Endoscopic and Histologic Findings in a Cohort of Uric Acid and Calcium Oxalate Stone Formers

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Abstract

Objectives—To characterize the endoscopic and histologic renal papillary lesions in a cohort of uric acid (UA) stone formers (SF).

Methods—Data was prospectively obtained during percutaneous nephrolithotomy between 2009–2013. Renal papillae were endoscopically analyzed to quantitate surface area (SA) occupied by plaque or plug, and biopsies were obtained. UA SF were compared to non-SF controls and patients with >50% CaOx in the absence of UA.

Results—There were 23 UA SF; of which 19 stones (83%) were admixed with CaOx and 4 (17%) were pure. Compared to CaOx SF and controls, UA SF had a higher prevalence of diabetes and obesity, greater serum creatinine and UA, lower eGFR and urine pH, and elevated UA supersaturation. Characteristics of UA SF were compared to 95 CaOx SF, and 19 controls. Overall, 23 (100%) UA SF had endoscopic plaque and 13 (57%) plugs. Endoscopically, UA SF displayed a greater incidence of plugging (57% vs 45% vs 11%; *p*=0.006) relative to CaOx SF and controls. Likewise, UA SF had a greater %SA of plugging (0.1 vs 0.0; *p*=0.002) and plaque (2.0 vs 0.9, *p*=0.006) than controls; but similar amounts to CaOx SF. Histologic plugs were similar in UA and CaOx SF, although CaOx SF demonstrated greater interstitial inflammation on endoscopic biopsy.

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Conclusions—UA and CaOx SF have similar amounts of plaque, while UA SF have more endoscopic but not histological collecting duct plugs. These data suggest overlap between the pathogenesis of UA and CaOx stones. The anchoring site for UA stones remains uncertain.

Keywords

uric acid stones; endoscopy; Randall's plaque; intramedullary collecting duct plugging; percutaneous nephrolithotomy

INTRODUCTION

Approximately 5–10% of all stone formers (SF) in the United States make uric acid stones (UA)[1]. Urinary characteristics that contribute to UA stone pathogenesis include low urine volume, hyperuricosuria and, most importantly, overly acidic urine[2]. Indeed UA supersaturation markedly increases at a pH of < 5.5[3]. It has been previously reported that patients with the metabolic syndrome are at increased risk of UA stone formation due to an abnormally low urinary pH as a result of reduced renal ammoniagenesis that appears to be caused, at least in part, by insulin resistance[4–10]. Although these factors clearly promote UA crystallization, the mechanisms by which these crystals are retained in the kidney and grow into a stone are poorly defined.

Alexander Randall hypothesized that calcium stones form as deposits upon interstitial calcifications in the renal papillae, which were later named Randall's plaque [11]. In recent years, extensive work has been completed including endoscopic mapping and histopathology to further elucidate the association between Randall's plaque and intramedullary collecting duct (IMCD) plugs, and the growth of calcium stones[12–15]. Investigators have described an association between the presence of plaque and multiple urinary parameters (low urine volume and pH, and high calcium)[16]. Previous studies have demonstrated IMCD plugging as a potential precursor lesion in patients with bowel disease and malabsorption[17], as well as a subgroup of calcium oxalate (CaOx) stone formers (SF)[18]. A study of bowel resection patients demonstrated their IMCD plugs to be made of apatite and ammonium acid urate despite some of the stones being UA in composition[17]. However, to date no systematic anatomic studies have been completed to evaluate anatomic papillary lesions in a group of patients with UA stones in the absence of bowel disease. Here we report detailed mapping and biopsy results in a cohort of UA SF as compared to control patients without stones and a group of idiopathic CaOx SF. Results suggest an overlap in the pathology and pathogenesis of CaOx and UA stones.

PATIENTS AND METHODS

After Institutional Review Board approval, all non-pregnant patients over the age of 18 years undergoing percutaneous nephrolithotomy (PCNL) for urolithiasis by a single surgeon (AEK.) between September 2009 and June 2013, and who were able to give informed consent, were prospectively enrolled in this study. All patients had preoperative CT imaging for surgical planning, and a CT scan on postoperative day one to assess for residual fragments. Analyses were limited to 3 groups of enrolled patients: UA stones, CaOx stones, and controls. Patients were classified as UA if the stone contained any UA, and CaOx if a

calcium stone contained > 50% CaOx in the absence of primary or enteric hyperoxaluria, bowel resection, renal tubular acidosis, medullary sponge kidney or primary hyperparathyroidism. Stones were classified based upon the % composition of UA including: majority (>80% UA), mixed (20–80% UA) and minority (<20% UA). Patients with a diagnosis of upper tract urothelial carcinoma and no prior history of nephrolithiasis who underwent nephroureterectomy, percutaneous tumor resection, or ureteroscopic tumor ablation were enrolled as a biopsy control group of non-SF.

Metabolic evaluation including 24-hour urine studies were obtained with patients on a random diet either preoperatively, if the patient was non-obstructed, or 6 weeks postoperatively. Due to a lack of comparable laboratory data within our non-SF controls undergoing endoscopy, a group of age and gender controlled non-SF in the community, collected as part of a parallel protocol, were matched in a 2:1 fashion to UA SF. Routine blood chemistries were obtained at a study visit. Stone composition was determined by micro-CT with confirmatory IR analysis, as previously described[18].

After stone removal, the kidney undergoing PCNL was endoscopically mapped and a representative papillae was biopsied[18,19]. The papillary biopsy was taken from a calyx that would provide the best biopsy specimen within the confines of the surgical access and instruments. Endoscopic mapping and biopsy occurred after stone or tumor treatment. Quantification of papillary surface area (SA) covered by plaque and plug was completed using digital video data obtained at time of nephroscopy as previously described[19]. A plug was defined as a crystalline structure extruding from a duct of Bellini that could be physically removed, and a plaque was defined as discolored and slightly raised urothelium consistent with subepithelial crystal deposition[20].

Papillary biopsy samples were fixed and sectioned as previously described, with one slide stained using Hematoxylin and Eosin and one with the method of Yasue for the presence of calcium[18]. Slides were read by a single renal pathologist (LHH) blinded to clinical details of the case and scored as none, mild (0–25% SA), moderate (26–75% SA) or marked (>75% SA) involvement with the following pathologies: 1) punctate tubular basement membrane (BM) Yasue staining; 2) dense tubular basement and adjacent interstitial Yasue staining; 3) intratubular Yasue positive calcifications; and 4) interstitial inflammation. The presence or absence of polarizing crystals (characteristic of CaOx) was also noted.

A Chi squared test was used for categorical data and Kruskal-Wallis test for continuous variables. All reported *p*-values were two sided, with *p* < 0.05 considered statistically significant. The median test, to evaluate the percentage of patients above the median, was utilized to compare differences in IMCD plug and plaque between each cohort. Statistical analyses were performed using SAS software version 9.3 and JMP version 9 (SAS Institute, Cary, NC; www.sas.com).

RESULTS

At the time of this analysis a total of 137 patients were enrolled in the study, of which 23 (17%) were UA SF with a median age of 60 years (IQR 56–70). Clinical characteristics are

depicted in Supplemental Table 1. UA SF had a greater median body mass index (BMI) (36 vs. 29 vs. 30 kg/m^2; $p = 0.03$) and increased prevalence of diabetes (52% vs. 22% vs. 16%; $p = 0.007$) relative to CaOx SF and controls. CaOx SF had a greater median number of stones than UA SF; whereas controls were older than both UA and CaOx SF. When stratified by the %UA composition, there were 10 (44%) majority, 8 (35%) mixed and 5 (22%) minority UA stones; of which 4 (17%) were pure and 19 (83%) were admixed UA stones that contained a mean 62% CaOx (range 10–97%) (Supplemental Figure 1). Among the UA SF, 2 (9%) had a history of small bowel surgery and 1 (4%) a horseshoe kidney.

Relative to CaOx SF and age-gender matched controls, UA SF had a greater serum creatinine (1.1 vs 1.0 vs 0.8; $p < 0.0001$) and UA (6.4 vs 5.8 vs 5.0; $p = 0.0004$), lower estimated GFR (69 vs 77 vs 95; $p < 0.0001$), and bicarbonate (26 vs 26 vs 28; $p = 0.0002$) (Supplemental Table 2). CaOx and UA SF had a greater serum calcium than controls. On urinary chemistries, UA SF had a lower urinary pH (5.7 vs. 6.0 vs. 6.3; $p = 0.0024$) and higher UA SS (delta Gibbs 2.0 vs. −0.2 vs. −2.1; $p = 0.0001$) compared to CaOx SF and matched controls (Supplemental Table 3). Urinary CaOx SS was, however, similar in UA and CaOx SF.

Endoscopic mapping of UA SF identified the presence of IMCD plugging in 13 (57%) patients (Figure 1A) and Randall's plaque in 23 (100%) (Figure 1B), with a median %SA coverage of 0.1% (IQR 0.0–1.0) and 2.0% (IQR 1.0–3.1), respectively. The mean endoscopic % SA plug and plaque was 0.4% (±0.7) and 0.9% (±0.9) in pure and 0.7% (± 1.6) and 2.4% (±1.4) in mixed UA SF. When stratified based upon the % composition of UA within the stone, compared to majority and mixed, minority UA stones were found to have higher % SA plugging (0.5%±0.6 vs 0.0%±0.1 vs 2.0%±2.7, $p = 0.04$), while there was no difference found in mean %SA plaque across groups (1.5±0.9 vs 2.6±1.9 vs 2.7±1.1, $p = 0.2$).

Endoscopic Randall's plaque was noted in one or more calyces of 23 (100%) UA SF, 95 (100%) CaOx SF and 17 (90%) controls. Likewise, IMCD tubular plugging was noted in 13 (57%) UA SF, 43 (45%) CaOx SF and 2 (11%) controls ($p = 0.006$). Endoscopically, the median %SA covered with papillary plaque ($p = 0.009$) and plug ($p = 0.006$) was significantly lower among non-SF controls relative to SF (Table 1). Since the %SA occupied by plaque and plug were not normally distributed, a median test was applied and demonstrated that UA SF had a significantly greater %SA plaque ($p = 0.006$) and plug ($p = 0.002$) than controls and similar amounts relative to CaOx SF.

Figure 2 demonstrates typical intraluminal, punctate and dense BM calcifications in a UA SF. Histology of papillary tip biopsies demonstrated that CaOx SF had a greater prevalence of interstitial inflammation (p=<0.0001) and trend towards greater punctate BM calcifications ($p = 0.054$) (Figure 3A and Supplemental Table 4). Intraluminal calcifications (plug) and dense BM calcifications were similar between the two stone types. When the UA group was stratified by % UA composition, those with minority UA (hence majority CaOx) tended towards more dense BM staining than mixed or majority but this did not reach statistical significance (Figure 3B and Supplemental Table 5).

DISCUSSION

In this study we examined urinary profiles, papillary anatomy and histology in a group of UA SF. Compared to CaOx and controls, UA SF had an elevated UA SS due to a lower urinary pH; however the three groups had similar urinary CaOx SS. In general, the distribution of plaque and plug was similar in UA SF and CaOx SF by both endoscopic mapping and histological examination of papillary tip biopsies; although there was a significantly greater interstitial inflammation and a trend towards more BM calcifications (plaque) among CaOx SF. Likewise, among UA SF, minority UA stones tended to have more plugs compared to mixed and majority stones. Plaque levels, meanwhile, were found to be similar across the three groups. These data suggest that UA SF are at risk for both CaOx and UA stones, and that their underlying pathology at the level of the papillum is similar. Indeed, UA stones often had alternating layers of CaOx and UA by micro CT. Among UA SF the amount of plaque may reflect the overall prevailing CaOx SS in a given patient, which also influences the relative percentage of CaOx versus UA in the final stone. Importantly, however, the key precursor lesion in the UA group, plaque, plug, or neither, is not immediately apparent.

Currently, the pathogenesis of UA stone formation is incompletely understood. It is generally assumed that UA stones form secondary to "free solution crystallization" within the renal pelvis and calyces[3,21,22]. Established risk factors include low urine volume, as seen in patients with ileostomies[17,23], elevated urate excretion, encountered in those with gout[23]; but most importantly, low urinary pH which appears to be the most important risk factor[4,7,8,10,24,25]. This is due to the chemistry of UA which has a pKa of 5.3. Thus, when the urine pH approaches 5, the amount of protonated UA available for crystallization increases exponentially. Potential causes of an overly acidic urine include a high dietary acid load due to excessive protein intake [8], gastrointestinal losses of bicarbonate do to diarrhea or ostomy, chronic kidney disease, renal lipotoxicity[26,27] and insulin resistance[4,5,7–9,25]. It has recently been reported that proximal tubular cell ammonium production from glutamine is influenced by insulin, and appears to be impaired in states of insulin resistance[4,10,28]. Indeed, our group of UA SF had a greater BMI, prevalence of diabetes and serum creatinine than the CaOx SF and controls.

Despite evidence that supports a key role of metabolic disturbances (mainly low urinary pH) in the pathogenesis of UA stones, little data exists evaluating the contribution of upper urinary tract anatomic lesions such as Randall's plaque and IMCD tubular plugging[17,18]. In the current study, on endoscopic mapping, UA SF had a greater prevalence of IMCD tubular plugging (57%) compared to other groups, as well as a greater median % SA coverage with plug relative to non-SF controls (0.1% vs 0.0%; p=0.002). IMCD tubular plugging was previously described by Evan and colleagues in 7 patients with ileostomies that included 4 with UA stones. They theorized that this resulted in IMCD plugging[17]. In the current study we evaluated patients with UA stones regardless of gastrointestinal status, and also found that among the current cohort containing just 2 patients with a small bowel resection, IMCD plugging is still quite prevalent.

Papillary biopsies were available in the majority of our UA cohort. Of the 14 patients with available biopsy data, 12 (86%) demonstrated intraluminal crystals (histological "plugging"). While the Yasue stain detects calcium[29], it does not detect non-calcium containing deposits[17]. Thus, it is possible that at least some of the plugs detected endoscopically were not calcium based. Evan and colleagues utilized micro-Fourier transform IR spectroscopy to characterize tubular deposits in a cohort of SF with bowel disease. Unexpectedly, these contained apatite, as found in calcium phosphate SF's[30]; as well as sodium and ammonium acid urate[17]. The latter would not be seen by Yasue. Unfortunately, due to the biopsy fixative used in our study we were unable to determine the composition of the IMCD plugs observed.

The majority of UA SF had some amount of CaOx in their stones. Indeed, in many it was the major component. However, papillary anatomy and histology did not differ greatly within the UA group based upon the percentage of stone composed of UA. In addition, with the exception of interstitial inflammation, papillary anatomy and histology were similar between UA and CaOx patients; supersaturation for CaOx was similar across UA SF, CaOx SF and controls, while UA SS was higher in UA SF compared to the other two groups. These data suggest the UA SF are concurrently at risk for both CaOx and UA, while CaOx SF are at risk for calcium (but not UA) stones. Unfortunately, the current study does not clearly identify the nature of the key precursor lesion for UA stones. Among the UA group do stones anchor upon the substantial Randall's plaque that was present, perhaps using a CaOx "bridge"? Can CaOx develop upon a UA nidus (perhaps in a plug)? Although both possibilities are consistent with our results, the current study did not characterize the attachment of stones to the renal papilla.

Limitations of the current study include its relatively small patient population and we attempted to control for this with a prospective, standardized design. Moreover, we recognize that the majority of UA SF were admixed with CaOx by micro CT analysis; which has demonstrated superior results in accurately characterizing stone composition relative to traditional methods. Indeed, to accurately define anatomic and histologic differences in a subset of pure UA SF a larger cohort would be necessary. Meanwhile, the endoscopic non-SF control population had limited laboratory data; therefore, we utilized an age-gender matched non-SF population with robust serum and urinary data to enhance our analysis. Since we were unable to determine plug composition, prospective studies of known UA SF are necessary to determine IMCD plug composition, but may be difficult since such patients are often treated with dissolution therapy. Finally, these data are from a single, tertiary referral institution and require external validation. Nevertheless, our study is the largest and most complete study of papillary anatomy in a group of idiopathic UA SF to date.

CONCLUSIONS

As others before us, we found significant differences between the UA SF patient phenotype compared to non-SF controls and idiopathic CaOx SF, namely: a lower urinary pH, higher serum creatinine and UA, lower GFR, greater BMI, and higher prevalence of diabetes. Moreover, we identified an increased incidence of endoscopic tubular plugging among UA SF relative to other cohorts, as well as significantly greater papillary plug SA coverage

compared to non-SF controls. Meanwhile, except for interstitial inflammation which was more prevalent among CaOx SF, histologic and endoscopic papillary plaque characteristics overlapped between SF cohorts. These results suggest that IMCD tubular plugs may play a role in crystal retention. However, the role of plaque in UA stone formation remains an open question, especially since the vast majority of UA stones contain some CaOx. Indeed, the prevailing metabolic abnormalities, mainly UA SS, may drive the formation of UA or CaOx within the stones, and this appears to fluctuate over time, as reflected by the alternating layers of crystal types in the final stone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

ABBREVIATIONS

CaOx	calcium oxalate
IMCD	intramedullary collecting duct
PCNL	percutaneous nephrolithotomy
SF	stone former
SS	supersaturation
SA	surface area
UA	uric acid
BM	basement membrane

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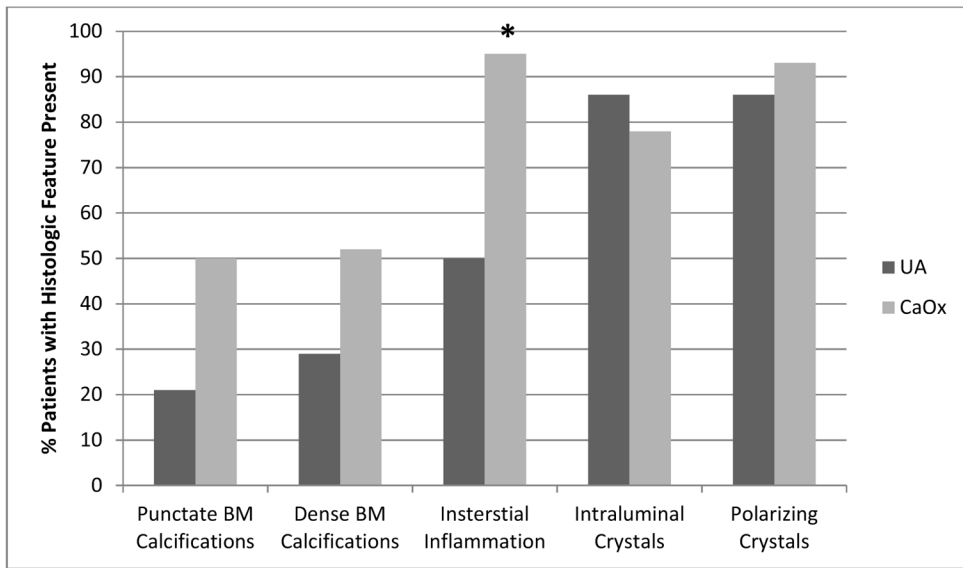
Figure 1.
Figure 1A and B. Endoscopic mapping of UA papilla with A.) presence of IMCD tubular plugging (red arrow) and B.) papillary plaque (green arrow).
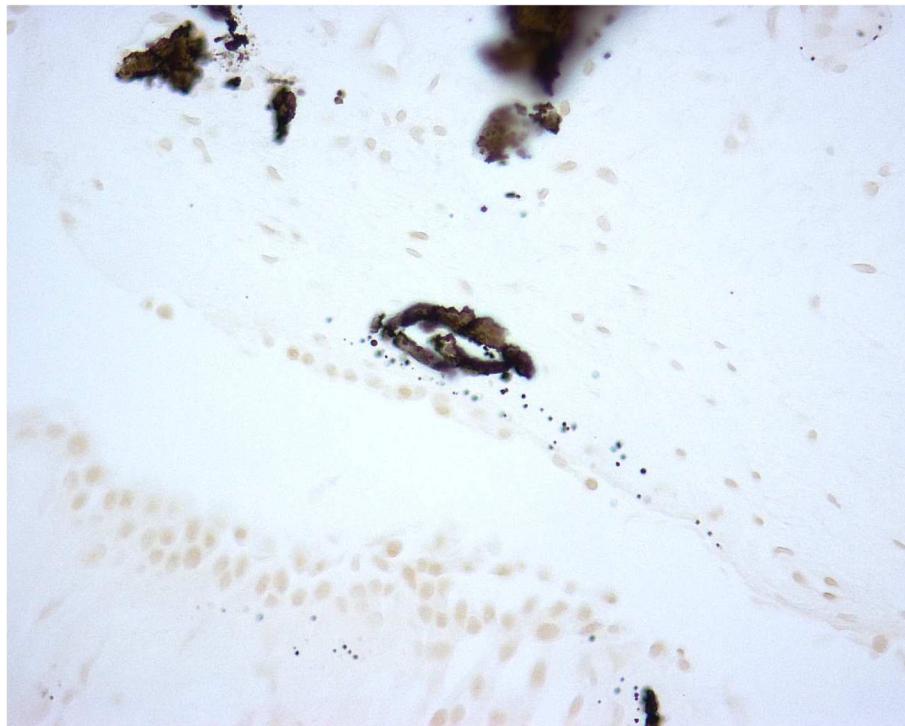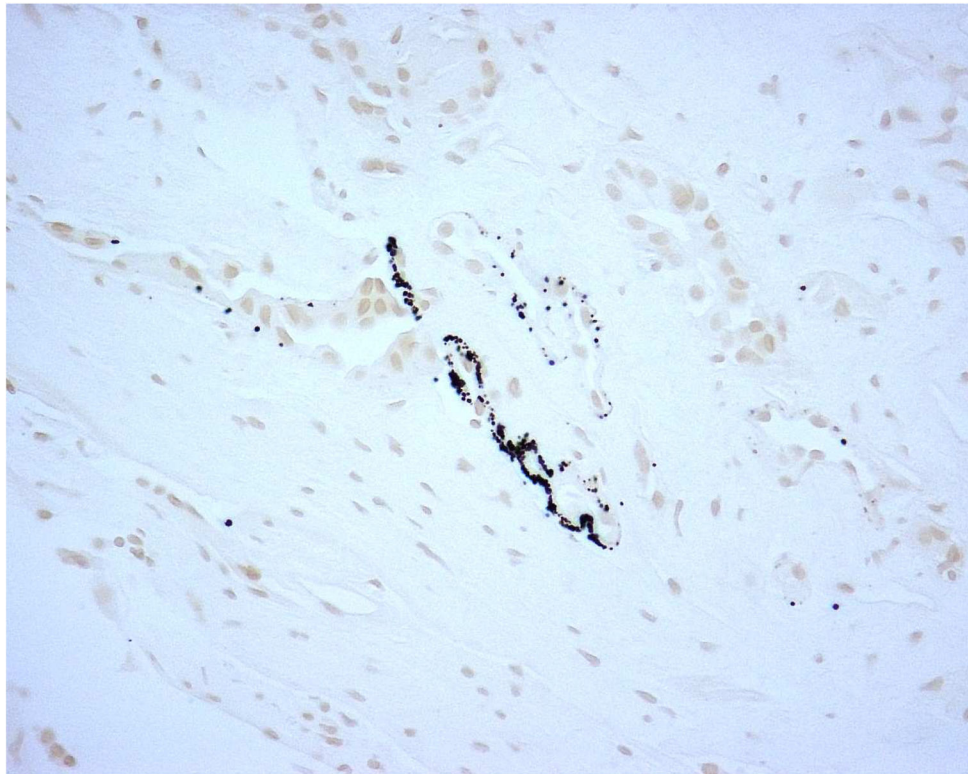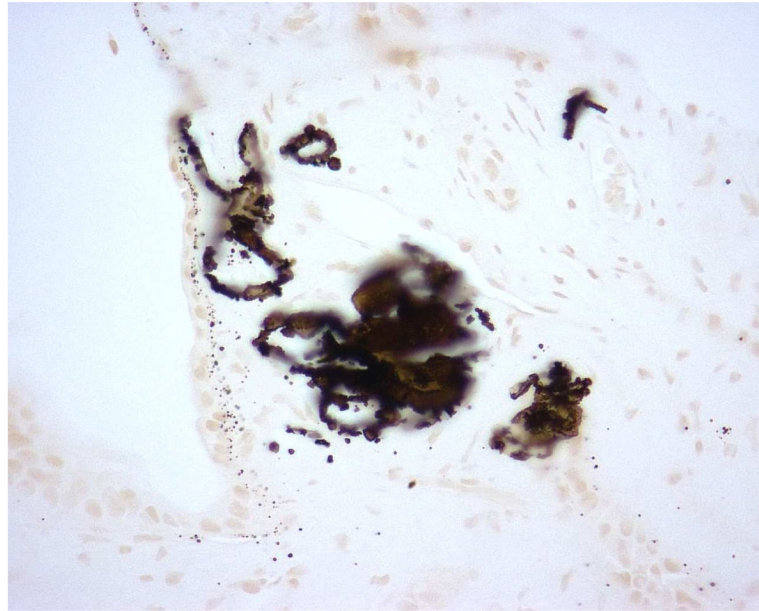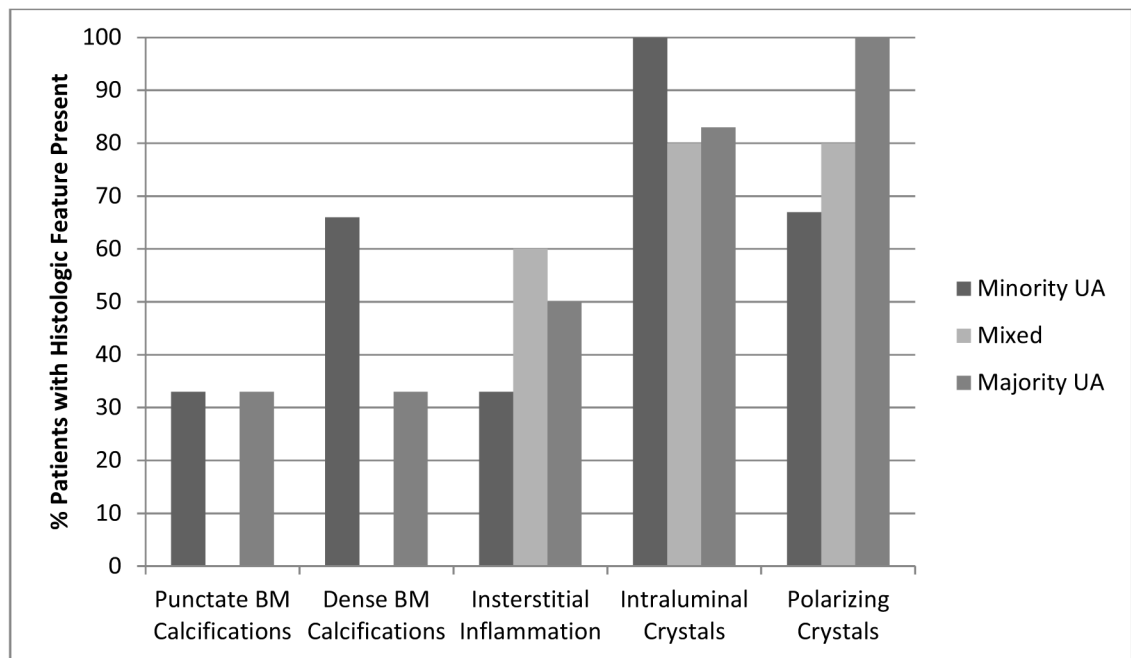
Figure 2.
Yasue-stained papillary biopsies from UA patients demonstrating A.) punctate BM calcifications; B.) dense BM calcifications; and C.) IMCD tubular plug

*p < 0.05

Figure 3.
Quantification of plaque and plug in papillary biopsies. Panel A: CaOx patients had more interstitial inflammation than UA patients and tended towards more punctate calcifications. Panel B: UA stone formers with majority CaOx (minority UA) tended to have more dense calcifications than the others, although this did not achieve statistical significance

Table 1

Endoscopic Precursor Lesions

	Non Stone Forming Endoscopic/Biopsy N = 19	CaOx N = 95	Uric Acid N = 23	*p*-value
% Plaque SA (median; IQR)	0.9 (0.6–1.5)	2.0 (1.0–4.3)	2.0 (1.0–3.1)	0.009
% Plug SA (median; IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.7)	0.1 (0.0–1.0)	0.006
Number with plaque > 0 (%)	17 (90)	95 (100)	23 (100)	0.002
Number with plug > 0 (%)	2 (11)	43 (45)	13 (57)	0.006

Papillary and plaque data obtained at the time of endoscopic mapping.

Abbreviations: Calcium oxalate, CaOx; Surface area, SA