying the kidneys providing evidence for the assertion that the majority of the calcifications represented surgically removable stones rather than nephrocalcinosis. Stone analysis in this patient revealed calcium phosphate (100% hydroxyapatite) which is typical of distal RTA.

Case 3: MSKD

The hallmark of MSKD is cystic dilation and ectasia of the terminal collecting ducts. As in distal RTA, nephrocalcinosis is common, and the two conditions may be difficult to distinguish with KUB alone. Intravenous pyelography is much more helpful in demonstrating the cystic dilation of the collecting ducts. Hypercalciuria is

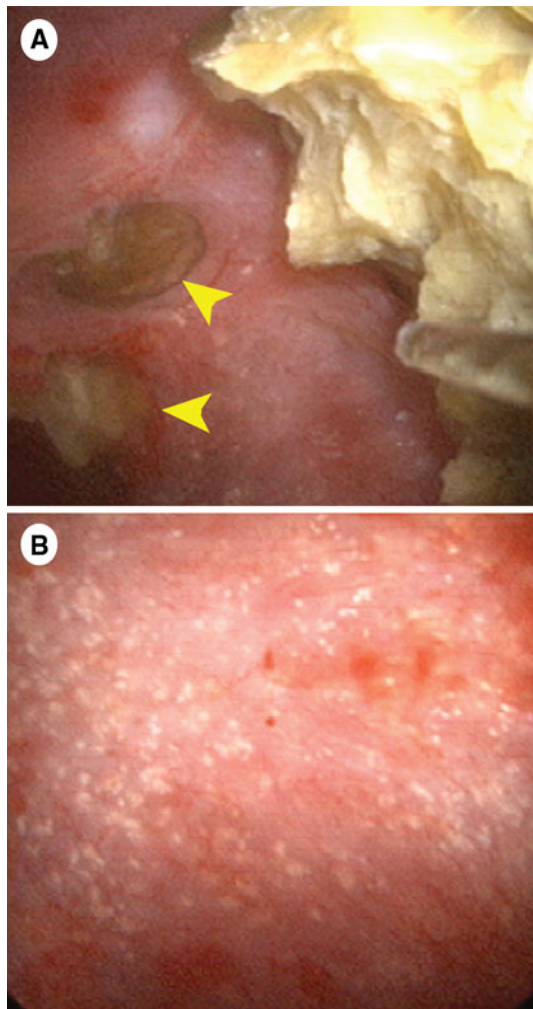


Fig. 5 Endoscopic views in a patient with Type 1 distal RTA. **a** Close-up view during procedure, demonstrating large calyceal stone and smaller stones protruding from dilated duct of Bellini (*arrowheads*). **b** Lower power image following removal of calyceal stones in the same patient, demonstrating only finely stippled scattered calcifications remaining



Fig. 6 Post-operative KUB in same patient with distal RTA. Almost all the X-ray dense material visible in Fig. 4 has been removed, demonstrating that the finely stippled calcification seen in Fig. 5b is not apparent on plain X-ray

also often present in these patients increasing the risk of stone formation.

Figure 7 demonstrates the pre-operative KUB findings in a patient with documented MSKD. Note the multiple clusters of grapelike calcifications at the corticomedullary junction of the left kidney. Another noteworthy finding in MSKD compared to distal RTA is that calcifications in MSKD may be bilateral, unilateral or segmental where distal RTA is bilateral. Figure 8a shows the typical endoscopic findings in MSKD including flattening of the renal papillae. The normal papillary architecture has been replaced by cystic cavities of varying size. Often, stone material is visualized extruding from the openings of these cavities which represent dilated terminal collecting ducts, or just under the surface of the urothelium if the opening of the cystic cavity has narrowed or closed. Figure 8b demonstrates the use of a holmium laser fiber to open such a cavity for stone removal. Figure 9 is a post-operative KUB following PCNL in this patient again demonstrating that the majority of the calcifications seen on pre-operative KUB were actually surgically removable stones. Stone analysis in this patient revealed a mixture of calcium oxalate and calcium phosphate (79% COM, 21% HA).

Case 4: common calcium oxalate stone former

By common calcium oxalate stone former, we mean calcium oxalate stone formation in the absence of a systemic disorder such as primary hyperparathyroidism or sarcoidosis. Recent evidence suggests that CaOx calculi begin as small stones attached to the renal papillae at sites of Randall's plaque (RP) [5]. RP represents interstitial deposits of calcium phosphate (apatite) beginning at the basement membrane of the thin loops of Henle. When compared with other radiographic modalities such as plain



Fig. 7 Pre-operative KUB findings in patient with MSKD

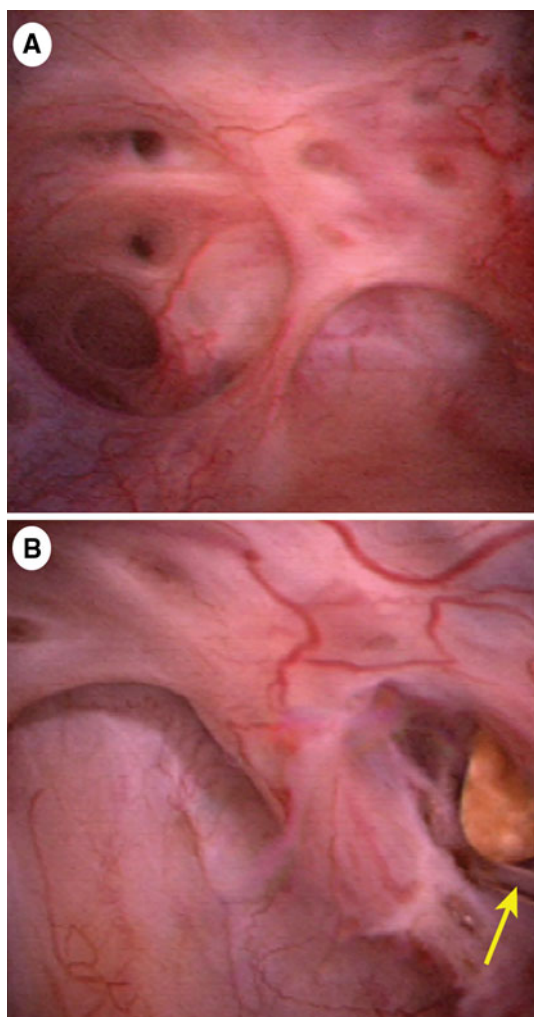


Fig. 8 Intraoperative images demonstrating the typical endoscopic findings in MSKD. **a** Deformations in calyceal spaces appear as a web of openings within the kidney. **b** Higher power view where laser fiber is shown incising the tissue of a cystic cavity where stone material is present



Fig. 9 Post-operative KUB following left PCNL in this same patient with MSKD

films, tomograms, and ultrasound, CT has been shown to provide much better sensitivity for the detection of stones [7]; however, present CT interpretation criteria cannot reliably distinguish papillary tissue calcifications from papillary stones. Figure 10 demonstrates high-resolution CT images following left PCNL in a common calcium oxalate stone former. During primary PCNL, extensive RP was noted at the papillary tips as well as small calyceal stones. While the high-resolution CT images obtained post-operatively revealed fine calcifications at the papillary tip, it was unclear whether this represented CT imaging of RP or small residual stones. Second-look nephroscopy confirmed these calcifications to be extensive RP without residual stone. This represents another case in which direct optical evaluation was necessary to distinguish tissue calcification from stone.

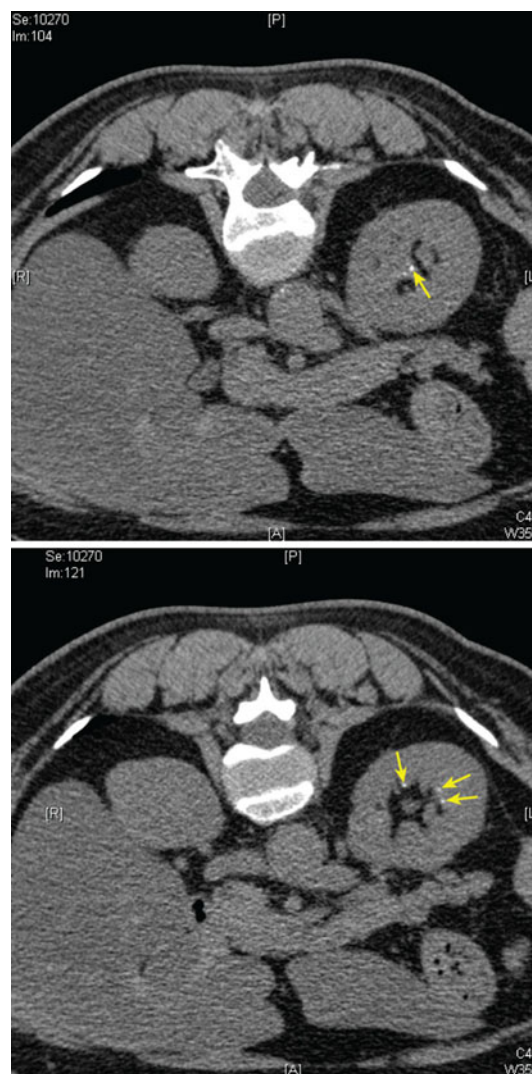


Fig. 10 High-resolution CT images following left PCNL in common calcium oxalate stone former. Calcifications confirmed to be Randall's plaque by second-look nephroscopy

Discussion

Since its introduction by Albright in 1934, the term “nephrocalcinosis” has been used in the world literature with various meanings from microscopic calcification at the time of necropsy to gross calcification evident only radiographically [4, 8–11]. Most simply, it denotes deposition of calcium in the kidneys; however, the more contemporary use of the term refers to the radiographic demonstration of diffuse, fine renal parenchymal calcifications. Nephrocalcinosis is known to occur in concert with a number of conditions (Table 1); however, the more common include distal RTA, MSKD and primary hyperparathyroidism. These conditions are also commonly affected by calculus formation. In fact, the unveiling of the primary disorder may be precipitated by a symptomatic stone episode. Apart from treating the symptomatic stone, it has often been the opinion of the treating urologist that little could be done to improve the circumstance of nephrocalcinosis in these afflicted patients. Following elucidation of the disorder inciting the nephrocalcinosis, many patients are relegated to medical treatment of the underlying metabolic derangement. For the unfortunate patient who suffers recurrent bouts of symptomatic nephrolithiasis, repeated instrumentation may lead to chronic urinary tract infection (UTI) further complicating the situation.

In addition to chronic UTI, conditions associated with nephrocalcinosis may also result in permanent insult to the kidneys with a decline in renal function. It is under these circumstances as well as the case of symptomatic nephrolithiasis occurring in the context of nephrocalcinosis that we have had the good fortune of being referred cases which we believe may alter the current treatment paradigm of patients diagnosed with nephrocalcinosis. As the cases presented illustrate, the differentiation between nephrocalcinosis and nephrolithiasis is often quite difficult to make radiographically. Indeed, radiographs commonly underestimate the degree of calyceal stone burden. Kerbl and Clayman [12] arrived at a similar conclusion when they reported that definitive differentiation of calyceal versus parenchymal stones is best done by direct optical evaluation.

Treatment by PCNL afforded the opportunity to thoroughly map and endoscopically view the entire kidney in the cases presented. In the cases of pre-operatively judged nephrocalcinosis (RTA, MSKD, primary hyperparathyroidism), the majority of the calcifications seen preoperatively were actually calyceal stones or stones trapped in dilated ducts of Bellini or cystic cavities demonstrating the propensity of radiographs to underestimate the degree of nephrolithiasis.

Criticism of this report may be that these are simply rare cases that do not represent the normal circumstance;

however, on the contrary these are merely illustrative cases that represent but a few treated in such a manner by the authors. A recent report by Evan and colleagues [13] expands on the findings in the authors’ subset of treated patients with distal RTA again demonstrating that most of the calcifications visible on radiographs represent surgically removable stones rather than calcifications within the renal tissue itself, a finding found to be especially true in patients with well-preserved renal function. Therefore, we conclude that these patients may benefit significantly from PCNL to preserve renal function and combat chronic UTI and pyelonephritis.

Although renal papillary tip calcifications (RP) fall outside our current definition of nephrocalcinosis, they do represent a type of microscopic “nephrocalcinosis” by the most fundamental definition. The subject is particularly timely in the context of the CT era where imaging technology now allows the identification of even the minutest of calcifications. In the common calcium oxalate stone former, evidence suggests that calcium oxalate stones begin development attached to Randall’s plaque [5, 14–17]. The significance of RP in calcium nephrolithiasis is further supported by the findings that fractional coverage of RP is significantly higher in common calcium oxalate stone formers than in controls [18], and that plaque coverage independently correlates with the number of stone events [19]. Despite the significant improvements in imaging technology, differentiation between RP and small stones remains difficult. Traditionally, second-look nephroscopy has been utilized following an initial percutaneous nephrolithotomy (PNL) to assess for and extract any residual stone fragments.

Arguments have been made to utilize CT alone to assess for residual stones, reserving flexible nephroscopy, which had been considered the “gold standard” method for detecting and then removing residual fragments, to extract stones detected by CT [20]. The sensitivity of current CT technology to detect the presence of calcifications within the urinary tract can sometimes result in an overestimation of residual stone burden, especially in situations where papillary tissue calcium deposits may be present. As a result, ancillary procedures may be performed because of the CT findings. A recent study examined this issue by comparing the sensitivity of non-contrast helical CT to that of flexible nephroscopy [21]. In this study, patients undergoing PNL for large stone burden underwent post-operative non-contrast helical CT scan to assess for residual stone fragments. These patients then underwent flexible nephroscopy. The study revealed that CT provided 100% sensitivity in detecting residual stones after PNL and that no stone detected through flexible nephroscopy was missed by CT. However, the high sensitivity of CT to detect calcifications within the kidney would have resulted in a 15%

rate of unnecessary flexible nephroscopy, as these patients did not have collecting system stones detected. Therefore, the calcifications seen on CT in these cases were not stones but most likely papillary tissue calcium deposits.

High-resolution CT scanning allows more precise imaging, and with wider applicability may prove useful in the differentiation of RP from new stone growth in the recurrent stone former. Similar to the case of gross nephrocalcinosis, evaluation of the common calcium oxalate stone former represents another circumstance in which endoscopic evaluation is necessary to delineate the radiographic findings.

Conclusion

The differentiation between nephrocalcinosis and nephrolithiasis is difficult using radiographs alone. The first three cases presented here demonstrate that in conditions commonly associated with nephrocalcinosis, the majority of the calcifications may actually be surgically removable stones. However, direct optical evaluation is necessary to distinguish stone from nephrocalcinosis. Our findings suggest that the current treatment paradigm for these patients consisting of medical management of any metabolic derangements and surgical management of only acute stone episodes is inadequate. Particularly in the earlier stages of renal disease, patients may benefit significantly from thorough stone removal to reduce UTI and preserve renal function. In the modern era of CT-based technology, our ability to detect even minute calcium deposits overlying the renal substance presents a further challenge in distinguishing RP from small renal stones, and another instance in which endoscopic evaluation is necessary to differentiate tissue calcification from stone.

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