Urinary Bladder Carcinoma Suggestive of Enzootic Hematuria with Secondary Hydronephrosis in a Holstein Cow

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History and Physical Examination

A three-year-old Holstein cow, in the third month of her second lactation, was evaluated at the New York State College of Veterinary Medicine in February 1987 for a depressed appetite and decreased milk production of one month's duration. The cow had calved uneventfully and milk production had peaked at nearly 100 lbs per day prior to illness. Early in the course of disease, she had received a 7-10 day regimen of systemic penicillin from the owner without any apparent beneficial response. No treatments were administered within the two weeks immediately prior to presentation at the Large Animal Clinic. At the time of admission to the Large Animal Clinic, her daily milk production was between 5 to 20 pounds.

The cow was from a milking herd consisting of 85 cattle housed in a conventional tie-stall barn and milked twice a day. The diet consisted of a commercial grain supplement with corn silage and haylage in the summer and fall, and grain supplement with corn silage plus dry alfalfa hay at other times of the year. In addition, during the warmer months cattle were allowed access to ample pasture which contacted an overgrown wooded area containing several species of ferns including Bracken Fern *(Pteridium aquilinum).*

Physical examination revealed the cow to be thin and 5% dehydrated. Indistinctly lobulated, grossly enlarged left kidney surrounded by a fluid density, and bilateral ureteral dilatation were detected per rectum. As the ureters were followed caudally by palpation per vagina, a soft tissue density (2 cm diameter) was located at the neck of the bladder near the ureteral orifices. Considerations for the fluid in proximity to the left kidney included urine within a stretched renal capsule secondary to lower urinary tract obstruction, inflammatory infiltrate secondary to pyelonephritis from ascending infection, or perirenal edema as observed in tubulointerstitial insult from toxins (eg. plants, drugs), ischemia, or nephritis secondary to toxemia or bacteremia.

Symmetric enlargement of both ureters suggested an ascending process from the lower urinary tract but the cow did not demonstrate pollakiuria nor did the ureters seem painful to palpation as might be seen with ascending infection. This seemed to indicate the possibility of a urinary bladder mass or adhesions in the trigone area interfering with urine passage through the ureteral orifices, followed by an increase in intra-ureteral pressure and subsequent nephropathy.

Ancillary Findings

Results of a hemogram were normal with the exception of a mild elevation in plasma total solids (10.4 g/dl) that reflected the systemic dehydration. Serum albumin (3.4 g/dl) and globulin (4.70 g/dl) levels were both within normal reference ranges, as were serum electrolyte values. Azotemia was the sole serum biochemical abnormality (creatinine concentration 6.4 mg/dl; urea nitrogen 63 mg/dl) that when viewed in light of the cow's minimal magnitude of dehydration indicated probable renal dysfunction. Urinalysis revealed hyposthenuria (sp. gr. 1.007) confirming primary renal disease with tubular damage, and also mild hematuria. An agar gel immunodiffusion test (AGID) for Bovine Leukemia virus was negative.

A transabdominal ultrasound examination from the right flank using a 2.25 MHz mechanical sector transducer revealed bilateral hydronephrosis and hydroureter. The left kidney with calices dilated to 3.5 cm was more severely affected than the right kidney with calices dilated to 2.5 cm. A large encapsulated anechoic area—indicating fluid—was appreciated surrounding the left Kidney *(Fig 1).* This fluid area was felt to most likely represent urine accumulation or less likely hemorrhage between the kidney and the renal capsule. Fluid echoes were also detected

dissecting the fascial planes of the retroperitoneal space.

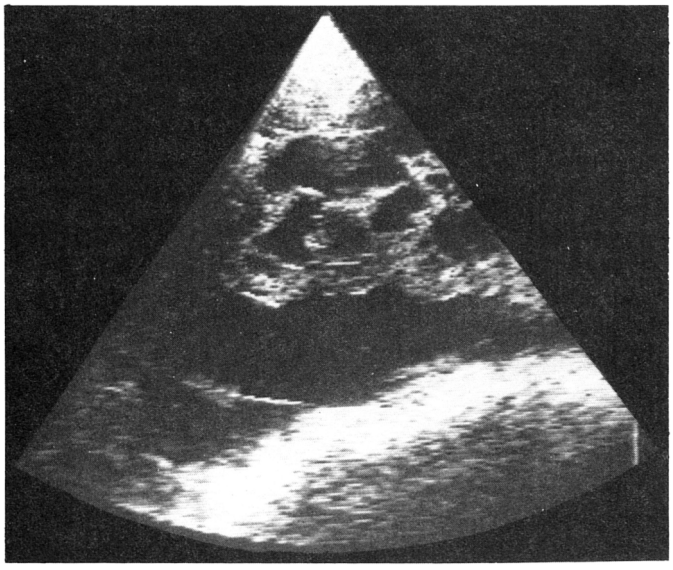

Figure 1: Transabdominal ultrasound image of left kidney. Dilated renal calyces present surrounded by perirenal anechoic area indicative of fluid.

A transrectal ultrasound examination using a 5 MH_Z linear array transducer revealed a lobulated 3 cm x 1 cm intraluminal soft tissue mass at the neck of the bladder *(Fig 2)*.

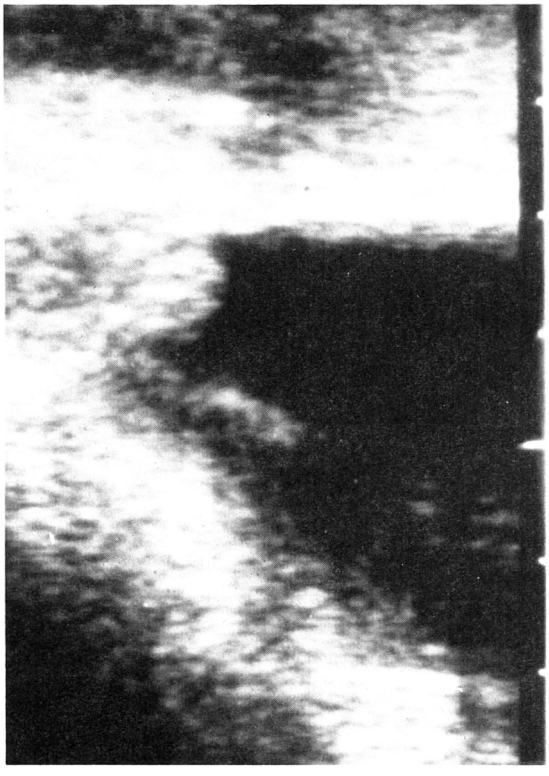

Figure 2: Transrectal ultrasound image of urinary bladder neck. A globoid intralumenal mass can be seen filling the lumen at the bladder neck.

Endoscopic evaluation of the lower urinary tract identified a soft tissue mass with multiple papillary or tentacle like projections originating intraluminally from the dorsal surface of the neck of the bladder. The location of the mass prohibited visualization of the ureteral orifices. Tissue was obtained for biopsy through the biopsy port of the endoscope.

Assessment and Pathologic Findings

The biopsy specimen revealed a polypoid hyperplasia of the transitional epithelium of the bladder. There were multiple nodules and ribbons of transitional epithelium with many cystic spaces lined by transitional epithelium. The epithelium appeared well organized and was 6-10 cell layers thick.

Presumably, the mass lesion identified in the neck of the bladder was causing an impedance to urine flow into the bladder. With a greater degree of hydronephrotic changes in the left kidney, the obstruction of the left ureteral orifice was either of longer duration and/or the obstruction was more complete than that on the right side. The inability to concentrate urine with concomitant azotemia and dehydration indicated a compromise of at least 75% of the total functional renal tubular mass in this cow. The owner of the cow at this time elected to have the cow sent to slaughter due to the poor prognosis and for economic considerations. The urinary tract was retrieved from the slaughter house for pathologic examination.

Gross inspection of the urinary tract confirmed bilateral hydronephrosis with dilated renal calices, ureters 2-3 times normal size, and a small (3 cm x 1 cm) papillary polyp intimately associated with both ureteral orifices in the trigone of the urinary bladder *(Fig 3)*.

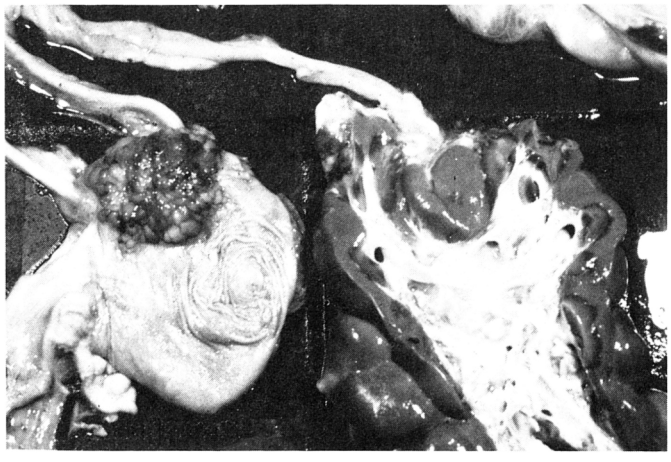

Figure 3: Focal papillary mass in the trigone of the urinary bladder. Bilateral hydroureter and dilated renal calyces are also present.

Histologically, the kidneys showed a severe locally extensive renal necrosis. There was a moderate to severe increase in both periglomerular and interstitial fibrosis. Moderate multifocal glomerular sclerosis was present with a scattered to coalescing lymphocytic infiltrate in the cortical interstitium. There was multifocal extension of the cortical lymphocytic infiltrate into a thickened renal capsule.

Microscopic examination of the bladder mass revealed hyperplasis of the overlying epithelium that was thrown into many papillary-like projections. Multifocal invasion of epithelial cells through the basement membrane was present *(Fig 4).*

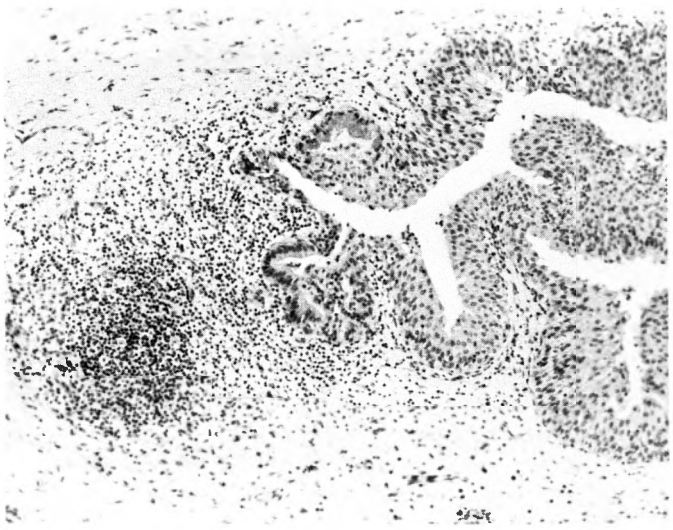

Figure 4: Focal epithelial invasion into the underlying stroma suggestive of carcinoma "in situ." A mixed inflammatory infiltrate is also present within the connective tissue stroma.

The underlying stroma was well vascularized and composed of dense interlacing sheets, bands and whorls of mature connective tissue. Multiple discrete perivascular lymphocytic nodules were present in the connective tissue stroma. The focal epithelial infiltration into the underlying stroma was suggestive of carcinoma "in situ."

Discussion

The morphologic changes seen in the bladder mucosal epithelium and underlying submucosa in this case are compatible with changes that may be seen in bovine enzootic hematuria.[1] The typical histopathologic changes seen with enzootic hematuria include epithelial proliferation and desquamation, with infiltration of columns of transitional epithelium into the lamina propria.[1,2] The link between enzootic hematuria and chronic bracken fern *(Pteridium aquilinium)* ingestion has been well documented,[2,4] although other contributory factors either singly or in concert with other causes may include bovine papilloma virus,[5] or ingestion of multiple other fern species.[2] The chronic inflammatory insult may lead to development of several tumor types in the bladder including papilloma, transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma, hemangioma, and fibroma.[3] The main clinical sign associated with enzootic hematuria is intermittent hematuria first seen when the animal is 4-6 years of age.. The disease course is then usually several years before resulting in death.[2] Affected animals are anemic, leukopenic, and urinalysis characteristically reveals hematuria, pyuria, and proteinuria.[2]

The location of the lesion in the bladder of this cow seems to suggest deposition or concentration of an etiologic agent from the ureters, and historically the cow did have access to bracken. Another report describes similar pathologic findings—bladder lesion, hydronephrosis—in four Holstein cows although the exposure to toxic plants was not mentioned or known.[6] It may be possible that the development of a proliferative bladder lesion surrounding the ureteral orifices in some cases may lead to renal failure through hydronephrosis and therefore interrupt the usual more chronic course of enzootic bovine hematuria.

References

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