Characterization of Inner Medullary Collecting Duct Plug Formation Among Idiopathic Calcium Oxalate Stone Formers

Marcelino Rivera, Patrick A. Cockerill, Felicity Enders, Ramila A. Mehta, Lisa Vaughan, Terri J. Vrtiska, Loren P. Herrera Hernandez, David R. Holmes III, Andrew D. Rule, John C. Lieske, and Amy E. Krambeck

OBJECTIVE To study the prevalence of, risk factors for, and renal functional consequences of ductal plug formation in idiopathic calcium oxalate (iCaOx) stone formers (SF).

PATIENTS AND METHODS Accessible renal papillae were videotaped to determine the percent surface area (SA) occupied by plaque and ductal plug in a consecutive cohort of iCaOx SF undergoing percutaneous nephrolithotomy for stone removal.

RESULTS Between 2009 and 2014, iCaOx SF comprised 96 of 240 enrolled patients. Of these, 41 (43%) had ductal plugs. Mean plaque SA did not differ between the low and high % plug groups (2.1% vs 3.4%, respectively). The amounts of mean % SA plaque and ductal plug were not strongly correlated (Spearman's $\rho = 0.12$, $P = .3$). Patients with >1% mean SA plug had a higher urinary pH (median 6.5 vs 6.0, $P = .02$) and elevated urinary hydroxyapatite supersaturation (median 5.4 vs 3.7 delta G; $P = .04$). Those with >1% plugging had more extensive ductal dilation ($P = .002$) compared to those with ≤1%. However, estimated glomerular filtration rate was the same (median 75.4 mL/min/1.73 m^2 vs 74.7 mL/min/1.73 m^2). Number of prior stone events was associated with mean and maximum papillary SA occupied by plug ($P < .05$ for both), but not plaque ($P = .3$ and $p = .5$, respectively).

CONCLUSION Within a cohort of iCaOx SF, macroscopic plaque and ductal plugs often coexist. Intraluminal features known to favor calcium phosphate crystallization appear to play a role in plug formation. The pathogenic significance of these plugs remains to be established, although their extent appears to correlate with stone burden. UROLOGY 94: 47–52, 2016. © 2016 Elsevier Inc.

In 1937, Alexander Randall was the first to conclude the existence of a calcium plaque deposited in the renal papillae and observed renal calculi attached to these plaques.[1] Since then, investigations have demonstrated the apatite composition of Randall's plaque, its formation within the medullary interstitium, and the relationship of plaque surface area (SA) corresponding to severity of disease.[2-4] Nearly 80 years since this discovery, significant advances in the understanding and treatment of calcium oxalate (CaOx) stone disease have been made; however, much is still unknown regarding calculogenesis in CaOx stone formation.

Idiopathic CaOx (iCaOx) stone formers (SF), the most common group in the United States, are defined as individuals with predominantly CaOx stones without any systemic disease as a cause of stone formation such as inflammatory bowel disease, prior bowel resection, pancreatic malabsorption, renal tubular acidosis, primary hyperoxaluria, hyperparathyroidism, Dent's disease, medullary sponge disease, or sarcoidosis.[5] Investigations into stone formation in individuals with systemic disease as a cause of CaOx stone formation, in particular small bowel disease, have discovered evidence of cellular injury and inflammation associated with stone formation, Randall's plaque, and duct of Bellini deposits of apatite.[6] Interestingly, previous studies on iCaOx SF failed to demonstrate evidence of ductal deposits or cellular injury, with only predominant overgrowth of stone on plaque.[7-9]

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From the Department of Urology, Mayo Clinic, Rochester, MN; the Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN; the Department of Radiology, Mayo Clinic, Rochester, MN; the Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; the Department of Physiology and Biomedical Engineering, Biomedical Imaging Resource Core, Mayo Clinic, Rochester, MN; and the Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN

Address correspondence to: Amy E. Krambeck, M.D., Department of Urology, Mayo Clinic, 200 1st SW, Rochester, MN 55905. E-mail: krambeck.amy@mayo.edu

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It has been proposed that 2 distinct cellular histopathologic phenotypes exist between calcium SF: Randall's plaque and ductal plugs.[3,6,7] However, a recent investigation of a random consecutive cohort of iCaOx SF has demonstrated ductal plugging in iCaOx SF without evidence of underlying systemic disease, and frequently coexisting with Randall's plaque.[9] Ductal plugging is proposed to arise from tubular injury and altered inner medullary collecting duct or duct of Bellini loss of acidification with concurrent rise in local urinary pH as well as calcium phosphate supersaturation (SS) and crystallization.[6,10] A recent report also described renal papillary pathology and potential renal functional consequences of papillary ductal plugging among hydroxyapatite (HA) SF.[10] Thus, in the current study we evaluated the presence of, risk factors for, and renal functional consequences of ductal plug formation among an ongoing consecutive cohort of iCaOx SF with detailed clinical history, papillary mapping data and histology, and structural and compositional stone analysis.

PATIENTS AND METHODS

This study was approved by the Mayo Clinic Institutional Review Board. Since September 2009, we have prospectively enrolled patients undergoing percutaneous nephrolithotomy in a prospective cohort. All nonpregnant patients over the age of 18 years undergoing elective percutaneous nephrolithotomy for symptomatic upper tract urinary stone disease were informed of our study and offered enrollment. For the current study, the 240 patients enrolled as of December 2014 were evaluated. Computed tomography images were available before the procedure to assess current stone burden. Twenty-four-hour urine studies are obtained with patients on a random diet and performed 6 weeks after stone removal. Percutaneous access was placed in either an upper or lower pole posterior renal calyx to maximize stone removal. One fragment of the removed stone was sent for culture and the remaining for detailed structural and compositional analysis by micro-CT and directed infrared spectroscopy as previously described.[11] The majority of the removed stone material analyzed by micro-CT was used to define the overall stone composition breakdown.

Patients were classified as iCaOx SF if their stones lacked brushite (BR), struvite, uric acid (UA), or drug components, and contained >50% CaOx monohydrate, CaOx dihydrate, or a combination of the 2. Those with any clinical history consistent with systemic disease as a cause for CaOx stone disease including malabsorption from bariatric weight loss surgery, small bowel resection, inflammatory bowel disease, or pancreatic disease; renal tubular acidosis; primary hyperoxaluria; or hyperparathyroidism were excluded from the study. A total of 96 of the 240 patients met these criteria as iCaOx SF.

After all stone materials were removed, the internal papillary structures of the kidney were systematically evaluated and videotaped using a flexible digital nephroscope as previously described.[12] The location of each papilla was determined using fluoroscopy with instillation of contrast through the nephroscope. The collected video data were then used to digitally quantify the percent SA covered by plaque and ductal plug (Fig. 1). Representative still images of each papilla were captured from the video footage. All videos and images were reviewed to determine the location and distribution of the papillae, plaque, and plugs. By using video editing software, the area of the papillae, individual plaques, and plugs were outlined to calculate the percent SA of the plaque and plug. Once the entire kidney was mapped, a papillary tip biopsy was taken endoscopically from an accessible, representative calyx that best illustrated renal pathology. The calyx was selected based on the ability to provide the best biopsy specimen within the confines of the surgical access and instruments. All biopsies were then inspected and characterized by a dedicated renal pathologist (LPHH). A duct of Bellini plug was defined as a crystalline structure protruding from a duct of Bellini that could be physically removed, and a plaque was defined as the presence of discolored and slightly raised urothelium consistent with subepithelial crystal deposition that could not be removed. Assessment of ductal dilation and papillary flattening was performed by a single surgeon (AEK) to decrease variability

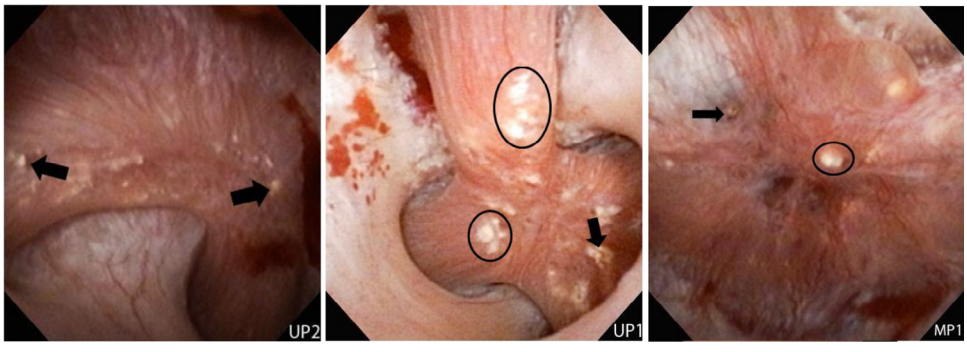

Figure 1. Upper pole (UP2 and UP1) and midpole (MP1) calyx from 3 iCaOx patients. Ductal plugs are marked with the arrow and plaque encircled.