Current Understanding of the Role of Randall's Plaque

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Abstract

The mechanisms by which urinary calculi develop in humans are not entirely understood. In the 1930s, Randall described white plaques on the papillae of cadaveric kidneys from patients with calculi and postulated that this was the site of stone formation in all stone formers. His theory was not well received and for many years was abandoned. It is now known that in certain subsets of stone formers (idiopathic calcium oxalate stone formers), stone formation does occur by overgrowth on Randall's plaque. However, many other types of stone formers do not demonstrate evidence of classic Randall's plaque and must therefore possess a different mechanism for stone formation. Careful endoscopic assessment and renal tissue biopsies from unique stone-forming patients (i.e., those with cystinuria, primary hyperparathyroidism, renal tubular acidosis, and primary hyperoxaluria) has revealed evidence of crystalline plugging within dilated ducts of Bellini with associated inflammation and cell injury. These findings are not identified in idiopathic calcium oxalate stone formers and lead one to believe that alternate pathways to the development of nephrolithiasis must be at play. In this chapter we review the composition and anatomic location of Randall's plaque as well as describe the stone-plaque interface and mechanism of stone overgrowth. Additionally, we review the specific endoscopic and histologic abnormalities in stone-forming patients with cystinuria, brushite stone disease, gastric bypass, ileostomy, primary hyperparathyroidism, renal tubular acidosis, and primary hyperoxaluria and propose potential mechanisms for stone formation.

Introduction

Original Description of Randall's Plaque

In the late 1930s, Alexander Randall proposed that kidney stones grew on the renal papilla attached to underlying deposits or "plaques." Randall examined more than 1,100 cadaveric kidneys, by opening the renal pelvis and carefully examining each papilla with a lens. During these evaluations, he observed white-colored areas on the papillary tips in approximately 20.5 % of the renal units. These white plaques appeared to lie underneath the surface of the urothelium, and

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further evaluation of these papillary lesions with light microscopy suggested that they were located within the interstitium of the kidney. Chemical analysis of the plaques revealed the presence of calcium, nitrogen, carbon dioxide, and phosphorous [1, 2].

In addition to the presence of the calcium-containing plaques, Randall also noted that in some of the renal units, small stones were firmly attached to the areas of plaque. After further evaluating the attached stones, he observed that these calculi appeared to be growing from the interstitial calcium plaque. Additionally, some areas of plaque were noted to have no overlying urothelium and were therefore exposed to urine within the calyx. Finally, he identified some detached stones that had phosphate-containing areas on their surface, which could have potentially represented prior sites of attachment to calcium plaques [1, 2].

Despite the importance of these findings, Randall's theory that stones formed attached to papillary plaques was not widely accepted for several reasons. First, he did not have the necessary technology to determine the exact mineral composition of the papillary plaques nor the composition of mineral at the plaque-stone interface. Second, he proposed that *all* types of kidney stones formed by overgrowth on plaques. His theory was widely disregarded, and it was not until recently that his ideas were reevaluated with regard to the formation of kidney stones. It is now quite clear that Randall's plaque plays an important part in calculus formation in a certain subset of stone formers, namely, idiopathic calcium oxalate stone formers (i.e., calcium oxalate stone formers without evidence of systemic, stone-forming diseases such as primary hyperparathyroidism, distal renal tubular acidosis, sarcoidosis, bowel disease/resection/bypass, or medullary sponge kidney) [1, 2].

Current Understanding of Randall's Plaque

Plaque Location

Evan et al. have extensively studied Randall's plaque in a wide variety of stone formers using a papillary mapping and biopsy protocol [3]. Their initial studies of idiopathic calcium oxalate stone formers (ICSF) revealed that lesions consistent with Randall's plaque were identified at the time of endoscopy in 100 % of these patients. In contrast, in a group of non-stone-forming patients undergoing renal surgery for other indications (i.e., renal neoplasm), no visible Randall plaques were identified. The plaques of the ICSF patients were irregular in appearance and located on the papillary tips, near the openings of ducts of Bellini (Fig. 25.1a). Most plaques appeared to be sub-urothelial; however, occasional plaques seemed to lack urothelial layers. Initial evaluation of the biopsy specimens with light microscopy revealed that the

plaques were always in the interstitium of the kidney and followed the thin loops of Henle up the inner medulla. Further evaluation with electron microscopy demonstrated deposits ranging in size from 50 nm to deposits that formed dense bands, which completely surrounded loops of Henle (Fig. 25.1b). Interestingly, the great majority of tubular cells associated with surrounding plaque deposits showed no evidence of cellular damage or injury. Occasionally, in tubules completely encased by dense crystalline deposits, some cells appeared to be damaged, as evidenced by detachment from the basement membrane and cytoplasmic vacuolization [3]. If the non-stone-forming patients in whom no Randall plaques were visualized, either extremely few or no Yasue-positive deposits were identified.

To further characterize the initial site of crystal deposition in the formation of plaques, biopsy specimens of tissue immediately adjacent to regions of Randall's plaque were evaluated in order to identify the most minimal sites of crystal deposition. Light microscopy revealed very small Yasue-positive (calcium substitution staining) deposits primarily surrounding the thin loops of Henle. Further evaluation with transmission electron microscopy demonstrated that the deposits were located within the basement membrane of the thin loops of Henle and vasa recta, and, regardless of deposit size, the basement membranes of the thin loops of Henle were always involved. Again, no obvious deleterious changes within the cells of the loops of Henle were identified [3].

Plaque Composition

To precisely identify the crystalline composition of the plaque deposits, Evan et al. performed infrared and X-ray diffraction analyses. In all instances, infrared analysis of the Yasue-positive deposits revealed the presence of calcium phosphate in the form of hydroxyapatite. This finding was subsequently confirmed by X-ray diffraction analysis in all cases [3].

Calcium Oxalate Stone Growth on Plaques in ICSF Patients

In 2006, Matlaga and associates reported on the endoscopic findings of stone attachment to Randall's plaque in ICSF patients. In their series of 24 kidneys from 23 ICSF patients, they identified Randall's plaque in 100 % of renal units and found stones attached to areas of underlying plaque in 48 % (Fig. 25.2a, b) [4]. Additionally, Williams and colleagues have used microcomputed tomography (μ[mu]CT)—a technique that distinguishes mineral composition based on differences in X-ray attenuation—to evaluate stones from ICSF patients confirmed as being attached to plaque at the time of surgical intervention. In their initial study of μ(mu)
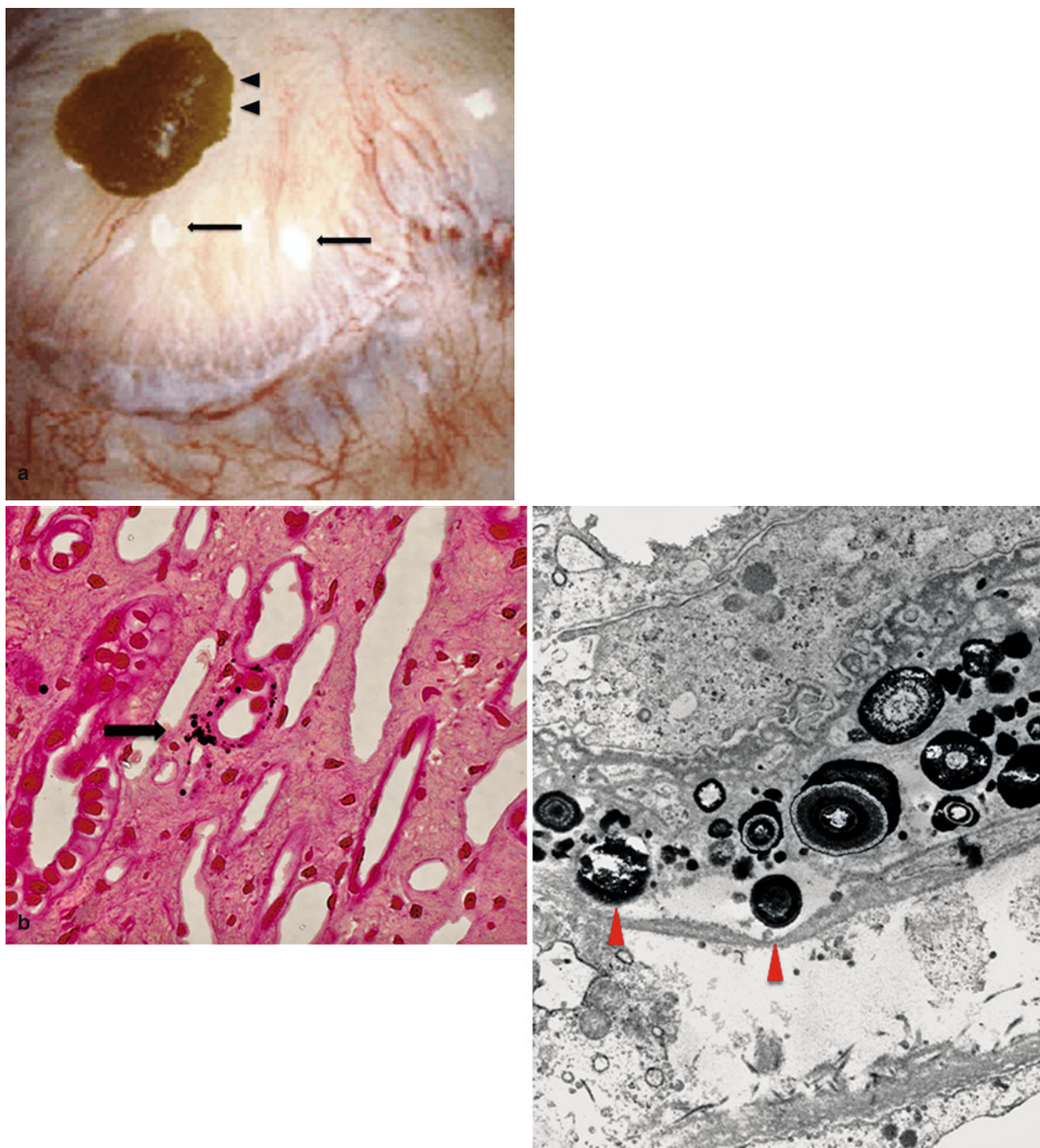
Fig. 25.1 (**a**) Endoscopic view of an ICSF patient. Multiple Randall's plaques are identified (*single arrows*). Additionally, an attached stone is present (*double arrowheads*). (**b**) Light microscopic view (*single black arrow*) and transmission electron microscopic view (*red arrowheads*) of Yasue-positive deposits with the basement membranes of thin loops of Henle

CT evaluation of a small series of attached stones, apatite deposits were identified in all of the predominantly calcium oxalate stones studied and in some instances were identified within concave, stone-surface patches, which could have represented the site of plaque attachment [5]. Because the stone orientation in relation to papillary plaque was not known at the time of μ(mu)CT analysis, this study could not confirm that these stones grew attached to plaque, but it was important in further driving efforts to confirm the accuracy of Randall's theory in ICSF patients.
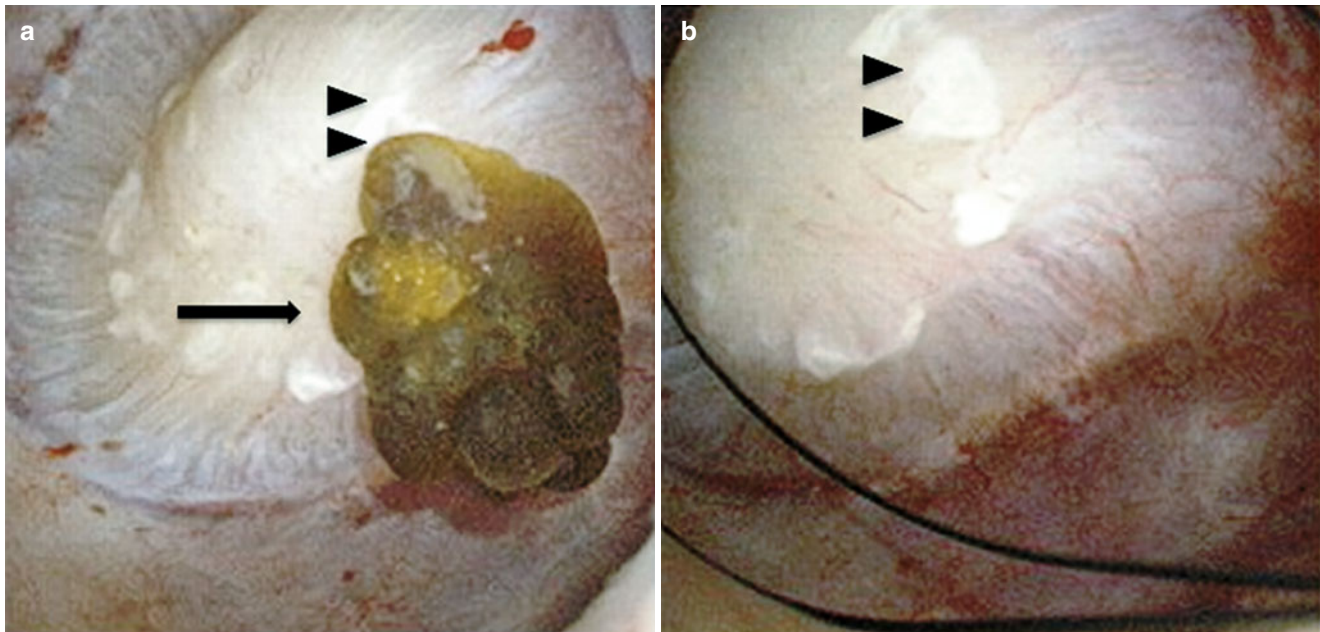
Fig. 25.2 (**a**) Typical attached stone in an ICSF patient (*single arrow*). Randall's plaque is noted on the papilla around the stone (*double arrowheads*). (**b**) Same papilla as in (**a**), after the stone has been manipulated with a Nitinol basket. The area of plaque to which the stone was attached is easily identified (*double arrowheads*)

While the endoscopic observation of stone attachment to Randall's plaque in ICSF stone patients has lent some proof to Randall's original theory of stone growth, it does not provide any understanding of how the process might occur—i.e., the mechanism by which a calcium oxalate stone actually forms on a plaque. It has previously been proposed that elevated urine calcium and reduced urine volume lead to the formation of Randall's plaques in human renal papillae [6]. To date, the process by which these plaques grow toward the surface of the papilla and eventually become exposed to urine via loss of urothelial integrity remains largely unknown.

However, through a series of sophisticated immunohistochemical, infrared spectrometry and μ(mu)CT analyses, Evan et al. have begun to shed new light on the processes that may be occurring at the stone-plaque interface [7]. At the time of exposure to intraluminal urine, the plaque becomes exposed to a number of urinary proteins, including Tamm-Horsfall protein (THP) and osteopontin. These proteins, which are both prevalent in human urine, have an affinity for apatite crystals and appear to form a layer (possibly with other, as yet undetermined proteins) that covers the surface of the exposed plaque. Subsequently, amorphous apatite crystals form within this new protein-matrix layer, a process that appears to be driven by urinary supersaturation of calcium phosphate. Additional urinary proteins are then able to attach to the apatite crystals, forming yet another protein-matrix layer. This again allows for another burst of calcium phosphate crystallization. This process appears to repeat itself, generating a ribbon-like morphology of protein and apatite crystals covering the area of exposed plaque [7].

At some point, apatite crystallization appears to overtake the inhibitory effects of urinary proteins and apatite crystals begin to extend into the collecting system lumen. Eventually, calcium oxalate with or without additional apatite overgrowth begins, again driven by urinary supersaturation. While it has not been precisely determined why the initial crystal type to attach to the exposed plaque is apatite, it is most likely due to the fact that the protein-matrix layer initially formed on the exposed plaque has an affinity for calcium phosphate crystals [7]. The findings of Evan and colleagues, along with the previous work of Kuo, outlining the relationship between elevated urinary calcium and papillary plaque coverage, are important in the urologists' understanding of the appropriate therapies for managing ICSF patients with hypercalciuria [6, 7]. These findings certainly strengthen the argument for urinary calcium reduction with agents such as thiazide diuretics in these patients, as this may reduce plaque abundance and will decrease the urinary supersaturation of calcium oxalate, which eventually drives stone formation.

Unattached Stones in ICSF Patients

In 2009, Miller and colleagues evaluated stones that appeared to be unattached from the renal papilla at the time of percutaneous or ureteroscopic interventions in ICSF patients [8].

In their analysis, 21 stones that were found free within the collecting system were compared to an additional 90 stones that were identified as being attached to renal papillae. Micro-CT technology was used to characterize the composition and ultrastructure of the attached and unattached stones. Of the 21 unattached stones analyzed, 12 showed clear evidence of prior attachment to renal papillae, with each containing a mucus-covered, concave region on only one surface, which by μ(mu)CT analysis contained apatite. The remaining nine unattached stones did not contain mucus-covered, concave, apatite-containing regions on a surface and instead had uniform, dark-brown surfaces. Analysis with μ(mu)CT revealed uniform surfaces with X-ray attenuation values consistent with calcium oxalate monohydrate. However, all nine stones demonstrated subsurface regions that contained apatite. This study provided further evidence to support the fact that most, if not all, stones form attached to papillary plaques in ICSF patients. While it could not be proven from this study, it is certainly possible that the unattached stones without surface apatite had previously grown attached to papillae and at some point became detached [8].

Prior to the study by Miller and colleagues, earlier work by Cifuentes et al. focusing on spontaneously passed stones revealed the presence of surface plaque in 72.4 % of the stones analyzed. Additionally, 13 of the stones with surface plaques contained calcified renal tubules, suggesting that the origin was from a papillary tip [9]. While there are still some aspects of stone formation on Randall's plaques that remain a mystery, the combined results of all of the aforementioned studies provide strong evidence that this is indeed the mechanism by which stone formation occurs in ICSF patients.

Stone Formation in Non-ICSF Patients

While there is strong evidence to support Randall's theory of calcium oxalate stone growth on interstitial plaques in ICSF patients, far less is known about the mechanisms of calculus formation in other stone-forming disease states. Patients with conditions such as cystinuria, brushite stone disease, gastric bypass for obesity, ileostomy for bowel disease, primary hyperparathyroidism (HPT), distal renal tubular acidosis (RTA), and primary hyperoxaluria (HOX) may display evidence of papillary interstitial plaques but additionally have other more dominant and unique papillary features, which suggest that alternate pathways to stone formation are at play.

Tubular Deposits/Ductal Plugging

Coe and colleagues have extensively studied the papillary features of seven additional distinct groups of stone formers (including cystinuria, brushite, gastric bypass, ileostomy, HPT, RTA, and HOX) as well as those of non-stone formers [10]. While some of these stone-forming phenotypes demonstrate endoscopic and histopathologic evidence of papillary interstitial plaques, they all additionally demonstrate tubular deposits of varying crystalline composition—a finding that is uniformly absent in ICSF patients. An additional unique finding that is distinct from ICSF patients is the fact that stone formers with tubular deposits demonstrate evidence of inflammatory response with destruction of epithelial cells and interstitial fibrosis [10].

Differentiating Tubular Deposits from Randall's Plaque

Endoscopically, tubular deposits appear quite different than classic Randall's plaques. Tubular deposits are yellow-colored, suburothelial lesions that often protrude out of the openings of largely dilated ducts of Bellini. Histologically, tubular deposits are located within innermedullary collecting ducts (IMCD) and ducts of Bellini as opposed to the interstitial location of Randall's plaque. Again, tubular deposits appear to be destructive in nature as there is evidence of inflammation and tubular cell injury and death. To date, it has not yet been proven that tubular deposits serve as anchors for stone growth; however, it seems clear that processes different from that of stone overgrowth on plaque are at play in the aforementioned stone-forming disease states, and this is an aspect of the pathology of nephrolithiasis that is actively being researched [10].

Stone-Forming Phenotypes

The papillary and histologic findings of seven distinct stone-forming phenotypes are described as follows (See Table 25.1 for a summary of the endoscopic and histopathological findings identified in the carious stone formers.).

Cystinuria
Endoscopic evaluation of the papillae of cystine stone formers reveals many dilated ducts of Bellini with plugs composed of cystine crystals, which on some occasions project into the collecting system. Randall's plaque may be identified in amounts equivalent to those found in non-stone formers (Fig. 25.3) [10, 11]. Analysis of papillary biopsies demonstrates dilation of IMCDs along with epithelial cell injury within the loops of Henle and IMCDs. Apatite crystals are identified within the loops of Henle and IMCDs, while the large plugs identified within the dilated ducts of Bellini are always composed of cystine. Evan and colleagues have proposed a hypothesis to account for these findings and suggest

Table 25.1 Relative amount of plaque coverage, papillary damage, and stone growth on plaque identified in the various stone phenotypes

Stone disease	Plaque presence	Papillary damage[a]	Stones on plaque
Idiopathic calcium oxalate stone former	++	–	++
Cystinuria	–	+	–
Brushite	++	+++	–
Gastric bypass	–	+	–
Ileostomy	+	+	–
Primary hyperparathyroidism	Variable	++	+/–
Renal tubular acidosis	–	+++	–
Primary hyperoxaluria	–	++	–

[a]Papillary damage is determined based on degree of pitting, papillary retraction, duct of Bellini dilation and deposits within ducts of Bellini noted during endoscopy and papillary mapping

Fig. 25.3 Endoscopic view of a papilla in a patient with cystinuria. There is minimal identifiable Randall's plaque. There is a large cystine plug within a dilated duct of Bellini (*single arrow*)

that cystine crystallizes within the ducts of Bellini, resulting in cell injury and obstruction of individual nephrons. These changes could then potentially lead to loss of fluid pH regulation in IMCDs and subsequently allow for apatite crystallization [10–12].

Brushite Stone Formers

Brushite stone formers typically have a significant degree of hypercalciuria and alkaline urine and tend to have aggressive stone disease [13]. Evan and colleagues have endoscopically and histologically studied a cohort of brushite stone formers [14]. Endoscopically, these patients have unique-appearing papillae in which three different types of deposits are
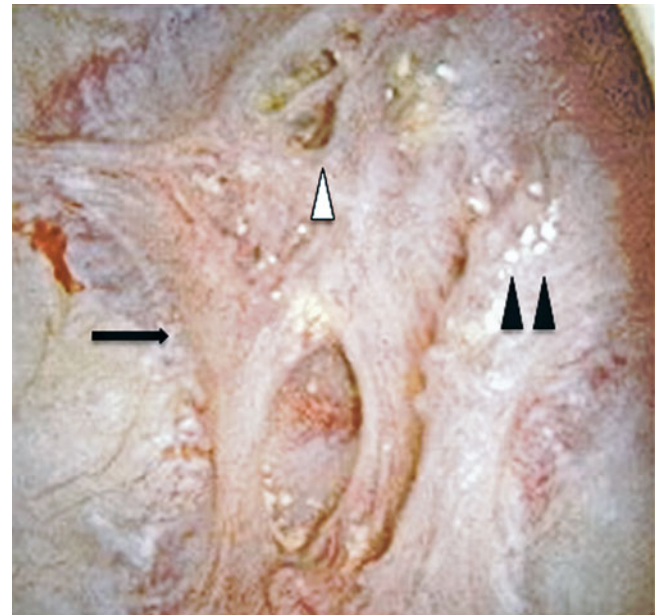

Fig. 25.4 Endoscopic view of a papilla in a brushite stone former. The papilla is quite abnormal, with areas of retraction and pitting (*single black arrow*). Areas of Randall's plaque are present (*double black arrowheads*). Dilated ducts of Bellini with plugs are also identified (*single white arrowhead*)

identified. Typical-appearing Randall's plaque is noted in this cohort of patients, yet stone overgrowth on these plaques is not observed. Also, yellow deposits arising from dilated ducts of Bellini (which project into the lumen of the collecting system) and suburothelial deposits (typically along the sides of the papillae) within the lumens of IMCDs are present. An additional abnormal endoscopic finding in brushite stone formers includes retraction of papillae and papillary pitting, which is typically associated with dilated ducts of Bellini. The prevalence of plugging and papillary changes is variable among this group of stone formers, but it is often severe (Fig. 25.4).

Histologically, there is evidence of extensive cell injury and interstitial fibrosis around the crystal-filled collecting ducts. Similar signs of interstitial fibrosis, tubular atrophy, and glomerulosclerosis are noted within cortical tissue samples as well. Mineral analysis of the tubular deposits in brushite patients reveals mostly apatite, although calcium oxalate may be found in small amounts on some occasions [10, 11, 14].

Gastric Bypass

Patients who undergo jejunoileal bypass for the management of obesity are at risk for forming calcium oxalate stones due to the metabolic abnormalities induced by the procedure. These patients develop fat malabsorption, intestinal saponification of calcium and magnesium, decreased binding of calcium and oxalate in the gut, and subsequent hyperoxaluria. Additionally,
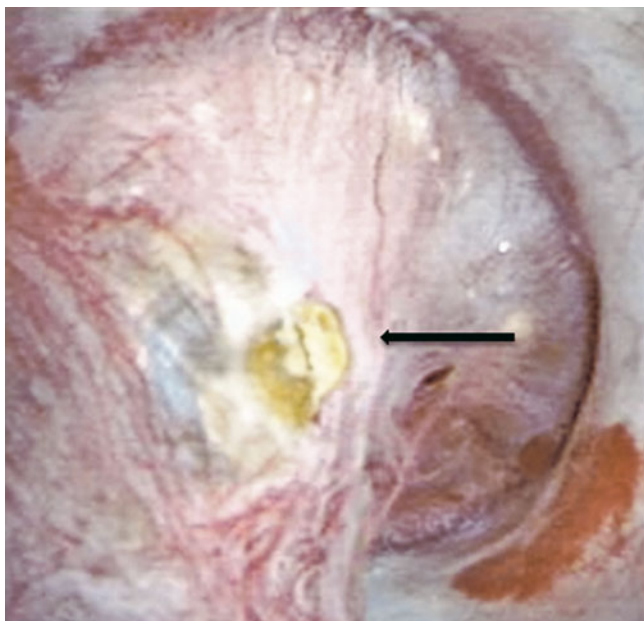
Fig. 25.5 Endoscopic view of a papilla in a patient who has undergone bariatric surgery. No Randall's plaques are identified. Note the nodular plug emanating from a largely dilated duct of Bellini (*single arrow*)

they are prone to low-volume, acidic urine, again due to malabsorption.

Evan and associates have studied patients who have undergone intestinal bypass and subsequently developed calcium oxalate stones as a unique cohort [3]. Interestingly, when evaluated endoscopically, these patients do not demonstrate evidence of typical Randall's plaque. Instead, nodular yellow deposits project off of the papillary urothelium in close proximity to the openings of ducts of Bellini (Fig. 25.5). Histologically, no interstitial apatite deposits are present. Crystals appear to be attached to the apical surfaces of collecting duct cells or fill the ducts completely, and there is associated cell injury and death. Analysis of the crystals within the IMCDs and ducts of Bellini reveals the majority to be apatite. This is a rather puzzling finding due to the fact that these patients generally have acidic urine with high calcium oxalate content, which does not promote supersaturation of apatite, a mineral that typically forms in an alkaline environment (see later discussion on mechanisms for tubular plaque formation) [3, 10, 11].

Ileostomy Patients

Ileostomy patients are prone to significant GI losses, low urine volume, and highly acidic urine. These patients lack a colon and therefore do not readily absorb oxalate. Therefore, the stone type to which they are most prone is uric acid. Endoscopically, these patients are also noted to harbor Randall's plaque and tubular deposits. They generally do not demonstrate evidence of stone overgrowth on plaque, although this may be seen on occasion. Microscopically, the

tubular deposits are identified within the thin limbs of the loops of Henle and within the collecting ducts. Again, there is associated cellular injury and fibrosis. This cohort of patients represents another paradox, in that their tubular deposits are composed of apatite and/or ammonium acid urate, both minerals that form in an alkaline environment [10, 15].

Primary Hyperparathyroidism

Patients with HPT are prone to forming both calcium oxalate and calcium phosphate (hydroxyapatite and brushite) stones and represent a unique cohort of stone formers. These patients have also been extensively studied by Evan and colleagues [16]. The renal papillae in these patients demonstrate a significant amount of variability with regard to plaque coverage. In some patients, Randall's plaque is found in amounts similar to that of non-stone formers, while in others, large quantities of Randall's plaque with attached stones are identified. In all patients with HPT, at least some of the papillae demonstrate evidence of tubular deposits and ductal plugging, but again, the degree to which this occurs is variable. Additionally, papillary changes including pitting and retraction are noted in varying degrees (Fig. 25.6) [16].

Histopathology reveals plugging of ducts of Bellini and IMCDs with crystals as well as associated cell injury/death and interstitial fibrosis. In some instances, the ductal plugging extends to the outer medullary collecting ducts (OMCDs) and cortical collecting ducts. In all patients studied by Evan and colleagues, the crystalline composition of the plugged ducts was uniformly apatite. The constellation of endoscopic and histopathologic findings in HPT patients is quite similar to those seen in brushite stone formers. However, to date, HPT patients are the only stone formers that have been noted to have both tubular deposits and stone overgrowth on Randall's plaque. The finding of abundant Randall's plaque in patients with HPT could in part be due to the associated induced hypercalciuria, a urinary parameter associated with plaque abundance. Unfortunately, to date, the papillary studies of HPT patients have been performed on those who have already undergone curative treatment for their hyperparathyroidism. Therefore, marked hypercalciuria and elevated urinary pH (parameters that are prominent in brushite and RTA patients) had not been documented prior to endoscopic surgery in this cohort and therefore cannot be presumed to be the cause for ductal plugging with apatite [16].

Renal Tubular Acidosis

Patients with distal RTA possess a defect in hydrogen ion secretion in the distal nephron, which results in metabolic acidosis, hypocitraturia, and persistently alkaline urine. Due to the alkaline nature of their urine, they are prone to developing calcium phosphate stones (apatite), although some patients may form stones that contain varying amounts of
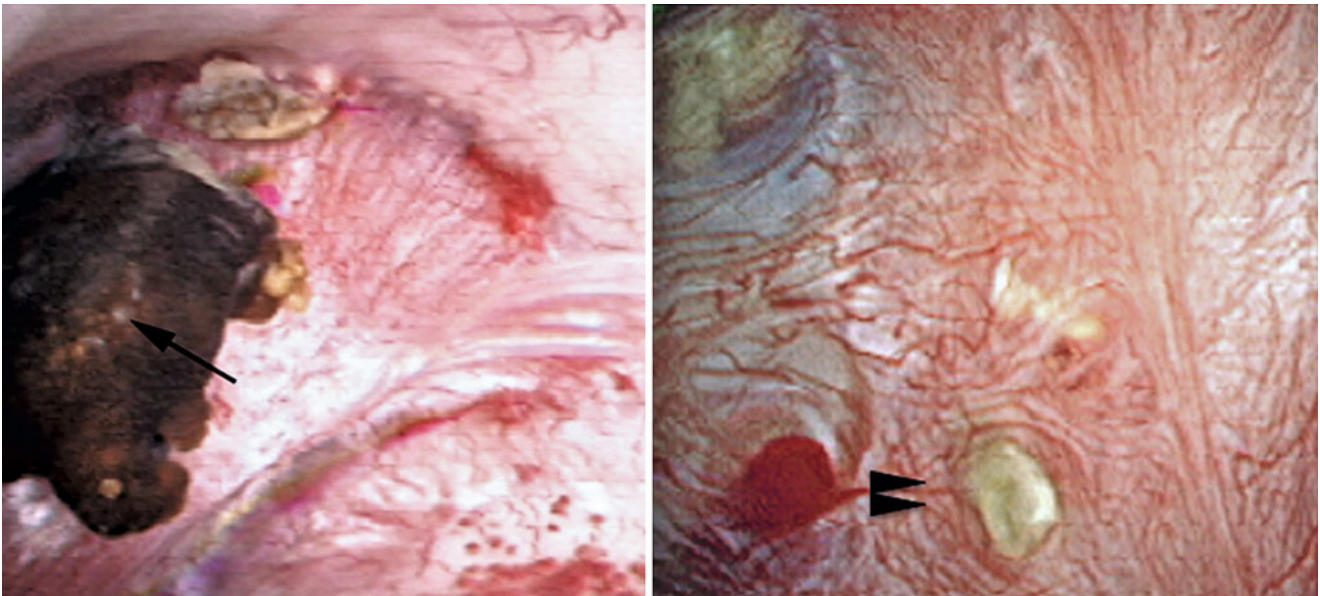
Fig. 25.6 Endoscopic view of a papilla in a patient with HPT. On *the left*, an attached calcium oxalate stone is present (*single arrow*). On *the right*, a plugged duct of Bellini is identified (*double arrowheads*)

calcium oxalate. Patients with this condition frequently have aggressive stone disease and demonstrate radiographic evidence of nephrocalcinosis.

Evan and colleagues have also studied the surgical pathology and histopathology in this unique cohort of stone formers [17]. Endoscopically, a broad spectrum of abnormalities are noted, with some patients demonstrating minimally abnormal papillae and others demonstrating severe pitting of the papillae and numerous dilated ducts of Bellini with protruding mineral plugs. Additionally, suburothelial densities are often encountered (Fig. 25.7). When the urothelium overlying these densities is unroofed, small stones within cavities are identified. These stones are actually isolated within the parenchyma. At the time of endoscopic intervention in these patients, the great majority of stones identified on radiographic films are identified within the collecting system and are amenable to surgical removal [17].

Analysis of papillary biopsies from these patients reveals apatite deposition (combined with trace amounts of calcium oxalate in rare instances) within IMCDs and ducts of Bellini with associated interstitial fibrosis and epithelial cell loss. In these patients the degree of fibrosis is extensive and is often found surrounding tubules that do not contain mineral deposits. Cortical biopsies reveal a range of glomerular diseases, but changes of interstitial fibrosis are generally mild [17].

Primary Hyperoxaluria

Patients with HOX have disorders of glyoxalate metabolism that are inherited in an autosomal recessive fashion. These abnormalities result in excessive oxalate production and urinary excretion, which in turn leads to calcium oxalate neph-
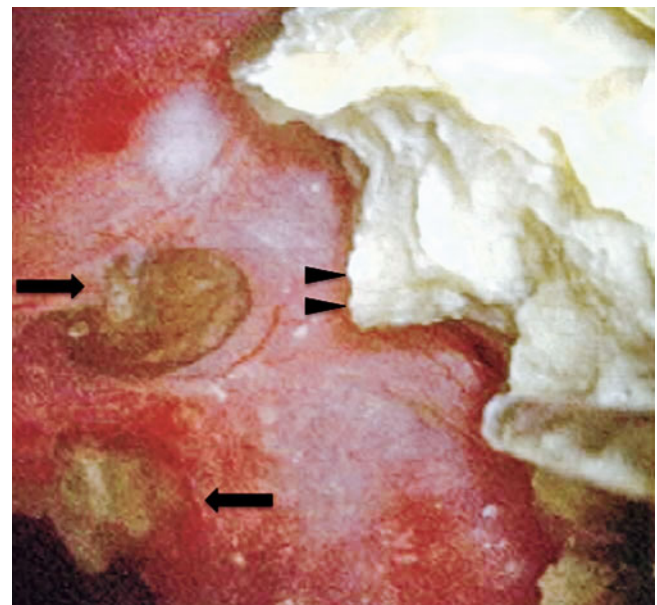

Fig. 25.7 Endoscopic view of a patient with RTA undergoing PNL. Note the large crystalline plugs within dilated ducts of Bellini (*single arrows*). No significant Randall's plaque coverage is identified. A large calyceal stone that has been partially treated is seen on the right (*double arrowheads*)

rolithiasis. These patients can potentially go on to develop end-stage renal disease (ESRD) and numerous other complications associated with dystrophic calcification of calcium oxalate.

This cohort of patients has been less well studied due to the rarity of the disease. However, endoscopic and pathologic evaluations of kidneys in HOX patients with ESRD

have been performed [10]. Endoscopically, HOX patients have minimal Randall's plaque in amounts similar to that seen in non-stone-forming patients. However, these patients do demonstrate papillary tubular deposits within ducts of Bellini and IMCDs. Analysis of tubular deposits reveals abundant calcium oxalate, a unique finding when compared to other stone-forming phenotypes in which ductal deposits are identified. In patients with HOX and ESRD, deposits can be identified in all segments of the nephron. As in other stone formers with ductal plugging, interstitial fibrosis and cell death is observed [10]. Table 25.1 summarizes the degree of plaque coverage, papillary damage, and stone growth on plaque in all of the aforementioned stone phenotypes.

Mechanisms of Ductal Deposit and Stone Formation

The process by which patients with prominent tubular deposits and ductal plugging form stones is not yet well understood and is currently the subject of active and elegant research. It is clear, however, that the pathway to stone formation must be different than that which occurs in ICSF, as patients with the aforementioned phenotypes (with the exception of some patients with HPT) do not demonstrate evidence of stone overgrowth on Randall's plaque. It is quite likely that different processes are occurring within the tubular deposit phenotypes [10].

If one reviews Finlayson's hypothesis that calcium oxalate is formed too slowly and in too small an amount to plug a renal tubule without an anchoring site, it would seem to hold true (with the exception of HOX patients who have exceedingly high oxalate excretion) based on the findings in the previously described stone formers [18]. Given the fact that tubular deposits are found in ducts of Bellini and IMCDs, one would expect that this is related to the urinary supersaturation of various crystals (i.e., calcium phosphate or calcium oxalate). This would explain why patients who do not form stones and have low supersaturations of calcium oxalate and calcium phosphate demonstrate no evidence of deposits. Calcium phosphate supersaturation in patients with cystinuria (likely as a result of alkaline therapy), brushite stone disease, RTA, and HPT are quite high, and it is possible that this results in deposits secondary to free solution nucleation. This free solution theory of ductal plugging also seems appropriate in HOX patients in whom the urinary supersaturation of calcium oxalate is exceedingly high when compared to all other stone formers [10].

However, how can one explain the finding of apatite and/or ammonium acid urate plugging in patients with ileostomy, when these patients have extremely low urinary pH and low calcium phosphate supersaturation? How can gastric bypass patients, who have high calcium oxalate supersaturation and

low calcium phosphate supersaturation, develop apatite plugs within their ducts? Somehow, it must be the case that tubule fluid pH is higher than that of the bulk urine, at least in some ducts of Bellini and IMCDs. How and why these localized defects in tubular urine acidification arise is not well understood and studies assessing the pH of bulk urine, normal ducts, and abnormal (plugged) ducts in ileostomy patients are currently underway [10].

Conclusion

One final and important distinguishing feature between the stone phenotypes in which tubular deposits are prominent and ICSF patients is the fact that patients with tubular deposits demonstrate evidence of interstitial fibrosis, cellular injury, and death, while ICSF patients do not demonstrate any evidence of tissue damage. The postulated mechanisms by which tissue damage occurs in the various types of stone formers are diverse. What is important is that these stone formers must be considered as being at risk for developing renal dysfunction at some point in their lifetime. Therefore, it is important that these patients are monitored closely and any metabolic abnormalities that they harbor must be managed aggressively. Additionally, the fact that these patients have cellular injury associated with tubular deposits makes one consider the possibility that aggressive stone removal, including removal of tubular plugs, may lead to a reduction in renal tissue damage in the future.

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