

of associated features including atrophy, inflammation and stromal reaction. Pathologic parameters of HGPIN were correlated with detection of PCa in subsequent biopsy (ies).

Results: 66.7% of patients with two or more cores involved by HGPIN had PCa on subsequent biopsy. In contrast, 38.6% of patients with only one core with HGPIN were detected to have PCa ($p=0.015$, Fishers exact test). Tufted and flat were the most common architectural patterns. The presence of micropapillary HGPIN was associated with greater likelihood of subsequent PCa detection ($p=0.041$, Pearson χ^2 test). By multivariate analysis, pattern of HGPIN (micropapillary and cribriform) was the only independent predictor of cancer on rebiopsy ($p=0.013$, RR 4.586). Other pathologic variables failed to have predictive value for subsequent detection of PCa.

Conclusions: Patients with initial diagnosis of HGPIN, which demonstrates micropapillary or cribriform architecture or is present in multiple cores, should be candidates for more aggressive investigation to detect PCa, potentially by early rebiopsy and more aggressive sampling.

Editorial Comment

High-grade prostatic intraepithelial neoplasia (HGPIN) is considered a precursor lesion of invasive prostate carcinoma. This is evidenced by several findings: HGPIN is more frequent in patients with than without prostate carcinoma; in some rare cases, it is possible to document a transition between HGPIN and invasive carcinoma; the mean age of patients with HGPIN is lower than patients with invasive carcinoma; and, there are similarities between phenotypic and genotypic findings between these 2 conditions.

Many terms were used to refer to this condition. In 1989, during a consensus workshop held in Bethesda, MD, USA (Urology. 1989; 34: (suppl.) 2-3) it was suggested to use the term prostatic intraepithelial neoplasia (PIN). In this consensus meeting was also agreed to refer in the pathology report only high-grade PIN (grades 2 or 3) and not low-grade PIN (grade 1). Bostwick et al. (Hum Pathol. 1993; 24: 298-10) described 4 architectural patterns of HGPIN: micropapillary, tufted, flat, and cribriform. These are considered morphologic variants without any predictive value.

This paper showed that the architectural patterns of HGPIN might have importance to predict prostate cancer on subsequent biopsies. By multivariate analysis, the micropapillary and cribriform patterns of HGPIN were independent predictors of cancer on rebiopsy. Based on this paper, for the urologist is worth asking the pathologist to include in the pathology report the architectural pattern of HGPIN.

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INVESTIGATIVE UROLOGY

Comprehensive evaluation of ureteral healing after electrosurgical endopyelotomy in a porcine model: original report and review of the literature

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Purpose: Endopyelotomy (EP) has yet to equal the success achieved with open dismembered pyeloplasty. To understand better the ureteral response to EP we performed a timed histopathological evaluation of the porcine ureter after Acucise (Applied Medical, Rancho Santa Margarita, California) EP.

Materials and Methods: In 28 domestic pigs bilateral Acucise EPs were performed and bilateral 7Fr stents were placed. The kidneys, ureters and bladder were harvested after EP at 0, 1, 2, 3, 6, 12 and 18 hours, 1, 3 and 5 days, and 1, 2, 4 and 8 weeks. The stents were removed after 4 weeks. The healing area of the ureter was sectioned. Half was fixed in formalin 10%, stained and evaluated by light microscopy. The other half was frozen and reverse transcriptase-polymerase chain reaction was performed to measure steady state levels of epidermal growth factor, transforming growth factor (TGF)-alpha, TGF-beta 1, TGF-beta 2, TGF-beta 3, keratinocyte growth factor, vascular endothelial growth factor, insulin-like growth factor, platelet derived growth factor, collagen type 1, integrin and fibronectin transcript expression. Immunohistochemistry for actin, desmin and myosin expression was completed. The same studies were applied to the mid portion of the unoperated ureter.

Results: Initial sealing of the ureterotomy defect was by blood clot and periureteral fat. Complete healing of the mucosa was observed at 2 weeks in animals without an associated urinoma. However, in no case did the muscle layer bridge the whole circumference of the ureter despite followup out to 8 weeks. In the operated ureter elevated expression of keratinocyte growth factor, vascular endothelial growth factor, TGF-alpha, TGF-beta 1, TGF-beta 3 and integrin was detected 2 hours after the operation and sustained for 7 to 14 days after the procedure. Immunohistochemistry revealed that most presumed myocytes seen in the defect were actually myofibroblasts. Persistent urinoma formation beyond the first few days appeared to slow the healing process.

Conclusions: Urothelium regenerated rapidly over an iatrogenic ureteral defect despite the absence of a lamina propria. Muscle cell coverage failed to occur completely at 8 weeks. In the initial 8 weeks of the healing process myofibroblasts appear to be prevalent. A persistent urinoma negatively impacts the healing process.

Editorial Comment

This paper by Andreoni and colleagues is welcome, because it updates our knowledge on the natural response of the ureter to an endoureterotomy, since current understanding on this topic is based on papers from 1940's (1). Using current methods in histopathology (eg cell specific stains) and immunohistochemistry (eg growth factors) the authors evaluated the acute and chronic impact on the ureter and renal pelvis of an Acucise catheter incision in the pig.

The authors found that in the pig the urothelium rapidly regenerates and covers the incision site within a few weeks, and that an urinoma formation appears to slow the healing process. Functional smooth muscle cells or smooth muscles bundles failed to bridge the defect completely even 8 weeks after endopyelotomy. In addition, the authors suggest that growth factors, including TGF- 1, TGF- and KGF, may have a role in promoting ureteral healing after endopyelotomy.

The most distinguished finding of the present study was that the nonepithelial cells found in the endopyelotomy defect appeared to be myofibroblasts and not smooth muscles cells, which was possible to be identified by immunohistochemical techniques. It is likely that the classic studies of intubated ureterotomy erroneously concluded that there was true regeneration of the ureter. The authors suggest that it might have been myofibroblasts and not smooth muscle cells responsible for apparent closure of the ureterotomy defect. Future investigations using electron microscopy or biochemical techniques would better clarify this issue.

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A porcine model of calcium oxalate kidney stone disease

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Purpose: The pig has been extensively used in biomedical research because of the similarities in organ structure and function to humans. It is desirable to have an animal model of oxaluria and urolithiasis with physiological, anatomical and nutritional characteristics that more closely resemble those of man. In this study we determined if feeding pigs trans-4-hydroxy-l-proline (HP) increased urine oxalate levels and if it would serve as a model for human hyperoxaluria and stone disease.

Materials and Methods: Male Yorkshire-Durox cross-bred pigs were fed HP for up to 20 days. Urine was periodically collected and analyzed for oxalate levels and the presence of crystalluria. After 20 days of feeding the kidneys were removed and examined grossly and microscopically for indications of injury, crystal deposition and stone formation.

Results: Feeding pigs 10% HP (weight per weight HP/food) produced hyperoxaluria, which reached a maximum and leveled off by day 6. Urine oxalate remained near this level until the study ended at 20 days regardless of the further increase in HP to 20% of the weight of the food. When the kidneys were removed and grossly examined, calcium oxalate encrustations were observed on multiple papillary tips. Histopathological observation of the papillary tissue showed tissue injury and crystal deposition.

Conclusions: Pigs fed HP have hyperoxaluria and calcium oxalate crystalluria, and calcium oxalate papillary deposits form that may be precursors of kidney stones. The use of the pig as a model of human hyperoxaluria and stone formation should prove ideal for studies of these human diseases.

Editorial Comment

In addition to be an excellent animal model for surgical experimentation due to its extra and intra-renal anatomy similarities to humans (1,2) swine have also been shown to be a good model for clinical urological studies, including the formation and treatment of renal calculi.

In this research study, the authors tested if feeding pigs with trans-4-hydroxy-l-proline HP would increase their urine oxalate levels and produce a model of hyperoxaluria and calcium oxalate stone disease. The addition of HP to the pig diet resulted in an increase in urine oxalate excretion. Urine oxalate levels appeared to reach the maximum level at day 6 for all 3 HP fed pigs. Increasing the HP in the feed up to 20% by feed weight resulted in no further increase in urine oxalate levels.

The authors found no morphological changes in corticomedullary or papillary areas in control pigs, on the other hand, changes indicative of cellular injury were observed in HP fed pigs. These changes included

diffuse corticomedullary interstitial fibrosis with tubular dilatation, oxalate crystal deposition in tubules and focal collecting duct epithelial cell necrosis with aggregates of calcium oxalate crystals located at the papillary tip in all HP fed pigs. All these findings clearly demonstrated the feasibility of pig use as a model of human hyperoxaluria and stone formation.

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Intravesical nitric oxide production discriminates between classic and nonulcer interstitial cystitis

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Purpose: Interstitial cystitis (IC) is one of the most bothersome conditions in urological practice. There are 2 subtypes, classic and nonulcer IC, with similar symptoms but different outcomes with respect to clinical course and response to treatment. Histologically there are fundamental differences between the 2 subtypes, classic IC presenting a severe abnormality of the urothelium and characteristic inflammatory cell infiltrates while inflammation is scant in nonulcer IC. Regulation of urinary nitric oxide synthase activity has been proposed to be of importance for immunological responses in IC. We present evidence of a profound difference between the 2 subtypes concerning nitric oxide production, mirroring the differences in inflammatory response in IC.

Materials and Methods: A total of 17 patients with both subtypes and active disease as well as patients with disease in remission were included in the study, all diagnosed according to National Institute for Diabetes and Digestive and Kidney Diseases criteria. Luminal nitric oxide was measured in the bladder of patients using a chemiluminescence nitric oxide analyzer.

Results: All patients with classic IC had high levels of NO. None of the other patients had any significant increase in NO levels in the bladder. The NO level in patients with classic IC was not related to symptoms but rather to the assignment to this specific subgroup of IC. The highest levels of NO were found in patients in the initial phase of classic IC.

Conclusions: The difference in NO evaporation between classic and nonulcer IC allows for subtyping of cases meeting National Institute for Diabetes and Digestive and Kidney Diseases criteria without performing cystoscopy. The findings in the present series together with previous findings clearly demonstrate that the 2 subtypes of IC represent separate entities. This separation further emphasizes the need to subtype all cases included in all scientific matters, ensuring that the 2 subtypes are evaluated separately in clinical studies.

Editorial Comment

Interstitial cystitis (IC) is often subdivided into 2 different subtypes: the classic “ulcerous” form of interstitial cystitis and the “early” or “nonulcer” form. The differences between the 2 subtypes are reflected in clinical manifestation and age distribution. It has also been demonstrated that the 2 subtypes respond differently to many treatment procedures (1). The main tool for differential diagnosis between the 2 forms of disease has been cystoscopy.

Classic IC presents at endoscopy with reddened mucosal areas. These are often associated with small vessels radiating towards a central scar that ruptures with increasing bladder distension. Histological specimens obtained from lesions demonstrate that classic IC is a destructive inflammation and some patients eventually develop a small capacity fibrotic bladder. Outflow obstruction of the upper urinary tract may also occur in the final stage of classic IC.

In nonulcer IC, the bladder mucosa is normal at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign. Histologically, there are no or scant inflammatory signs in nonulcer disease (1).

In the present pioneer study, the authors demonstrated that all patients with classic IC showed high or very high levels of NO. None of the other patients had any significant increase in NO in the bladder. The NO level in patients with classic IC was not related to symptoms but rather to the assignment to this specific subgroup of IC. However, disease stage seemed to influence NO levels with the highest levels of NO found in patients in the initial phase of classic IC. The difference in NO levels between classic and nonulcer IC allows for subtyping of cases without performing cystoscopy.

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RECONSTRUCTIVE UROLOGY

Creation of luminal tissue covered with urothelium by implantation of cultured urothelial cells into the peritoneal cavity

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Purpose: We established the culture condition of seeding urothelial cells onto a scaffold for implantation into the peritoneal cavity and evaluated the histology of implanted urothelial cells.

Materials and Methods: In part 1 of the study cultured porcine bladder urothelial cells were seeded onto 3 types of collagen gel made on microporous membrane, including collagen gel with or without cultured porcine bladder fibroblasts, or a feeder layer. The macroscopic and microscopic appearance of the gel with urothelial cells were examined in vitro. As an in vivo study, cultured porcine bladder urothelial cells were