Abdominal Radiology (2020) 45:2279–2285
https://doi.org/10.1007/s00261-020-02442-5

SPECIAL SECTION: DISTINGUISHED PAPERS FROM JSAR

MRI features of the nested variant of urothelial carcinoma of the urinary bladder: report of four cases

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Published online: 28 February 2020

Abstract
We report on four patients with the nested variant of urothelial carcinoma (NVUC) of the urinary bladder and focus on their magnetic resonance imaging (MRI) findings. MRI showed that all lesions had irregular wall thickening with little protrusion into the bladder lumen. All had extravesical invasion, and two had invaded other organs (uterus and seminal vesicle). On T2-weighted images, all tumors mainly showed relatively strong hypointensity similar to that of the muscularis propria, and in three cases there was also a thin hyperintense layer on the tumor surface, suggesting edematous mucosa. Diffusion-weighted images demonstrated different degrees of hyperintensity, which was faint in one case. Dynamic contrast-enhanced MRI was performed in two cases and both showed gradual contrast enhancement. It has been suggested that NVUC may produce unique MRI findings reflecting its pathological features. It would be useful for those who interpret bladder MRI to recognize this rare urothelial carcinoma variant.

Keywords Bladder cancer · Nested variant of urothelial carcinoma · MRI

Introduction

The nested variant of urothelial carcinoma (NVUC) is classified as a rare subtype of invasive urothelial carcinoma that accounts for approximately 0.3% of all invasive urothelial carcinomas [1]. Although the tumor has a bland histomorphologic appearance and has at times been misdiagnosed as a benign lesion [2], it is a clinically important subtype with poor prognosis. Its radiological findings have rarely been reported and to date no reports have focused on imaging findings with detailed explanations. We report our experience with four cases of NVUC of the urinary bladder, with a focus on their magnetic resonance imaging (MRI) findings, and compare these findings with pathological features.

Case reports

Case 1

A 64-year-old woman presenting with frequent urination had been diagnosed with cystitis in another clinic and took an anticholinergic drug. However, her symptoms did not improve and she was referred to our hospital. Her physical examination was normal. She had a history of surgery for left breast cancer at age 52. A blood laboratory test showed renal dysfunction, with an estimated glomerular filtration rate of 11.28 ml/min/1.73 m^2. Cystoscopy showed follicular changes in the bladder trigone and the bilateral ureteral orifices were obscured. Urine cytology was negative.

MRI revealed a large irregular mass involving the right to posterior walls, trigone, and neck of the urinary bladder, with significant extravesical extension, suggesting highly

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invasive bladder cancer (Fig. 1a, b). Although the tumor was basically hypointense on T2-weighted images (T2WI), a hyperintense thin layer, which appeared to be edematous mucosa, was observed on a part of the surface (Fig. 1a, b). It showed heterogeneous hyperintensity on diffusion-weighted images (DWI) (Fig. 1c). The apparent diffusion coefficient (ADC) of the lesion was also heterogeneous, with a mean of 1370×10^{-6} mm^2/s and 1032×10^{-6} mm^2/s in the lowest area (Fig. 1d). The tumor involved bilateral ureteral orifices and caused hydroureters (Fig. 1a). Uterine invasions were also noted (Fig. 1b), and the diagnosis of clinical T4a bladder cancer was made.

Transurethral resection of the bladder tumor (TURBT) was performed for pathological diagnosis.

Microscopic examination revealed that tumor cells without significant cytological atypia proliferated invasively in the edematous stroma and formed irregular nests; these were diagnosed as NVUC (Fig. 1e). In some areas, cancer cell nests were observed only in the deeper part and the surface was spared from cancer invasion (Fig. 1f).

Although chemotherapy, including Gemcitabine and Cisplatin (GC) and Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC), was performed, the disease progressed. She died 1 year and 10 months later due to small bowel obstruction and perforation caused by peritoneal dissemination.

Case 2

A 73-year-old man underwent computed tomography (CT) for left abdominal pain and gross hematuria. On CT, left hydronephrosis and bladder wall thickening were noted. His physical examination was normal. He had a history of treatment for lymphoma at ages 65 and 72 and surgery for right

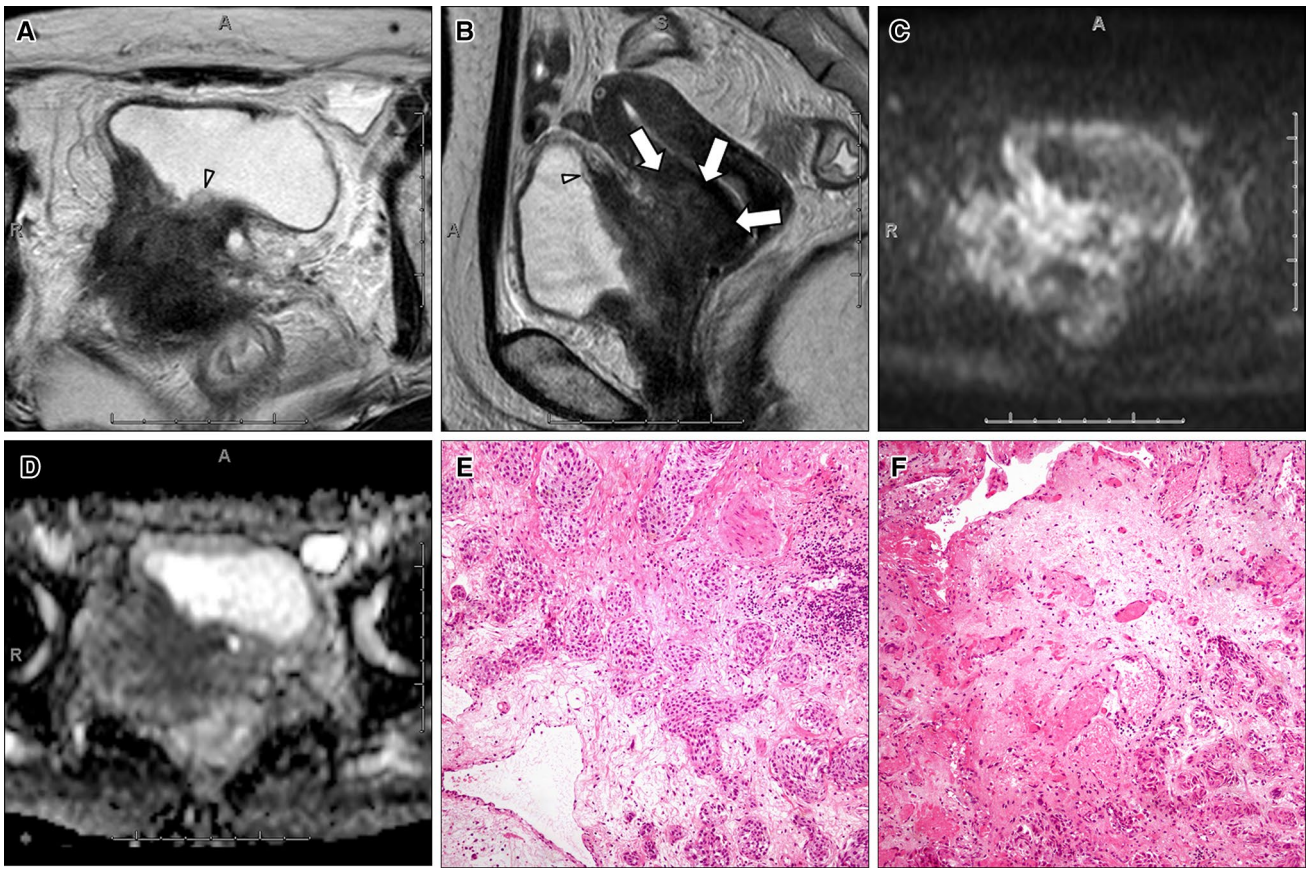


Fig. 1 Case 1: 64-year-old woman presenting with frequent urination. **a** On T2-weighted images, there was a large irregular mass involving the right wall and trigone of the bladder with significant extravesical extension, suggesting highly invasive bladder cancer. The tumor involved bilateral ureteral orifices. **b** Uterine invasion was also noted (white arrows), leading to a diagnosis of clinical T4a bladder cancer. Although the tumor was basically hypointense on T2-weighted images, a hyperintense thin layer, which appeared to be edematous mucosa, was observed on a part of the tumor surface (arrowheads in **a**, **b**). **c** The tumor showed heterogeneous hyperintensity in diffusion-weighted images. **d** The apparent diffusion coefficient of the lesion was also heterogeneous, with a mean of 1370×10^{-6} mm^2/s and 1032×10^{-6} mm^2/s in the lowest area. **e** Microscopic examination (hematoxylin-eosin, original magnification of × 40) revealed tumor cells without significant cytological atypia that proliferated invasively in the edematous stroma and formed irregular nests. **f** In some areas, cancer infiltration was observed only in the deeper part

lung cancer at age 73. Both diseases were well controlled. Blood biochemistry findings showed anemia (red blood cell count 2.89×10^6, hemoglobin 8.1 g/dl, and hematocrit 26.3%). Urine cytology was negative. Cystoscopy showed follicular and edematous changes in the trigone, making it difficult to identify bilateral ureteral orifices. The lesion was friable.

On MRI, irregular wall thickening without bulging into the bladder lumen was observed in the trigone and bladder neck, and both ureteral orifices were involved (Fig. 2a, b). The lesion showed a heterogeneous hyperintensity on DWI (Fig. 2c). The mean ADC was 1175×10^{-6} mm^2/s (Fig. 2d). It showed gradually increasing contrast enhancement on dynamic contrast-enhanced MRI (DCE-MRI), although there were some hypointense areas, suggesting necrosis or other degeneration (Fig. 2e). It spread out of the bladder wall with seminal vesicle invasion (Fig. 2b) and was diagnosed as clinical T4a bladder cancer. TURBT was performed for pathological diagnosis. Microscopically, small to medium-sized nests of cancer cells infiltrated the lamina propria of the bladder, and a diagnosis of NVUC was given (Fig. 2f). Part of the surface urothelium was intact, and the underlying stroma was highly edematous (Fig. 2g).

Although GC and external beam radiotherapy were performed, the disease progressed and multiple metastases appeared. He died 1 year and 7 months after the diagnosis.

Case 3

A 59-year-old man visited a local doctor for discomfort around the coccyx and frequent urination for 3 months. He was referred to our hospital for positive urine cytology (class IV). His physical examination was normal. His past medical history was unremarkable. The blood biochemistry results showed elevated alkaline phosphatase (926 U/l). His renal function and complete blood count were normal. Cystoscopy showed widespread non-papillary tumors.

MRI showed irregular thickening of the bladder walls, mainly the anterior wall, with an obscured margin. Although the lesion was basically hypointense on T2WI, part of the surface had a thin hyperintense layer that was thought to represent edematous mucosa (Fig. 3a). On DWI, the lesion showed heterogeneous hyperintensity (Fig. 3b) and the ADC decreased predominantly on the mucosal side (849×10^{-6} mm^2/s), with a mean ADC of 1015×10^{-6} mm^2/s (Fig. 3c). Based on our experience with cases 1 and 2, the possibility of NVUC was considered. There was reticular stranding of the prevesical fat on T2WI (Fig. 3a), and it was diagnosed as clinical T3b bladder cancer. In addition, multiple bone metastases were observed.

A transurethral biopsy revealed urothelial carcinoma arranged in irregular nests with a strong invasive tendency and invasion into muscularis propria (Fig. 3d, e). Diagnosis of NVUC was made. However, an edematous inflammatory stroma without cancer infiltration was observed on part of the surface (Fig. 3f).

GC therapy was performed, but the disease progressed, and he is currently being treated with MVAC and pembrolizumab.

Case 4

A 73-year-old man underwent CT for postoperative follow-up of colon and esophageal cancer. CT revealed right hydronephrosis and thickening of the bladder wall. He had a history of surgery for colon cancer at age 70 and esophageal cancer at age 72. His physical examination and the blood biochemistry were normal. Urine cytology was negative. Cystoscopy showed extensive surface irregularities and edematous mucosa around the right side wall, and the right ureteral orifice was obscured.

MRI showed an irregular broad lesion on the right side wall and trigone of the bladder, involving the right ureteral orifice with ureteral dilation (Fig. 4a). Although the lesion was basically hypointense on T2WI, part of the surface had a thin hyperintense layer that was thought to represent the edematous mucosa (Fig. 4b). It showed a faint hyperintensity on DWI (Fig. 4c) and the mean ADC was 1100×10^{-6} mm^2/s (Fig. 4d). In a DCE-MRI study, this lesion contrasted from the second phase (55 s after the start of injection), and it increased over time (Fig. 4e). It was diagnosed as clinical T3b bladder cancer.

The patient was diagnosed with "invasive urothelial carcinoma" by transurethral biopsy, but the MRI findings were similar to the characteristics of cases 1–3 and we asked a pathologist to review the pathological specimen.

Microscopically, highly atypical cells showed invasive growth that infiltrated the muscularis propria, indicating high-grade invasive urothelial carcinoma (Fig. 4f). However, in some parts, there was also urothelial carcinoma that showed no prominent cytological atypia but proliferated invasively while forming nests (Fig. 4g). It was diagnosed as mixed NVUC with the usual type of urothelial carcinoma. There were some areas where only the edematous stroma was admitted despite the presence of cancer cell nests in the deeper part (Fig. 4h).

He refused chemotherapy and wanted home palliative care. He died 1 year and 2 months after the diagnosis.

Discussion

NVUC is rare variant of urothelial carcinoma that was added to the WHO classification in 2004. It is characterized by an unusual, bland morphology that mimics some benign urinary bladder lesions but has a clinical behavior

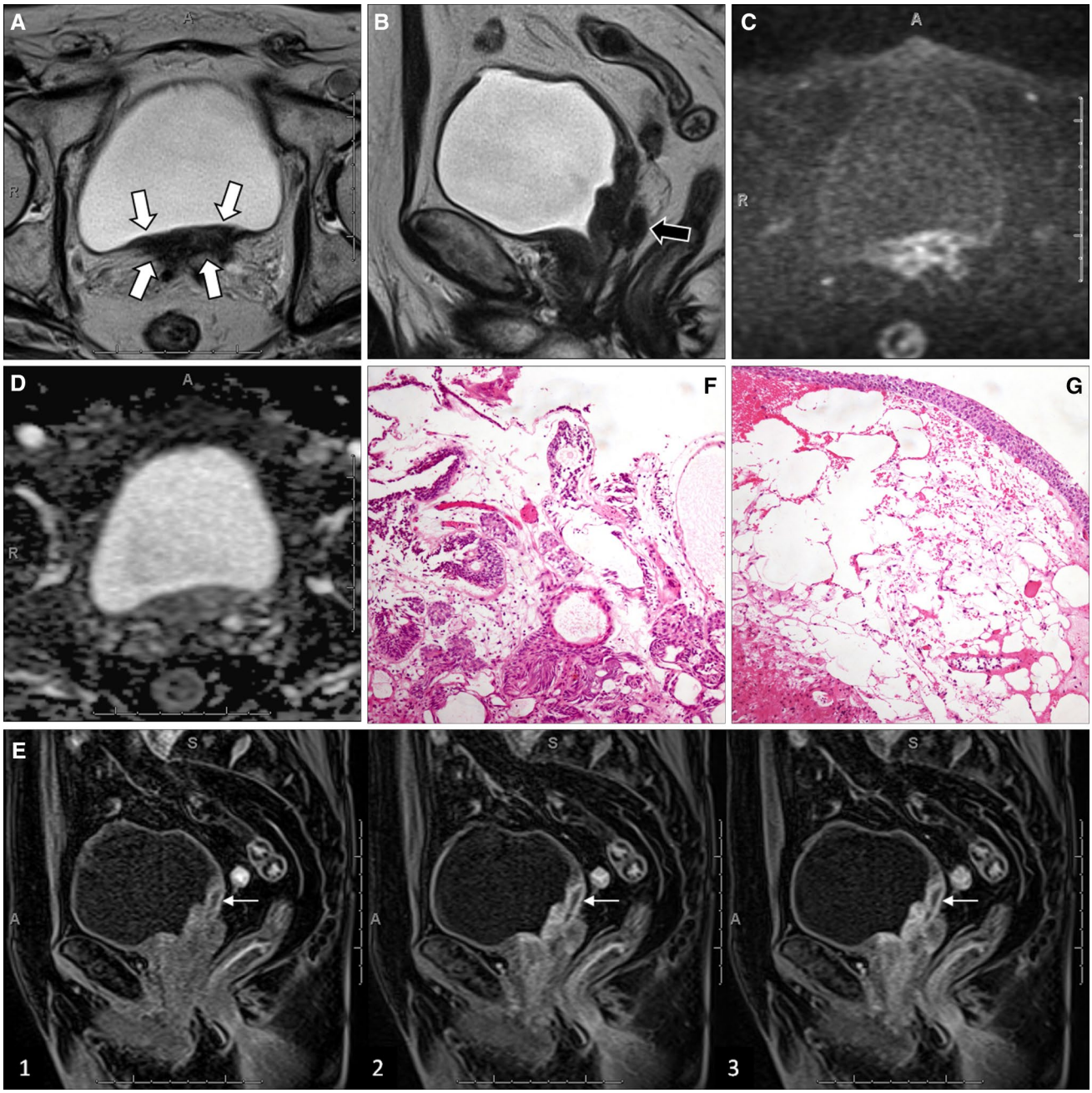


Fig. 2 Case 2: 73-year-old man with left abdominal pain and gross hematuria. **a** On T2-weighted images, irregular wall thickening without bulging into the bladder lumen was observed in the trigone (white arrows), and both ureteral orifices were involved. The tumor showed relatively strong hypointensity similar to that of the muscularis propria. **b** Sagittal T2-weighted images showed that the tumor spread out of the bladder wall and invaded the seminal vesicle (black arrow). It was diagnosed as clinical T4a bladder cancer. **c** The lesion showed heterogeneously hyperintensity in diffusion-weighted images. **d** The mean apparent diffusion coefficient was 1175×10^{-6} mm^2/s. **e** It showed gradually increasing contrast enhancement with dynamic contrast-enhanced MRI, although there were some hypointense areas, suggesting necrosis or degeneration (small arrows). **f** Microscopic examination (hematoxylin-eosin, original magnification × 40) revealed that small to medium-sized nests of cancer cells infiltrated the lamina propria of the bladder. **g** Part of the surface urothelium was intact, and the underlying stroma was highly edematous

that simulates that of high-grade conventional urothelial carcinoma. More atypia and focal anaplasia with increasing depth of invasion are often seen as one of its features [2]. They often coexist with the common type of urothelial carcinoma, with a reported frequency of 63% [3]. Almost all the patients with this variant of urothelial carcinoma are older men who most frequently have clinical manifestation of hematuria, urgency, or signs of ureteral obstruction [4].

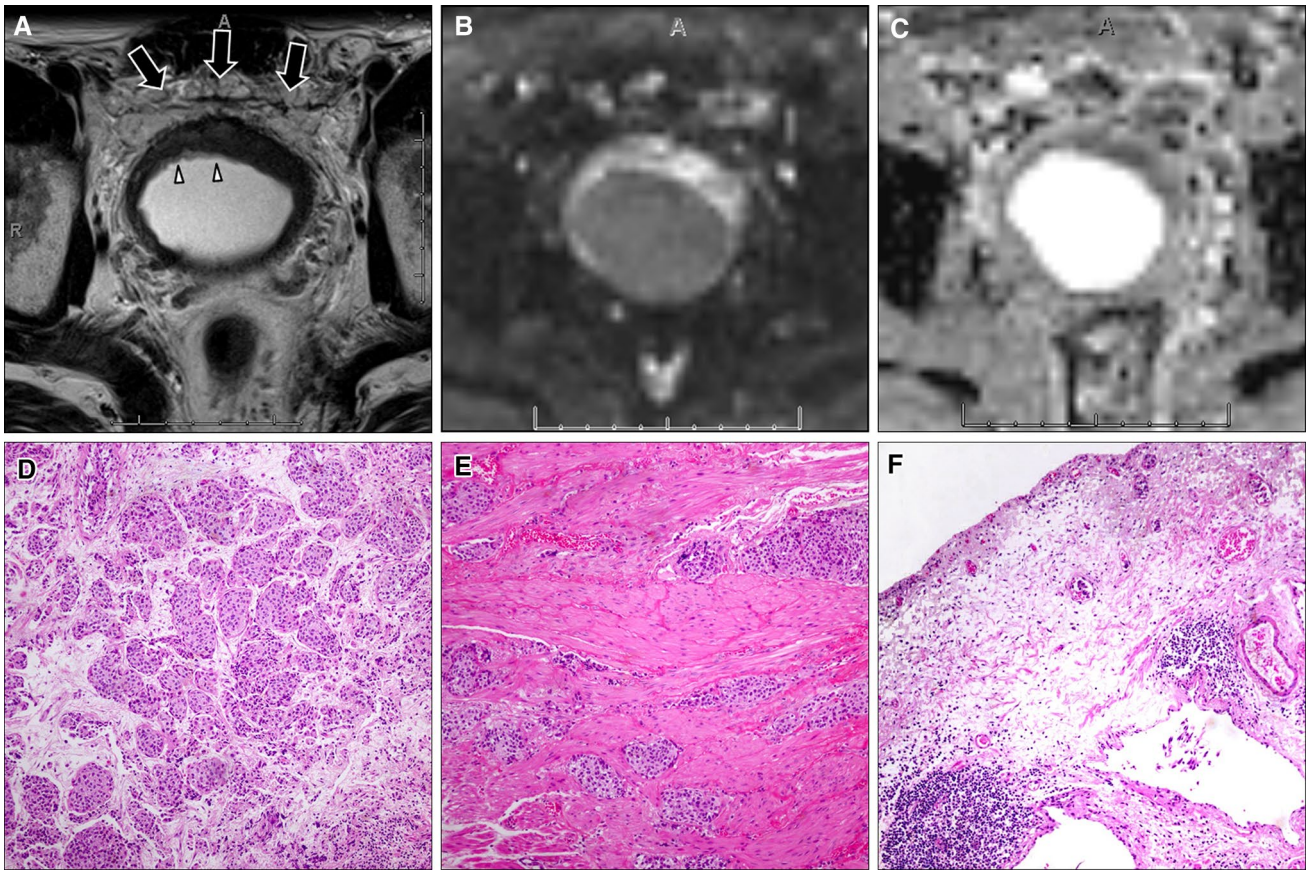


Fig. 3 Case 3: 59-year-old man complaining of discomfort around the coccyx and frequent urination for 3 months. **a** Axial T2-weighted images showed thickening of the bladder walls, mainly the anterior wall, with an obscured margin. There was reticular stranding of the prevesical fat (black arrows), and it was diagnosed as clinical T3b bladder cancer. Although the lesion was basically hypointense on T2-weighted images, part of the surface had a thin hyperintense layer that was thought to represent the edematous mucosa (arrowheads). **b** On diffusion-weighted images, the lesion showed heterogeneous hyperintensity. **c** The apparent diffusion coefficient decreased predominantly on the mucosal side (849×10^{-6} mm^2/s), with a mean apparent diffusion coefficient of 1015×10^{-6} mm^2/s. **d** Microscopic examination (hematoxylin-eosin, original magnification × 40) revealed urothelial carcinoma with no significant cytologic atypia arranged in irregular nests. **e** The tumor showed a strong invasive tendency, often involving the muscularis propria. **f** An edematous inflammatory stroma without cancer infiltration was observed on part of the surface

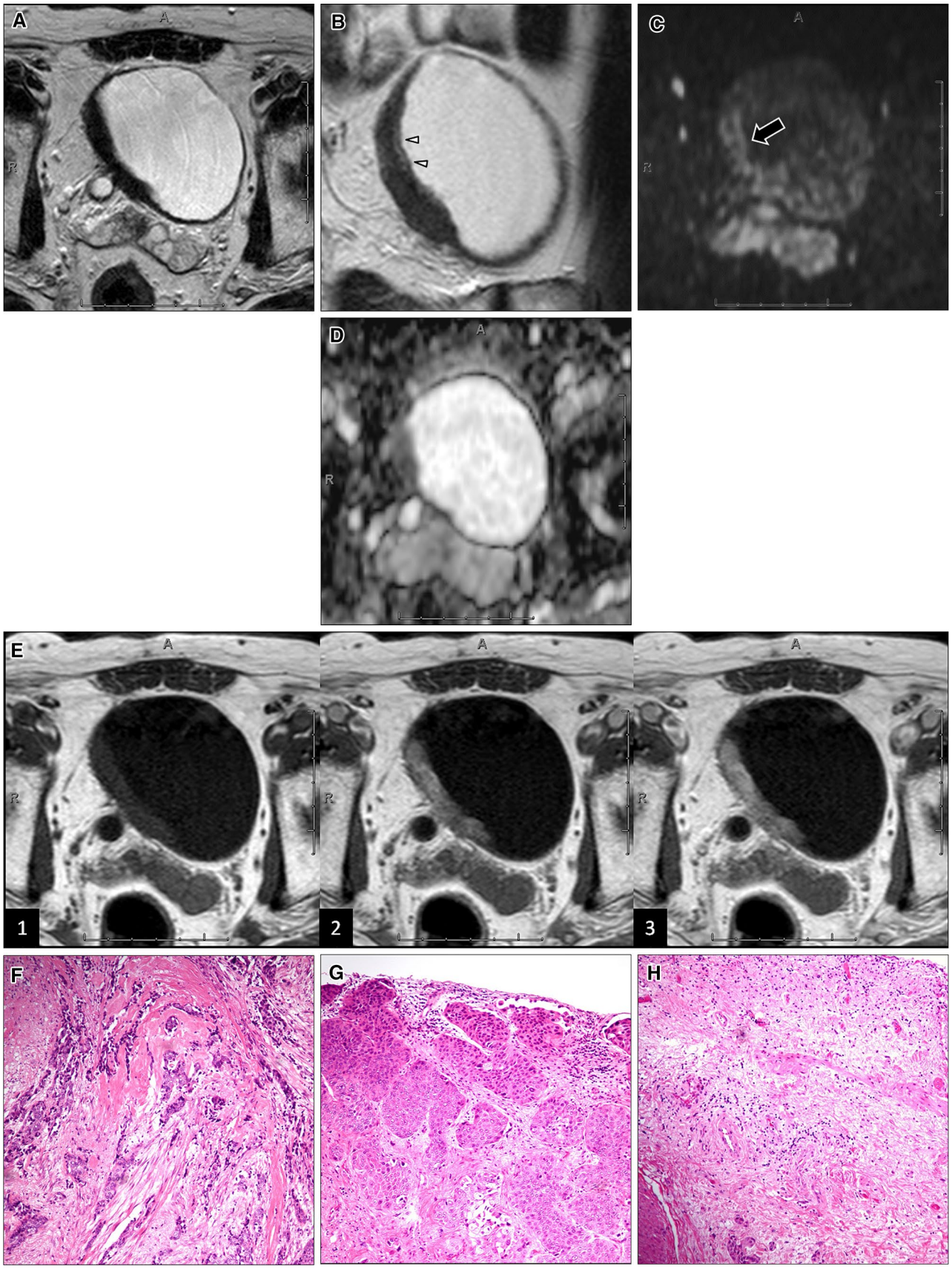
Cystoscopic findings have been variously reported as "a small, peculiar, submucosal bump," "an erythematous patch/plaque," "a small, non-papillary, non-sessile lesion," "a wide-based tumor," and "a slightly raised and gritty tumor" [5]. Although there are two clinical case reports in which MRI images are presented [6, 7], there are no comprehensive reports on imaging findings and details are unknown.

In the four cases of NVUC that we report here, the chief complaint was frequent urination in two cases and hematuria in one case. The other case was found incidentally on a follow-up CT for another disease.

On MRI, all showed irregular wall thickening without obvious protrusion into the bladder lumen and all had extravesical invasion, two of which invaded other organs. DWI demonstrated different degrees of hyperintensity, and it was faint in case 4. DCE-MRI was performed in two cases and both showed gradual contrast enhancement.

On T2WI, all tumors mostly showed relatively strong hypointensity similar to that of the muscularis propria. In our cases, it was often noted that the tumor nests infiltrated the muscularis propria while separating the muscle bundles. One possible explanation why they showed hypointensity on T2WI was that they might reflect the signals of the remaining muscularis propria. But that alone may not be a satisfactory explanation. In general, abundant fibrosis or hemosiderin deposition causes the tumor to show hypointensity on T2WI, but no such features were observed in our cases.

Three cases showed a thin T2-hyperintense layer on the tumor surface, suggesting edematous mucosa. This superficial hyperintensity was observed in at least one of the two previous reports that included MRI images [7], and it was observed at a high rate of four times out of six when combined with our cases, but it is not common in usual type of invasive urothelial carcinoma. Pathologically, NVUC has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◂**Fig. 4** Case 4: 73-year-old man who was found to have right hydronephrosis and thickening of the bladder wall by postoperative follow-up CT for colon and esophageal cancer. **a** T2-weighted images revealed an irregular bladder wall thickening with relatively strong hypointensity similar to that of the muscularis propria on the right side wall and the trigone, involving the right ureteral orifice with ureteral dilatation. **b** Oblique coronal T2-weighted images showed a thin hyperintense layer on part of the surface, and this layer was thought to represent edematous mucosa (arrowheads). **c** It showed a faint hyperintensity on diffusion-weighted images (black arrow). **d** The mean apparent diffusion coefficient was 1100×10^{-6} mm^2/s. **e** With dynamic contrast-enhanced MRI, this lesion contrasted from the second phase (55 s after the start of injection), and it increased over time. **f** On microscopy (hematoxylin-eosin, original magnification × 40), highly atypical cells showed invasive growth and infiltrated the muscularis propria, indicating high-grade invasive urothelial carcinoma. **g** In some parts, there was also urothelial carcinoma that showed no prominent cytological atypia, but it proliferated invasively while forming solid nests. **h** In some areas, only the edematous stroma was admitted, despite the presence of cancer cell nests in the deeper part

a strong tendency to infiltrate and spread into the lamina propria and muscularis propria, while the surface is often preserved [2]. We speculated that this preserved surface could be observed as a thin hyperintense layer on T2WI. In fact, in the specimens of our four cases, despite the presence of tumor infiltration in the deeper part, there were some areas without tumor cells on the epithelial side, where the subepithelial stroma was edematous and often accompanied by inflammatory cell infiltration.

Despite having a benign histological appearance, NVUC exhibits an aggressive clinical course [1, 3]. In comparison with pure high-grade urothelial carcinoma, NVUC was associated with muscle invasion on TURBT, extravesical disease on cystectomy, and metastatic disease [3, 8]. Although early diagnosis is important, NVUC is difficult to diagnose with urine cytology, and there are no specific findings with a cystoscope. Also, even a transurethral biopsy can be negative due to the deceptively bland appearance of NVUC, leading in some instances to a significant delay in diagnosis [2]. Among the four cases we experienced, we could suspect the possibility of NVUC prospectively in case 3 and conduct a pathological review in case 4 based on the MRI findings.

In conclusion, it is suggested that NVUC may have unique MRI findings reflecting its pathological features. It would be useful for those who interpret bladder MRI to recognize this rare urothelial carcinoma variant.

Funding No funding for the present study was received from any companies or organizations.

Compliance with ethical standards

Conflict of interest No authors have any conflict of interest related to this manuscript.

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