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Ureteral pseudodiverticulosis and urothelial cell carcinoma: rethinking the association

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Abstract

Purpose: To compare frequency of new and recurrent urothelial cell carcinoma (UCC) among patients with and without pseudodiverticulosis on imaging.
Methods: This retrospective case–control study compared all 113 sequential patients with ureteral pseudodiverticulosis on radiographic urography between 1/1/2002 and 12/31/2012. Six patients were lost to follow-up. 107 patients without pseudodiverticulosis were matched by imaging modality, clinical indication, and tumor grade. Known UCC and primary outcome of new or recurrent UCC were determined through pathology on cystoscopy or clinical follow-up.
Results: Nearly half of patients with pseudodiverticulosis had known UCC at the time of imaging (49/107, 46%). Mean cystoscopy follow-up was 7.0 and 4.6 years for pseudodiverticulosis cases with and without known UCC, respectively, and 7.5 and 7.3 years for controls, respectively. Mean clinic follow-up was 7.5 and 6.0 years for pseudodiverticulosis cases with and without known UCC, respectively, and 6.4 and 7.6 years for controls, respectively. Among patients with known UCC at the time of imaging, similar rates of recurrent UCC were demonstrated on follow-up among patients with pseudodiverticulosis (6/49, 12%) and without (7/49, 14%). Among patients with no known history of UCC at the time of imaging, no patients with pseudodiverticulosis developed UCC on follow-up and 5% (3/58) of patients without pseudodiverticulosis developed UCC.
Conclusion: Although half of patients with ureteral pseudodiverticulosis have a known diagnosis of UCC, the presence of pseudodiverticulosis did not signify an increased likelihood of developing new or recurrent UCC over the follow-up period.

Key words: Ureter—Pseudodiverticulosis—Urothelial cell carcinoma—Retrograde pyelogram

Ureteral pseudodiverticulosis is thought to develop from an epithelial proliferative response to subclinical inflammation, producing microscopic ureteritis cystica and glandularis [1]. It is typically seen as multiple tiny "outpouchings" of the ureter on radiographic urography studies such as retrograde pyelography or intravenous urography (Fig. 1). Although they have been described on CT urography [2], they are generally thought to be below the level of spatial resolution of CT urography. Higher resolution scanners and protocols are continually improving the spatial resolution of the urinary tract [3–5] and it may be visible on CT urography in the future.

Ureteral pseudodiverticulosis is classically thought of as a marker for development of urothelial cell carcinoma (UCC) and some sources have stated an association of 26–50% [6, 7]. The purpose of this study was to compare the frequency of new and recurrent urothelial cell carcinoma among all patients with pseudodiverticulosis on radiographic imaging at our institution to matched patients without pseudodiverticulosis.

Materials and methods

The institutional IRB waived informed consent for this retrospective observational study. Retrospective review of radiology reports between 1/1/2002 and 12/31/2002 identified 113 patients with the words "pseudodiverticulosis," "pseudodiverticula," or "pseudodiverticulum" in the radiology report. Although the search filter was set for all imaging modalities, only retrograde pyelograms,

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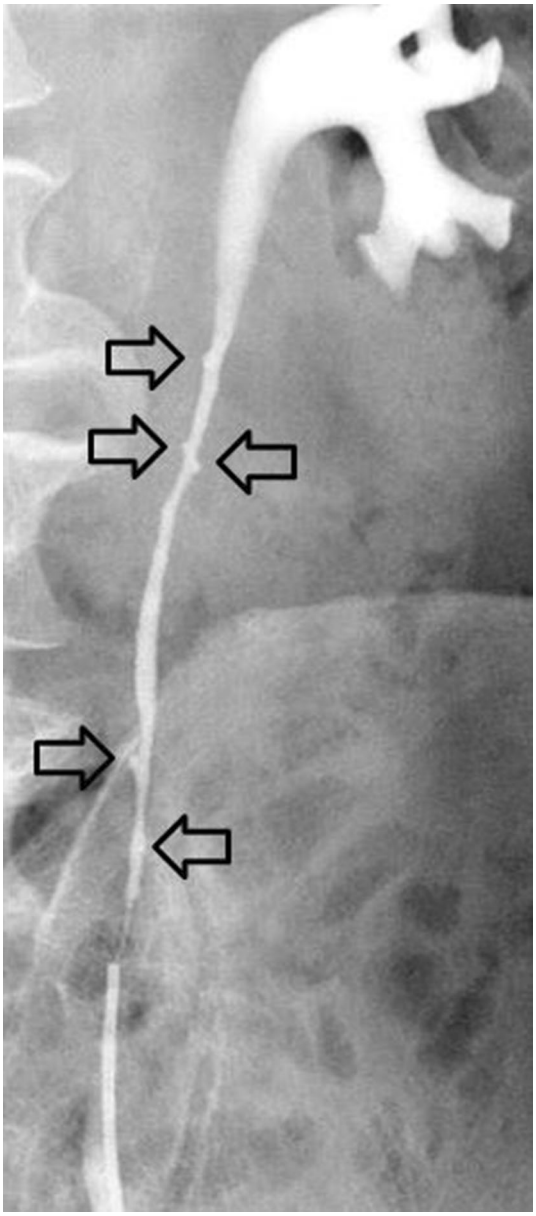

Fig. 1. A 62-year-old man with a history of low-grade urothelial cell carcinoma of the bladder before receiving a retrograde pyelographic surveillance study for upper tract disease. The pseudodiverticula (black arrows) manifest as tiny "outpouchings" of the ureter. A cystoscopy with bladder washings including UroVysion testing ten years after the transurethral resection of the original tumor did not show recurrent disease.

intravenous urograms, and antegrade nephrostograms contained the keywords. The reports were evaluated to ensure that keyword was used in a positive way (i.e., no reports with "no pseudodiverticulosis"). Common synonyms were also searched (e.g., "diverticulum" and "outpouchings"). Both the imaging and reports were reviewed.

The beginning time point for the search (2002) was chosen since patient clinic notes were mostly absent in the electronic medical record before this time. The end point for the search (12/31/2012) was chosen to allow at least five years of follow-up time; the clinical and procedural notes of the patients in the imaging data set were reviewed up to 12/31/2017.

Known UCC at the time of imaging and the primary outcome of new or recurrent UCC following imaging was diagnosed through clinic notes or pathology from any urological intervention, such as transurethral resection of the bladder, surveillance cystoscopy biopsy, or bladder washings. A patient was counted as having a cystoscopy only if the procedural note and pathology results were available. If there was only a reference to a cystoscopy over the interval, then this was counted as a clinic note. Not only the most recent, but all interval cystoscopies were reviewed. The patients with a history of UCC had urology notes, but, not surprisingly, not all of the patients presenting for hematuria had extended urologic follow-up if the initial workup was negative. For these patients, future clinic notes were reviewed to see if urothelial cell carcinoma was discussed or put on the problem list. Patient gender and age at the time of index imaging was obtained from the medical record.

A matched control group of 107 patients was created among patients with no mention of "pseudodiverticulosis," "pseudodiverticula," or "pseudodiverticulum" in the radiology report over the same time period. The purpose of the control group was to compare differences in the primary outcome of new or recurrent UCC. Therefore, control patients were sequentially matched by initial urography imaging modality and clinical indication as well as tumor grade among patients with known UCC. As for cases, known UCC at the time of imaging and new or recurrent UCC following imaging were diagnosed through clinic notes or pathology from any urological intervention, such as transurethral resection of the bladder, surveillance cystoscopy biopsy, or bladder washing.

Results

Demographic and radiology data as well as clinical indication are shown for cases and controls in Table 1. A flowchart of the study results is shown in Fig. 2. Six out of the 113 patients (5.3%) with pseudodiverticulosis on imaging were excluded due to the absence of clinic records in the electronic medical record or loss to follow-up (one of these patients had a known diagnosis of UCC). This left 107 patients in the final case data set. Although controls were not matched with cases by gender, similar proportions of males were found in both groups. Pseudodiverticulosis was most commonly detected on retrograde pyelograms (88.8%).

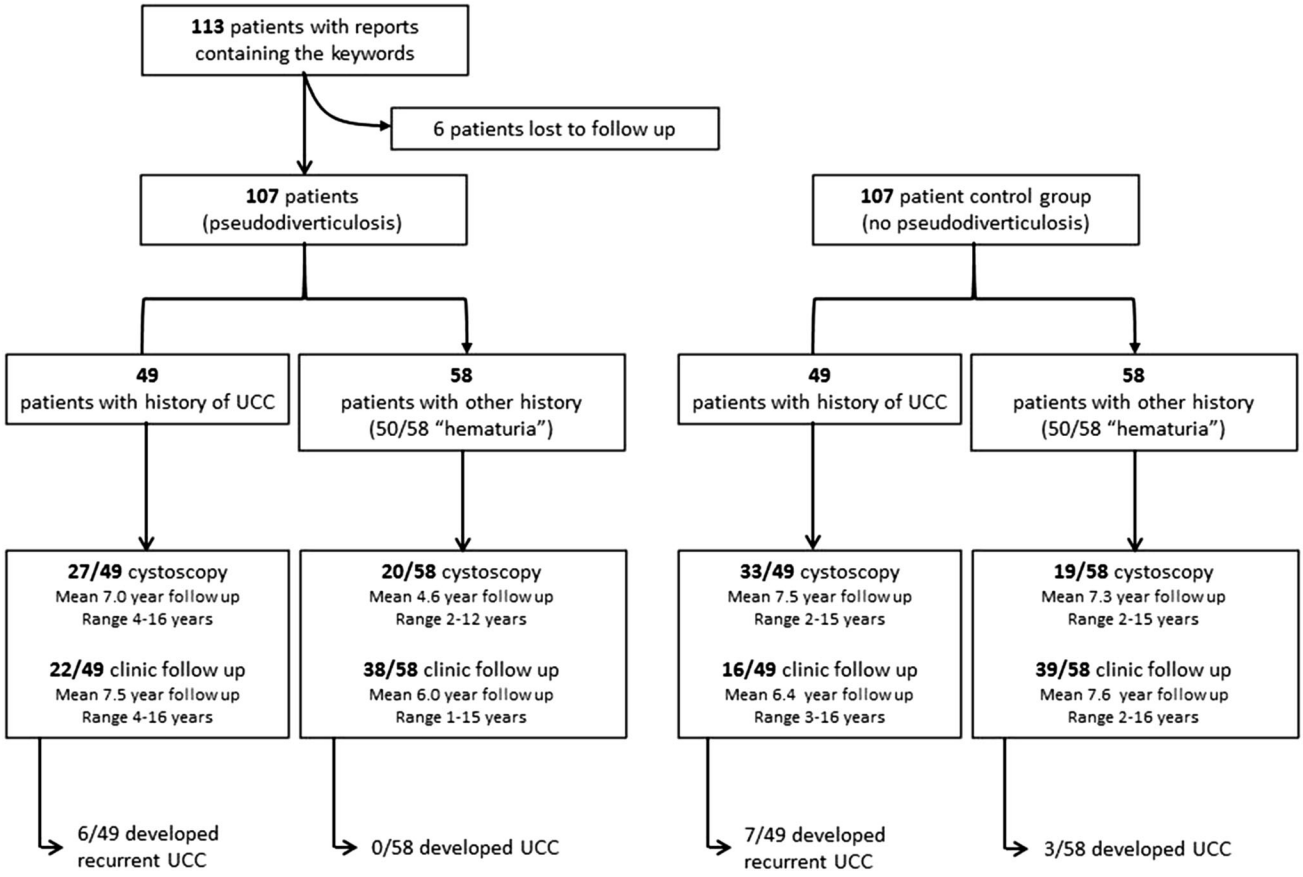

Fig. 2. Study results.

Table 1. Demographic and radiology data as well as clinical indication for cases and controls selected between 1/1/2002 and 12/31/2012

	Cases (n = 113)	Controls (n = 107)
No clinic notes/lost to follow-up	6	n/a
Total records reviewed	107	107
Age	68.1 ± 10.6 years	65.4 ± 10.5 years
Male	97 (90.7%)	93 (86.9%)
Female	10 (9.3%)	14 (13.0%)
Number of readers	5	5
Years of experience	10–31	10–31
Types of studies		
Retrograde pyelogram	95 (88.8%)	95 (88.8%)
Intravenous urogram (IVU)	8 (7.5%)	8 (7.5%)
Antegrade nephrostogram	3 (2.8%)	3 (2.8%)
Voiding cystourethrogram	2 (1.9%)	2 (1.9%)
Primary indication		
Hematuria	50 (46.7%)	50 (46.7%)
History of urothelial cell carcinoma/surveillance	49 (45.8%)	49 (45.8%)
Atypical cytology	3 (2.8%)	2 (1.9%)
Non-visualization of distal ureters on prior IVU	2 (1.9%)	3 (2.8%)
Other	3 (1.9%)	3 (2.8%)

Control patients were matched by imaging modality, primary indication, and tumor grade

Nearly half of patients with pseudodiverticulosis had a known history of UCC at the time of imaging (49/107, 45.8%). Most patients with pseudodiverticulosis and known UCC had non-muscle invasive bladder cancers (NMIBC) 42/49 (85.7%). Histology is reviewed in Table 2. Twenty-seven of these patients had available follow-up cystoscopy records (27/49, 55.1%) with mean time to cystoscopy of 7.0 years (range 4–16 years). For the remaining 22 patients, the average time to the most recent clinic note was 7.5 years (range 4–16 years). Six

Table 2. Urothelial cell carcinoma (UCC) grade among cases and controls

	Cases (n = 49)	Recurrent disease (n = 6)	Controls (n = 49)	Recurrent disease (n = 7)
Non-muscle invasive bladder cancer (NMIBC)	42 (85.7%)		42 (85.7%)	
Low grade	24/42 (57.1%)	1	26/42 (61.2%)	2
High grade	15/42 (35.7%)	5	15/42 (35.7%)	5
No grade available	3/42 (7.1%)		1/42 (2.4%)	
Muscle invasive bladder cancer (MIBC)	6 (12.2%)		6 (12.2%)	
Upper tract UCC	1 (2.0%)		1 (2.0%)	

Control patients were matched by imaging modality, primary indication, and tumor grade

patients with a prior history of pseudodiverticulosis and known UCC at the time of index imaging developed recurrent UCC (6/49, 12%): not surprisingly five of these had high-grade NMIBC histology and one had low-grade histology.

Patients with pseudodiverticulosis and no known UCC commonly presented for imaging with a clinical indication of hematuria (50/58, 86%). Twenty of these patients had available follow-up cystoscopy (20/58, 34.5%) with mean time to cystoscopy of 4.6 years (range 2–12 years). For the remaining 38 patients, the average time to the most recent clinic note was 6.0 years with a range of 1–15 years. No patients in this cohort developed new UCC on follow-up cystoscopy or clinic notes.

Among patients without pseudodiverticulosis (i.e., control patients), 49/107 (45.8%) had known UCC at the time of index imaging. Because patients were matched by tumor grade similar proportions of NMIBC, muscle invasive cancers and upper tract UCC were present in this group (Table 2). Thirty-three of these patients had available follow-up cystoscopy (33/49, 67.3%) with mean time to cystoscopy of 7.5 years (range 2–15 years). For the remaining 16 patients, the average time to the most recent clinic note was 6.4 years (range 3–16 years). Seven patients without pseudodiverticulosis and known UCC at the time of index imaging developed recurrent UCC (7/49, 12%): again, not surprisingly, five of these were previously diagnosed with high-grade histology and two with low-grade histology.

Of the patients without pseudodiverticulosis, 54.2% (58/107) did not have known UCC at the time of imaging. Nineteen of these patients had an available follow-up cystoscopy (19/58, 32.8%) with mean time to cystoscopy of 7.5 years (range 2–15 years). For the remaining 39 patients, the average time to the most recent clinic note was 7.6 years (range 2–16 years). Three of these patients developed UCC. All of these were low-grade tumors.

Discussion

Ureteral pseudodiverticulosis has been considered a serious marker for potential malignancy, thought to antedate the cancer by 2–10 years [6, 7]. We found that nearly one out of two patients with pseudodiverticulosis on imaging had a known history of UCC, predominantly bladder tumors and this is concordant with the literature (30–50%) [1]. Also concordant with the literature, most (85.7%) of these patients had NMIBC (NMIBC represents approximately 80% of bladder cancer diagnoses) [8]. These findings support the generalizability of our results.

Despite the association between pseudodiverticulosis and known UCC, we found no increased risk of developing new or recurrent UCC among patients with pseudodiverticulosis compared to patients without pseudodiverticulosis. Specifically, among patients with known UCC at the time of imaging, similar rates of recurrent UCC were demonstrated on follow-up among patients with pseudodiverticulosis (6/49, 12%) and without (7/49, 14%). Unsurprisingly, higher rates of UCC were demonstrated among patients with high-grade tumors. Among patients with no known history of UCC at the time of imaging, no patients with pseudodiverticulosis developed UCC on follow-up and 5% (3/58) of patients without pseudodiverticulosis developed UCC. These rates of recurrent and new UCC are also concordant with the literature [8]. These findings suggest that increased follow-up of patients may not be necessary if they have pseudodiverticulosis on imaging but no known UCC. It suggests that patients with known UCC should be monitored based on tumor histology rather than the presence of pseudodiverticulosis.

Limitations of the study include the follow-up interval. Recurrent UCC has been reported as far as 10 years after initial detection of pseudodiverticula [9]. We may have missed some cases of UCC developing in patients with UCC if the development of pseudodiverticulosis is indolent, but then it may not also make sense to screen them aggressively. Another limitation arises in the retrospective gathering of data from the medical record. Some patients in our study had short follow-up intervals due to death. Others, particularly those without a diagnosis of UCC or those with a negative initial workup for hematuria, had no or limited cystoscopy follow-up; in these patients we elected to evaluate subsequent clinic notes in order to limit selection bias.

In conclusion, we found an association between pseudodiverticulosis and known UCC at the time of radiographic urography imaging: one out of two patients with pseudodiverticulosis had known UCC. Yet, there was no difference in the frequency of new or recurrent UCC among patients with and without pseudodiverticulosis. These findings are important for radiologists and urologists to guide management of patients with pseudodiverticulosis

on radiographic urography imaging; our findings suggest no need for increased follow-up of patients with no known UCC and pseudodiverticulosis on imaging. For patients with known UCC, the tumor grade would seem to be a more important factor in determining follow-up than the presence of pseudodiverticulosis on imaging.

Compliance with ethical standards

Funding No funding for this study.

Conflict of interest No conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent A waiver for informed consent was granted by the institutional IRB

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