Abdominal Radiology (2019) 44:3827–3842
https://doi.org/10.1007/s00261-019-02276-w

REVIEW

Bladder cancer and its mimics: a sonographic pictorial review with CT/MR and histologic correlation

Andrew L. Wentland[1] · Terry S. Desser[1] · Megan L. Troxell[2] · Aya Kamaya[1]

Published online: 1 November 2019

Abstract
Bladder cancer is the most common cancer of the urinary system and often presents with hematuria. Despite its relatively high incidence, bladder cancer is often under-recognized sonographically. Moreover, even when bladder abnormalities are identified, numerous other entities may mimic the appearance of bladder cancer. Given the incidence and prevalence of bladder cancer, it is important to recognize its variable appearance sonographically and distinguish it from its common mimics. We review the sonographic appearance of bladder cancer and its mimics, providing correlative CT/MR imaging as well as pathology. We stress the importance and advantage of ultrasound as a dynamic imaging modality, with the ability to optimize distinguishing bladder cancer from similar-appearing entities.

Keywords Ultrasound · Sonography · Bladder cancer · Bladder mass · Bladder tumor

Introduction

Focused evaluation of the urinary tract is often performed in the initial evaluation of hematuria. Many urologic entities cause hematuria, including urinary stones, renal and urothelial tumors (including bladder cancer), urinary tract infections, and glomerulonephritis. Imaging studies performed for the evaluation of hematuria inevitably prompt inspection of the kidneys and ureters. Such evaluation is commonly performed by CT urography, although a recent study by Tan et al. demonstrated that renal and bladder ultrasound can safely replace CT urography in the evaluation of patients with microscopic hematuria [1]. Perhaps because it is well-accepted that direct visualization with cystoscopy is the best method for detecting bladder cancer, [1] radiologic evaluation of the bladder is often underemphasized in most imaging modalities. Nonetheless, the bladder is typically included in ultrasound studies of the male and female pelvis, kidneys, and gravid uterus. In these situations, while the bladder may not be the focus of the examination, incidental bladder lesions may be inadvertently overlooked especially if hematuria is not one of the explicit indications given for the examination. A fluid-distended bladder provides an acoustic window for sonographic evaluation of the pelvic organs, but while looking through it, one should carefully inspect the bladder itself so as to not miss bladder pathology. The aim of this review is to heighten awareness of the findings of bladder cancers on imaging studies, particularly ultrasound, with the hope that radiologists will resolve to give it as much attention as the structures whose visualization it facilitates. The imaging appearance of urothelial carcinoma of the bladder will first be discussed, followed by mimics of urothelial carcinoma, including other malignant masses, and benign conditions that may mimic malignancy.

Background

The bladder is a muscular sac for the collection, storage, and expulsion of urine from the ureters, located in the extraperitoneal compartment of the anterior pelvis. Figure 1 illustrates the gross anatomy of the bladder, as well as the relevant layers of the bladder wall. Bladder cancer is most commonly found along the posterior wall and the trigone [2], the latter of which is important for sensing distention and instigating micturition. The innermost layer of the bladder

✉ Aya Kamaya
kamaya@stanford.edu

[1] Department of Radiology, Stanford University School of Medicine, H-1307, 300 Pasteur Dr., Stanford, CA 94305, USA

[2] Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA

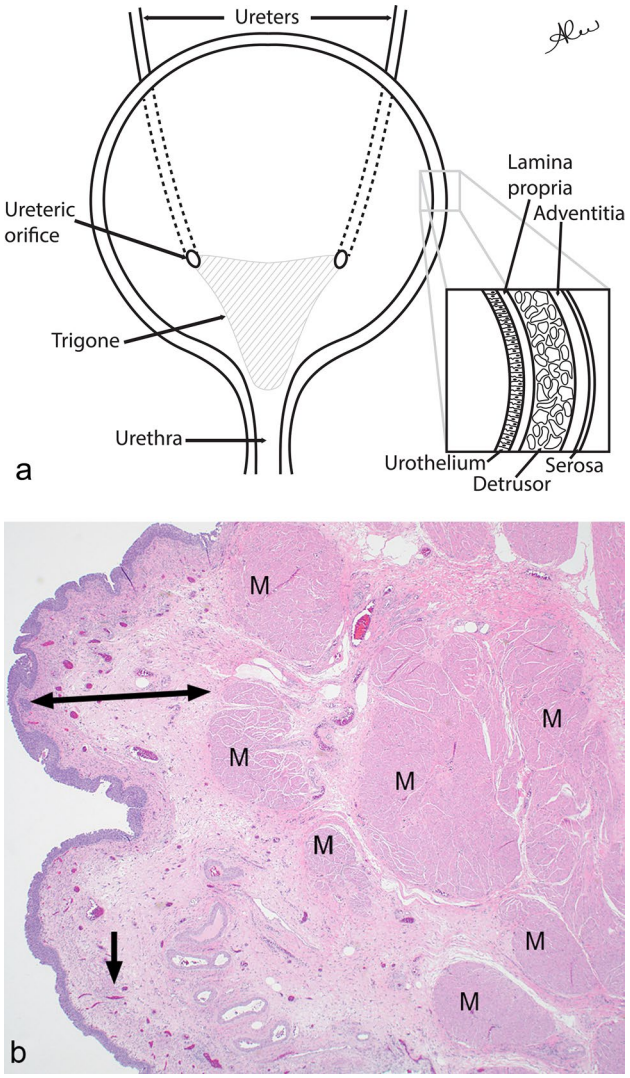

Fig. 1 **a** Diagram of the bladder. Two ureters enter the bladder posteriorly to transmit urine from the kidneys; urine exits through the urethra. The trigone, the region between the ureteric orifices and the urethra, is sensitive to distention and signals the need to micturate. Inset image of the bladder wall layers includes the innermost layer (urothelium), from which most bladder cancers arise. As cancer advances, tumor invades through the lamina propria into the bladder wall musculature (detrusor muscle), and eventually progresses through the adventitia and serosa and into surrounding organs. *Diagram designed in Adobe Illustrator and adapted from the article on Bladder Anatomy from Medscape* (*emedicine.medscape.com/article/1949017-overview*). **b** Histology of the bladder wall, corresponding to inset in **a**. Urothelium lines the lumen, supported by underlying lamina propria (double-headed arrow) containing numerous vessels and inconspicuous muscularis mucosa (small arrow). The detrusor muscle, or muscularis propria, consists of large bundles of smooth muscle (M). Adventitia and serosa are deep to the muscularis and not represented here. H&E, original magnification ×20

wall is the urothelium, the cell type from which most bladder cancers arise [3]. Bladder cancers may be superficial and non-invasive, muscular invasive, or metastatic, and have different etiologies, treatments, and prognoses.

Patients with bladder cancer typically present with microscopic or macroscopic hematuria [4]. Flank pain may be another presenting symptom especially in patients in whom bladder masses involve and obstruct the ureterovesical junction, leading to hydroureteronephrosis. Bladder cancers are typically diagnosed with cystoscopy and transurethral resection of the bladder tumor (TURBT) and staged using the standard TNM system. As with other hollow organs, bladder cancer is staged based on the depth of invasion through layers of the wall. Non-invasive carcinomas include papillary non-invasive urothelial carcinoma, staged as pTa, which can present as mass lesions. These are distinguished from flat urothelial carcinoma in situ, which are staged as pTis. In stage T1 lesions, the carcinoma invades the lamina propria. A stage T2 tumor invades into the muscularis propria—the detrusor muscle. Thereafter, tumors invade into the perivesical fat (T3) or surrounding organs (T4). Stage T1 tumors are typically treated with TURBT and adjuvant intravesical therapy. Stage T2 and above tumors require more aggressive management, typically including radical cystectomy. Tumors are also classified histologically as low grade or high grade using a system devised by the World Health Organization (WHO) and the International Society of Urologic Pathologists (ISUP), with higher-grade tumors having greater potential for invasion and a more aggressive course [5].

Approximately 95% of bladder cancer is urothelial (transitional-cell) carcinoma [6]. Squamous cell carcinoma is the second most common type, with less-common varieties including adenocarcinoma, small-cell carcinoma, and sarcoma. Extremely rare varieties of bladder tumors include well-differentiated neuroendocrine tumors (‘carcinoid’), rhabdomyosarcoma, paraganglioma, leiomyosarcoma, and lymphoma. Metastases to the bladder are rare but can originate from any primary site, particularly the gastrointestinal tract cancers, breast carcinoma, or melanoma.

Bladder cancer most frequently metastasizes to the pelvic and retroperitoneal lymph node stations [7]. Bone is the most common site for distant bladder cancer metastases; most appear sclerotic but can also be lytic or mixed lytic-sclerotic. For solid organs, the liver and lung are the most frequent sites of metastasis [7], with involvement of other organs occurring far less frequently.

Males are three times more likely to develop bladder cancer than females. Smoking is associated with 50–65% of cases of bladder cancer in men, and 20–35% in women [8]. Most bladder cancers occur in people over the age of 60 years [9]. In addition to age, additional risk factors include occupational or environmental exposure to chemical carcinogens such as aniline dyes—benzidine and beta-naphthylamine [10]—chronic bladder stones, chronic cystitis, analgesic (phenacetin) abuse [11], cyclophosphamide

use [12], and a history of radiation therapy to the pelvis [13, 14]. In developing countries, bladder cancer may be caused by schistosomiasis infection.

Sonographic technique

The bladder is optimally evaluated under moderate distention, as underdistention markedly limits evaluation of bladder wall thickening and focal masses, while overdistention leads to patient discomfort. The patient should be placed in a supine position, with lateral decubitus positioning used ad hoc to assess for lesion mobility, which can help to distinguish potential mimics of bladder cancer such as bladder stones or fungus balls. The time-gain compensation (TGC) may need adjustment to reduce reverberation artifact from the anterior bladder wall. If a focal mass is seen, careful evaluation with color and power Doppler can help identify internal vascularity, which would distinguish potential mimics such as blood clots or fungus balls from tumor. Spectral Doppler interrogation in areas of detectable blood flow can help demonstrate arterial or venous blood flow, which would be suspicious for bladder cancer. Newer flow sensitive Doppler techniques may increase sensitivity to detect internal vascularity, now available on many ultrasound machines.

A 3.5–6 MHz transducer is most commonly used for bladder evaluation. Findings along the anterior bladder wall can be assessed with greater spatial resolution using higher-frequency linear transducers (> 9 MHz). During the ultrasound examination, the bladder should be centered within the field of view; the bladder can be fully assessed by placing the probe immediately superior to the symphysis pubis and angling the probe laterally, inferiorly, and superiorly in both the transverse and longitudinal orientations. The posterior wall at the bladder base should be carefully interrogated, as transitional-cell carcinoma often resides in this region. In females, the bladder may be assessed using a transvaginal probe for improved spatial resolution if needed; a transrectal approach can be used in males if visualization of the bladder is limited transabdominally. Identification of a single lesion should prompt the search for additional lesions, as 30–40% of bladder cancers are multifocal [15].

Imaging and pathology findings of bladder cancer

Most urothelial cell cancers are located along the posterior wall at the base of the bladder [15]. Sonographically visible bladder cancer most commonly manifests as a polypoid mass arising from the bladder wall (Fig. 2). On sonographic evaluation, bladder masses are typically immobile with changes in patient position and often heterogeneous

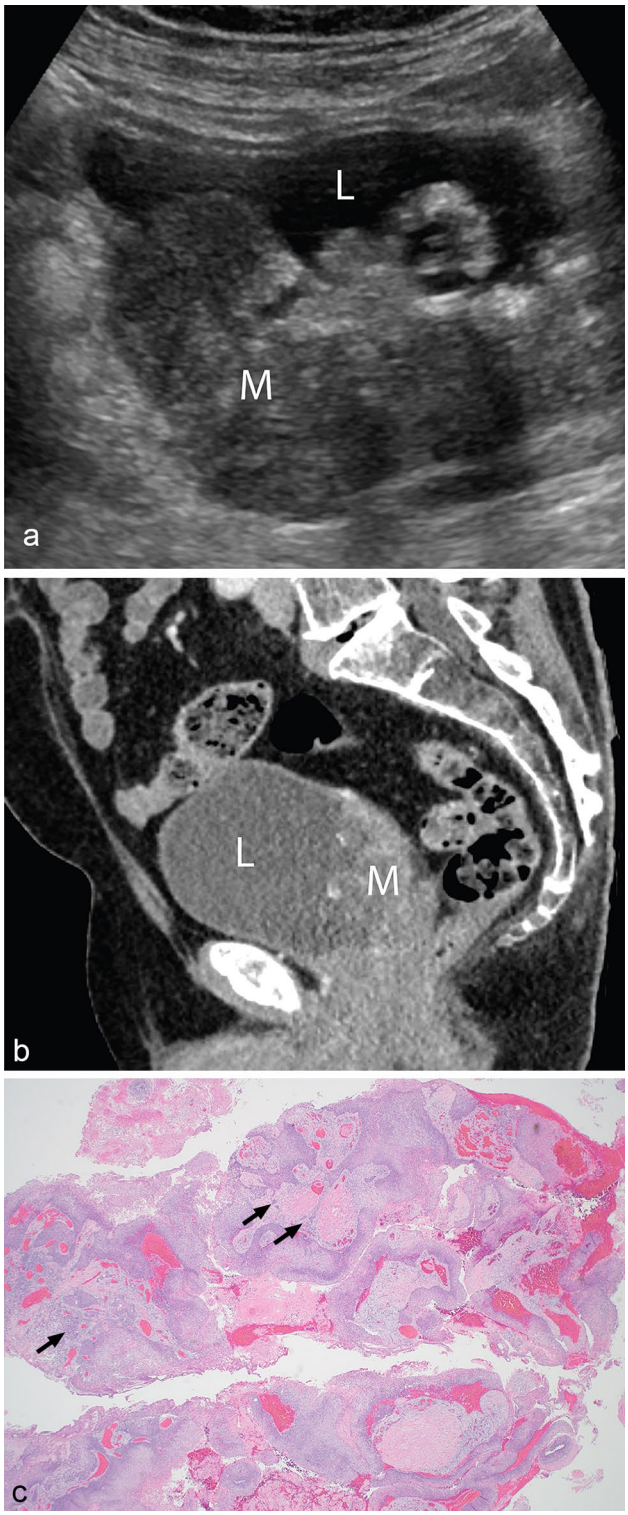

Fig. 2 72-year-old male with high-grade urothelial carcinoma. **a** Longitudinal ultrasound scan shows a large bladder mass arising from the posterior bladder wall with invasion and posterior extension of tumor. **b** Sagittal CT of the bladder shows a polypoid heterogeneously enhancing mass arising from the posterior bladder wall. Pathology **c** demonstrates polypoid fragments of exophytic high-grade urothelial carcinoma in the transurethral resection of bladder tumor (TURBT) specimen. Image shows considerable squamous differentiation and focal lamina propria invasion by cancer (arrows). H&E, original magnification ×20. *M* mass, *L* bladder lumen

in echotexture. The presence of flow detected on color Doppler helps to distinguish the solid tissue of a tumor from blood clot or debris. Bladder cancer typically appears as a lesion with soft-tissue attenuation on CT but is often better identified as a filling defect within a contrast-filled bladder on CT urography. When visualized by MR, bladder cancers typically are T1 isointense and mildly T2 hyperintense compared to the bladder wall. If large enough, bladder cancers can be identified as enhancing bladder masses on post-contrast CT or MRI.

In high-grade urothelial carcinoma, the mass may invade through the bladder wall musculature and can extend beyond the bladder into the abdominal wall, prostate, or uterus (Fig. 3). In particular, carcinomas arising in bladder diverticula may have early transmural extension related to the underlying bladder wall defect, conferring a worse prognosis. Lesions near the ureterovesical junctions may cause ureteral obstruction and result in hydroureteronephrosis.

Occasionally, bladder cancer may be sessile and only appear as focal bladder wall thickening with or without extension into the bladder lumen. While such focal thickening can be appreciated on ultrasound, CT, or MR, it may also be quite subtle and difficult to recognize depending on the degree of bladder distention. A focal area of bladder wall thickening > 3 mm for a well-distended bladder, and > 5 mm for a poorly distended bladder, is suggestive of pathology [16].

Focal calcifications are seen in 5% of urothelial cell cancers [15]. Idiopathic focal bladder wall calcifications are unusual, and thus the presence of focal calcifications in the bladder wall should raise suspicion for an underlying bladder tumor. Calcifications can also be seen in cystitis, schistosomiasis, tuberculosis, and after radiation treatment of the pelvis; however, in these entities calcifications are typically more diffuse than focal. Calcifications can be recognized on ultrasound as echogenic foci with or without shadowing, or as hyperattenuating foci on CT. Calcifications are more difficult to appreciate on MR, but are best seen as low signal foci on T1 or GRE acquisitions.

Sonography is reported to be 63% sensitive and 99% specific for the detection of bladder cancer [17]. Sonographic sensitivity may be limited in identifying tumors within a non-fluid-filled diverticulum and in detecting tumors of the bladder base in the setting of prostatomegaly, which may cause irregular impressions upon the bladder base. However, of note, imaging can be particularly beneficial in the detection of cancer within diverticula, as cystoscopy cannot evaluate diverticula with a narrow neck.

On pathology, urothelial carcinoma typically demonstrates papillary architecture. The degree of nuclear anaplasia denotes whether the tumor is low or high grade. Invasion into the lamina propria, muscularis propria, or vasculature can also be assessed histologically.

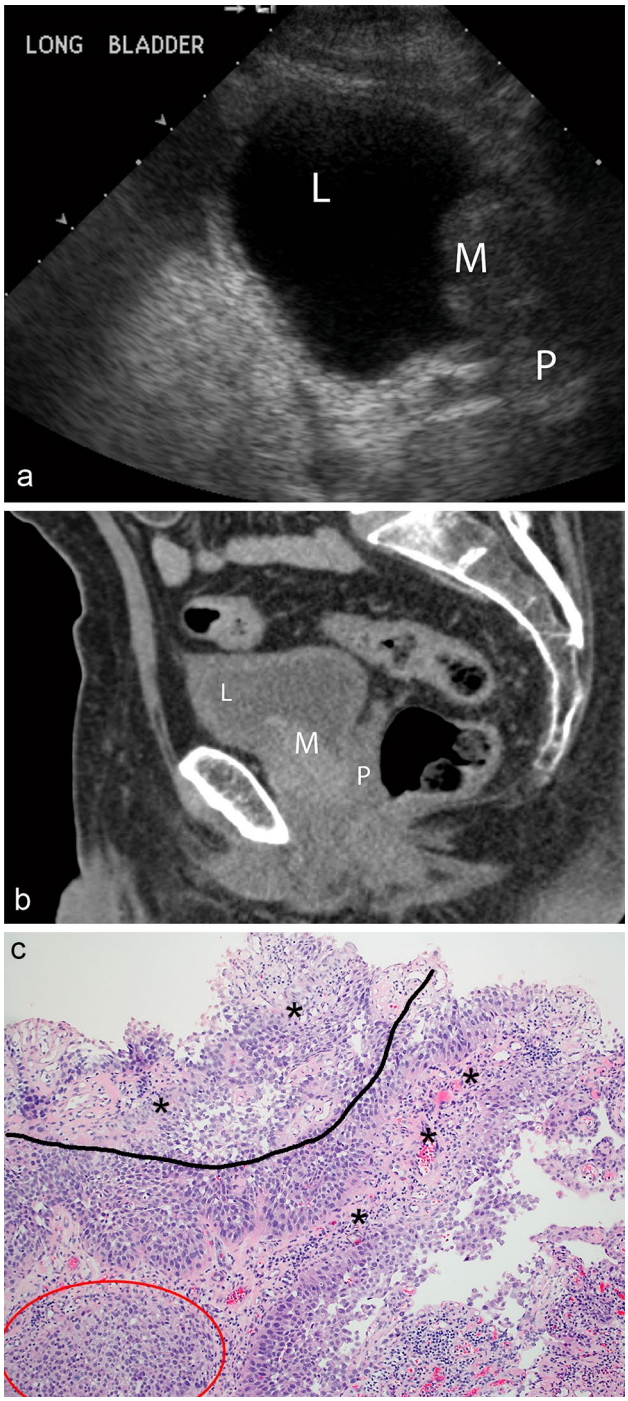

Fig. 3 72-year-old male with high-grade urothelial carcinoma. **a** Longitudinal ultrasound scan shows a large bladder mass arising from the posterior bladder wall with invasion and posterior extension of tumor. **b** Sagittal CT of the bladder shows the mass arising from the posterior bladder wall. Pathology **c** demonstrates high-grade urothelial carcinoma with papillary architecture (asterisks). Some of the malignant epithelium is degenerating in this TURBT specimen (above the black line). The tumor in the lower left represents involvement of a von Brunn nest (red circle). The prostatic invasion is not represented in this TURBT specimen. H&E, original magnification ×100. *M* mass, *L* bladder lumen, *P* prostate

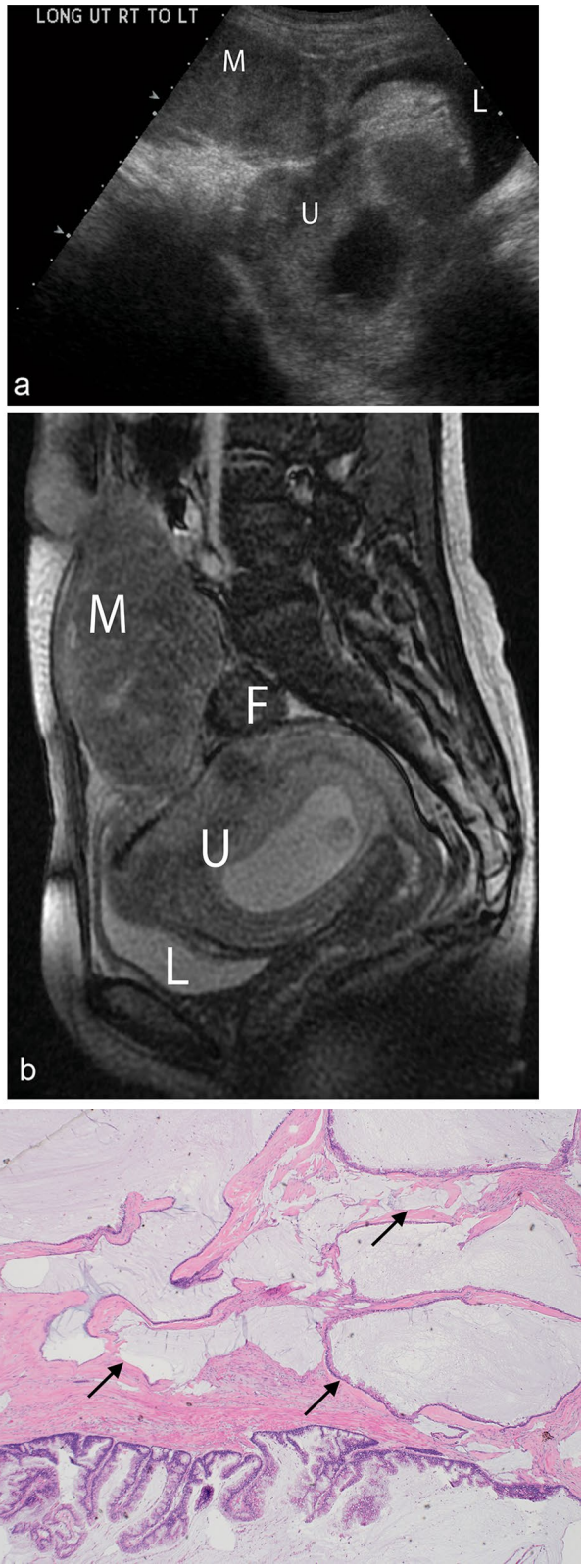

Fig. 4 36-year-old pregnant female with urachal carcinoma. **a** Longitudinal grayscale ultrasound of the pelvis shows a large mass superior to the bladder and anterior to the gravid uterus. **b** Sagittal MR of the pelvis shows the heterogeneous mass superior to the bladder and extending to the umbilicus. **c** Histologic sections of the urachal tumor demonstrate invasive mucinous carcinoma, a common histologic variant of urachal carcinoma. At bottom, there is malignant epithelium with surface villous structures. Elsewhere, invasive pools of pale gray mucin (arrows) are partially lined by tumor cells. H&E, original magnification ×20. *L* bladder lumen, *M* mass, *F* fibroid, *U* gravid uterus

Mimics of primary bladder urothelial carcinoma

Neoplasms mimicking urothelial carcinoma

Urachal carcinoma

The urachus is a remnant of the embryologic cloaca and allantois. The urachus extends from the anterosuperior surface of the bladder to the umbilicus. Of note, urachal remnants are seen in nearly 100% of newborns, but eventually the remnant regresses to become the median umbilical ligament. A urachal remnant is present in 3% of the general population at autopsy [18].

Carcinoma of the urachus is rare, representing < 1% of bladder cancers [19, 20]. It most often presents as an adenocarcinoma (69% of cases), with the remaining cancers attributed to urothelial, squamous, and sarcomatoid subtypes [18]. In 90% of cases, urachal carcinoma begins in the urachus adjacent to the bladder dome [18]; as the cancer grows, it extends cranially towards the umbilicus (Fig. 4).

Urachal carcinoma is most often seen in middle-aged and elderly men. It is often undetected until symptoms arise from local invasion or systemic spread. Urachal carcinoma can cause abdominal pain, hematuria, mucosuria, and purulent or bloody discharge from the umbilicus [18]. Furthermore, as the mass is typically extravesical in location, the patient is often asymptomatic initially, resulting in a late presentation. Urachal carcinoma is highly malignant, which often necessitates an en bloc resection of the mass as well as the umbilical ligament for long-term disease-free survival [21].

Urachal carcinoma will appear sonographically complex and heterogeneous in echotexture. Calcifications are present in 70% of cases [18], often along the periphery of the mass. Early urachal carcinomas, limited to the bladder dome, can look identical to invasive bladder cancer. The presence of a mass at the bladder dome that extends to the umbilicus is more easily appreciated on sagittal CT and MRI. Cystic components of the mass, when present, are hypo- or anechoic on ultrasound, near water attenuation on CT, and T2 hyperintense on MRI.

On pathology, urachal carcinomas are seen in the setting of a urachal remnant. Most commonly these tumors are mucin-producing [22], with prominent lakes of mucus. There is often invasion of the muscularis or deeper tissues.

Lymphoma

Lymphoma of the bladder is rare. By definition, primary lymphoma of the bladder occurs in the absence of known lymphoma elsewhere. More commonly, the bladder is secondarily involved with a known extravesical primary lymphoma [23].

Bladder lymphoma is most commonly seen in middle-aged women [22]. Patients may present with hematuria. Marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and diffuse large B-cell lymphoma are the most frequent types identified (Fig. 5). Bladder lymphoma presents most commonly as a solitary submucosal bladder mass (70%) (Fig. 5), with 20% occurring multifocally, and 10% presenting as diffuse bladder wall thickening [23]. There are no known distinct imaging characteristics to distinguish bladder lymphoma from other types of bladder cancer. Thus, bladder lymphoma typically appears as a lobular mass along the bladder wall with vascularity on color Doppler and enhancement on post-contrast CT or MRI.

Pathology of bladder lymphoma reveals a proliferation of large cells with a high nuclear:cytoplasmic ratio. Immunostains, such as for CD20, can be used to identify a proliferation of B cells in the setting of a diffuse large B-cell subtype of lymphoma.

Paraganglioma

A paraganglioma is a pheochromocytoma outside the adrenal gland. Of pheochromocytomas, 18% are paragangliomas, 10% of which are located in the bladder [24]. Paragangliomas account for 0.06% of all bladder tumors [25]. An interesting and classic presentation of patients with bladder paragangliomas is acute hypertension during micturition due to the release of catecholamines. This transient release of catecholamines may manifest as headache, blurred vision, or flushing with micturition [26]; however, 27% of patients may not have any symptoms associated with bladder paraganglioma.

Bladder paragangliomas appear as a soft-tissue mass arising from the bladder wall that protrudes into the bladder lumen [27] (Fig. 6). These tumors are often indistinguishable from urothelial cell or other bladder cancers. Potential distinguishing features from other bladder tumors include intense enhancement on post-contrast CT or MRI, or the presence of necrosis or hemorrhage within the lesion. If a bladder paraganglioma is suspected given the history and imaging appearance, further evaluation with an iodine-123-MIBG nuclear medicine study can be performed [27].

On pathology, a paraganglioma is epithelioid in appearance. The architecture is characteristically nested. Immunohistochemistry can be used to confirm the neuroendocrine origin of the mass.

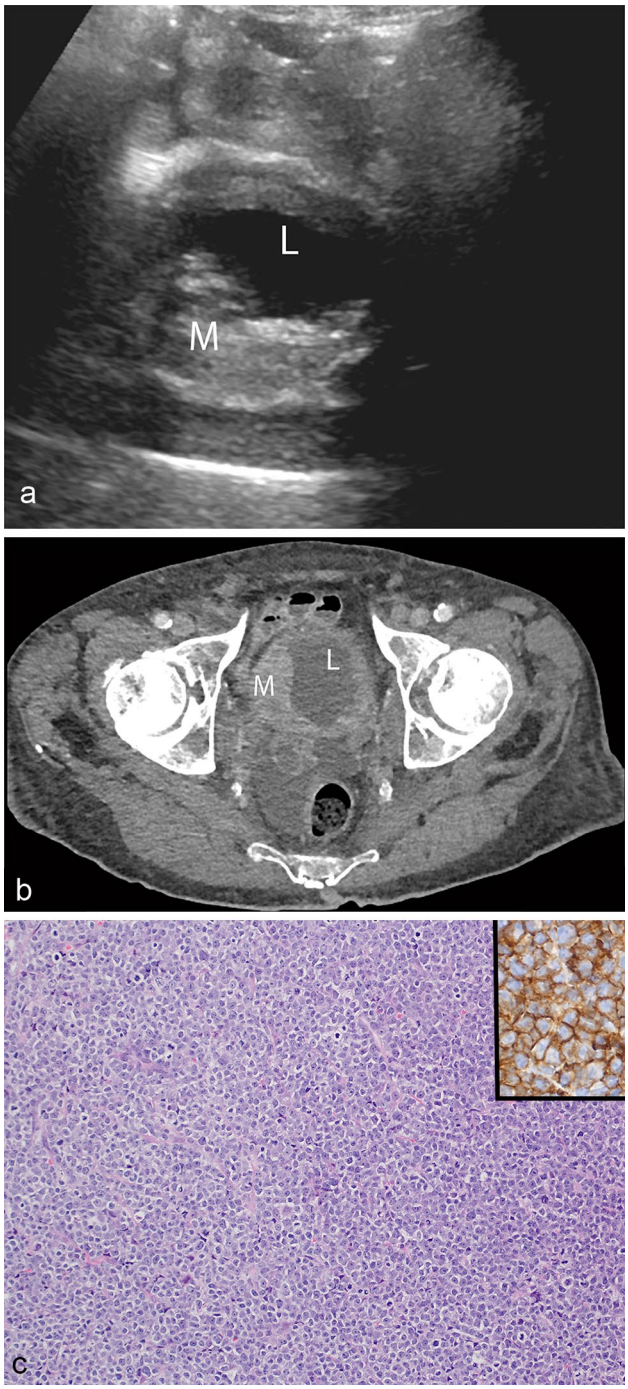

Fig. 5 85-year-old male with diffuse large B-cell lymphoma of the bladder. **a** Transverse grayscale ultrasound of the bladder shows a large heterogeneous mass along the right posterolateral bladder wall. **b** Axial CT in the same patient shows similar asymmetric thickening of the right bladder wall. No additional site of lymphoma was identified on subsequent staging studies. Of note, patient had a history of prostate cancer and pelvic radiation therapy. **c** Histologic section of bladder demonstrates effacement by sheets of large cells with high nuclear:cytoplasmic ratio. Inset shows immunostain for B-cell protein CD20, highlighting all tumor cells (brown-positive). H&E original magnification ×200, inset CD20 immunostain. *L* bladder lumen, *M* mass

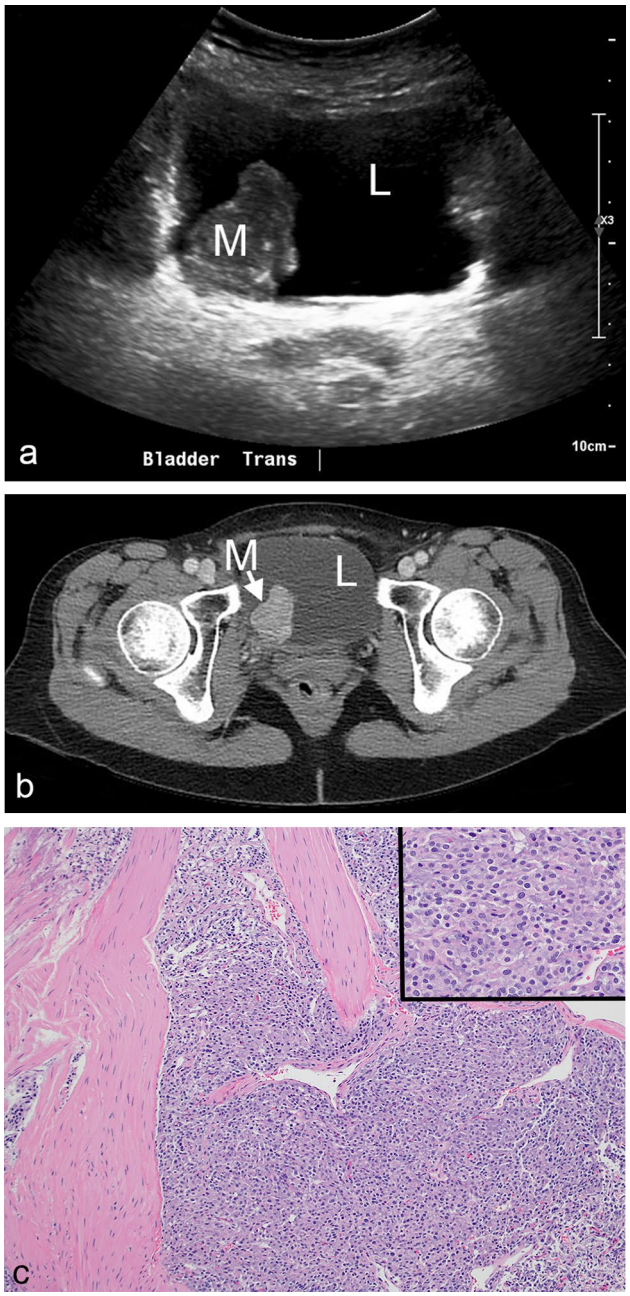

Fig. 6 60-year-old female with bladder wall paraganglioma. **a** Transverse grayscale ultrasound of the bladder shows a mass arising from the right posterior bladder wall. Internal vascularity was present on color Doppler (not shown). **b** Axial contrast-enhanced CT images show that the right posterior bladder wall mass is avidly enhancing. **c** Histologic section in a different patient with bladder paraganglioma shows epithelioid tumor within the detrusor muscle with vaguely nested architecture. Higher-power inset (upper right) highlights neuroendocrine chromatin and pink-purple cytoplasm. Immunohistochemical stains (not shown) confirm the diagnosis of paraganglioma. H&E, original magnifications ×100, inset ×200. *L* bladder lumen, *M* mass

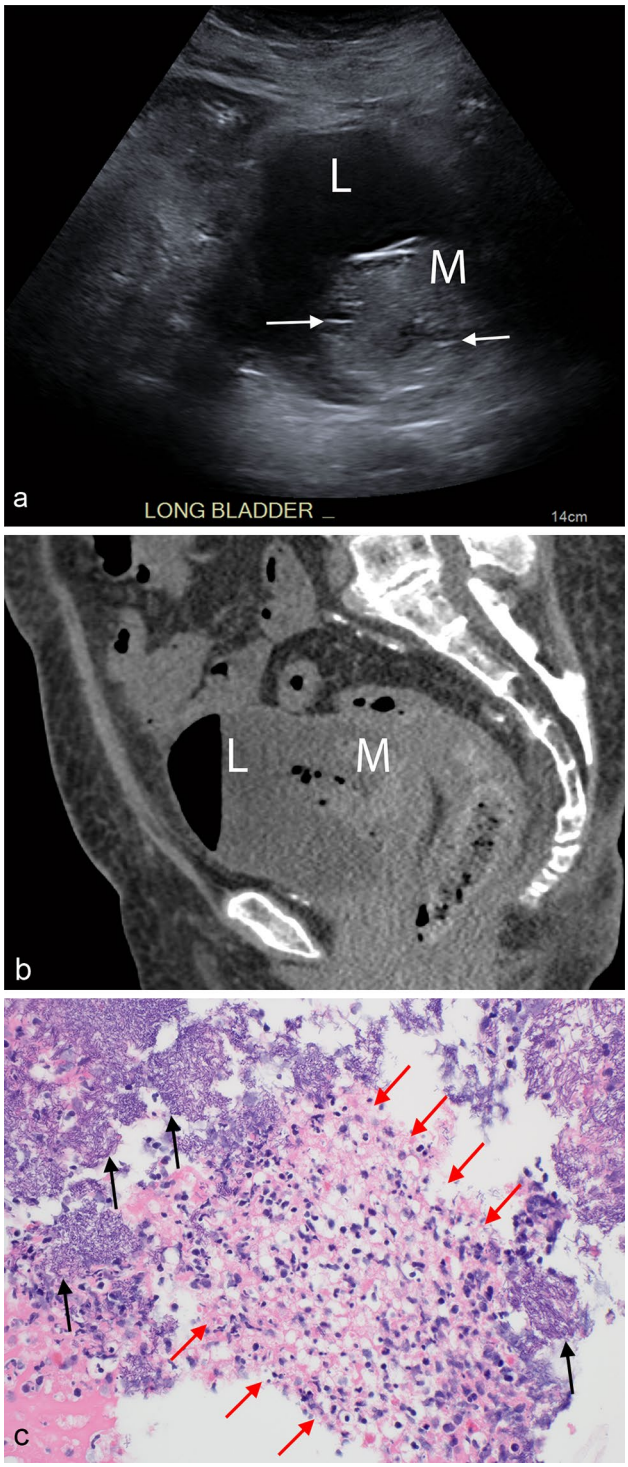

Fig. 7 65-year-old male with bladder abscess confirmed on pathology. **a** Longitudinal ultrasound image shows a rounded mass with several echogenic foci, consistent with gas (arrows). **b** Sagittal CT in the same patient shows a hyperdense mass with corresponding foci of gas. **c** Pathology confirms bacterial infection, which walled off in the bladder wall, forming an abscess. Sections show neutrophils (between red arrows) with abundant bacterial overgrowth (black arrows). H&E, original magnification ×400. *L* bladder lumen, *M* mass

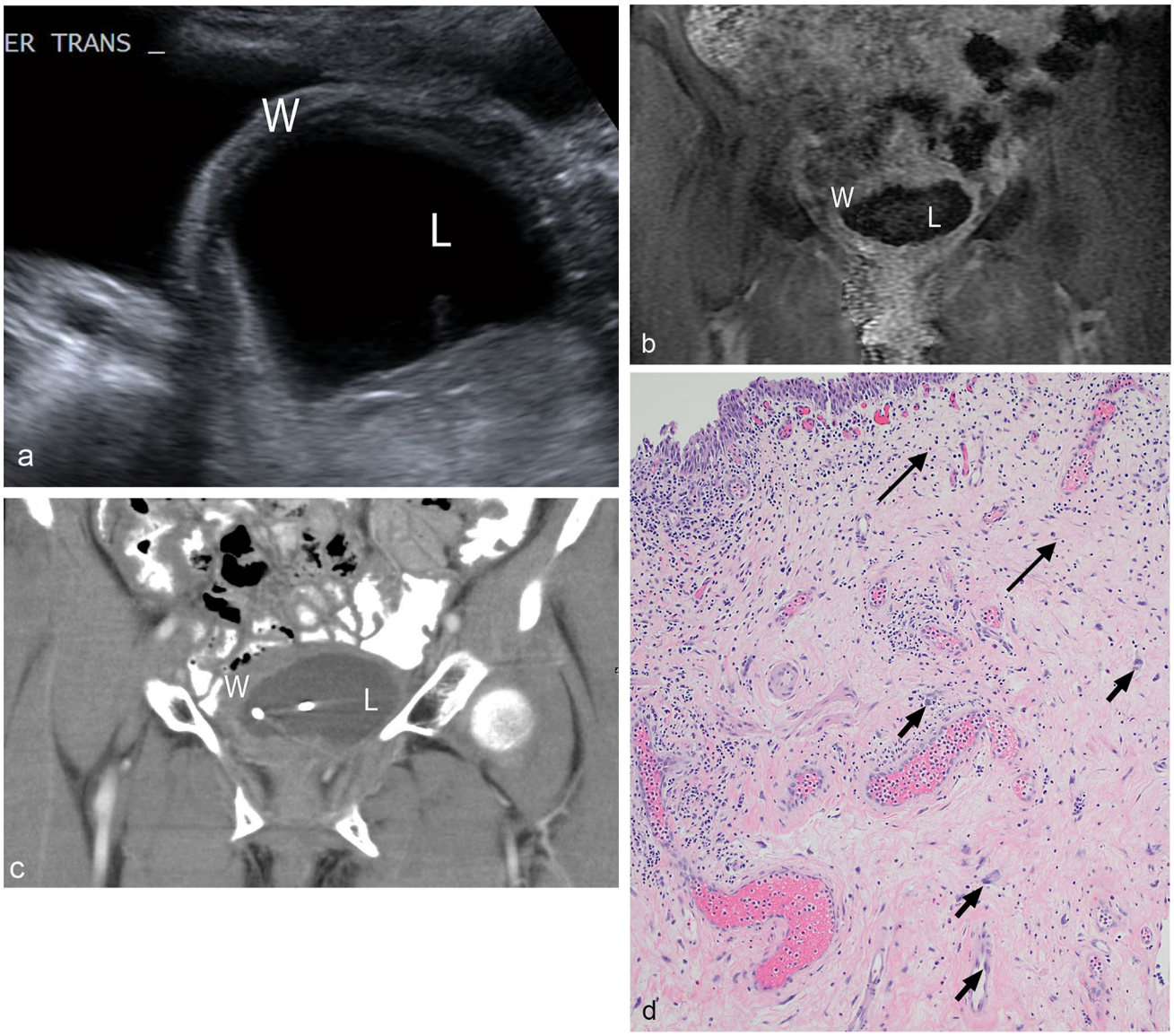

Fig. 8 64-year-old female with radiation-induced cystitis after radiation treatment of cervical carcinoma. **a** Transverse ultrasound image of the bladder shows diffuse marked thickening of the bladder wall. Radiation cystitis often prevents full distension of the bladder, as seen in this patient. **b** Coronal contrast-enhanced T1W MR and **c** coronal contrast-enhanced CT images confirm the bladder wall is diffusely thickened. **d** H&E stain shows the urothelium with reactive change. The lamina propria is edematous (long arrows), with scattered chronic inflammatory cells throughout. Vessels are congested with red blood cells and neutrophils. Stromal and endothelial cells are enlarged and atypical (short arrows), which are characteristic features of radiation. H&E, original magnification ×100. *W* bladder wall, *L* bladder lumen

Metastases

The bladder may be involved secondarily due to transmural extension of tumors in contiguous pelvic organs, or via drop metastases in peritoneal carcinomatosis. Metastases to the bladder most often arise from primary malignancies such as gastric carcinoma, breast carcinoma, or melanoma [28]. Lung cancer and renal cell carcinoma are less-common sources of bladder metastases. While lung cancer typically spreads hematogenously, the route via which renal cell carcinoma metastasizes to the bladder is unknown; proposed mechanisms of the latter include hematogenous, lymphatic, and canalicular routes (i.e. along the urinary tract) [29]. Bladder metastases often appear as vascular nodular lesions along the bladder wall and can be solitary or multifocal. While bladder metastases can look identical to primary bladder cancers, a multifocal appearance and/or patient history can help to distinguish between the two entities.

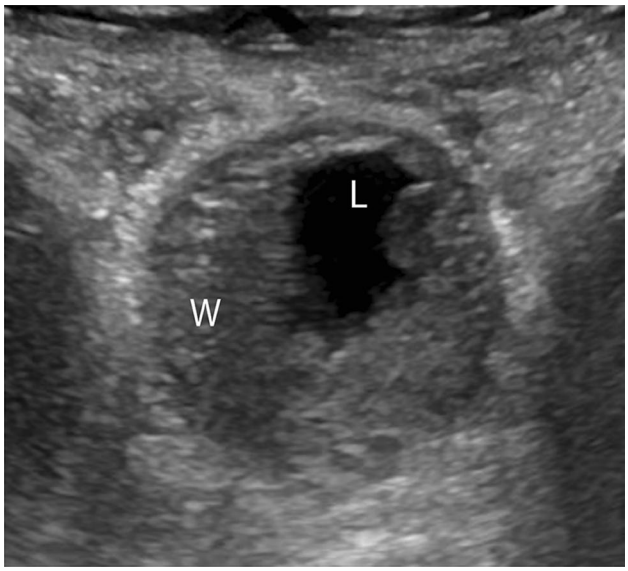

Fig. 9 50-year-old male with history of chronic lymphocytic leukemia and cyclophosphamide-induced cystitis. Transverse ultrasound image of the bladder shows severe bladder wall thickening, which results in marked restriction of bladder distension, resulting in a small bladder lumen. *W* bladder wall; *L* bladder lumen

Benign entities that can mimic urothelial carcinoma

Cystitis

Cystitis is a general term for inflammation of the bladder. Cystitis typically presents with dysuria, pyuria, frequency, and urgency, but can also present with hematuria, similar to bladder cancer. Common risk factors for development of cystitis include female gender (the shorter urethra in females may facilitate retrograde bacterial reflux into the bladder), sexual intercourse, spermicide use, bladder outlet obstruction, catheterization, or the presence of foreign bodies. Antibacterial properties of prostatic fluid may also be protective against cystitis in men [30].

Acute cystitis typically causes bladder wall thickening. Although bladder wall thickening can be appreciated on all imaging modalities, it can be challenging to determine if the thickened appearance is simply due to underdistention of the bladder versus true wall thickening. In these situations, ultrasound may be advantageous. First, the bladder may be imaged serially and if not optimally distended, repeat imaging may be performed after the bladder is optimally filled. Secondly, bladder wall edema may be better appreciated with ultrasound and appear hypoechoic and thickened. Hyperemia of the bladder wall may be appreciated on color or power Doppler imaging. Finally, perivesical inflammatory changes may be appreciated as echogenic fat on ultrasound, analogous to fat stranding seen on CT or MRI. Chronic cystitis also leads to thickening of the bladder wall, but can

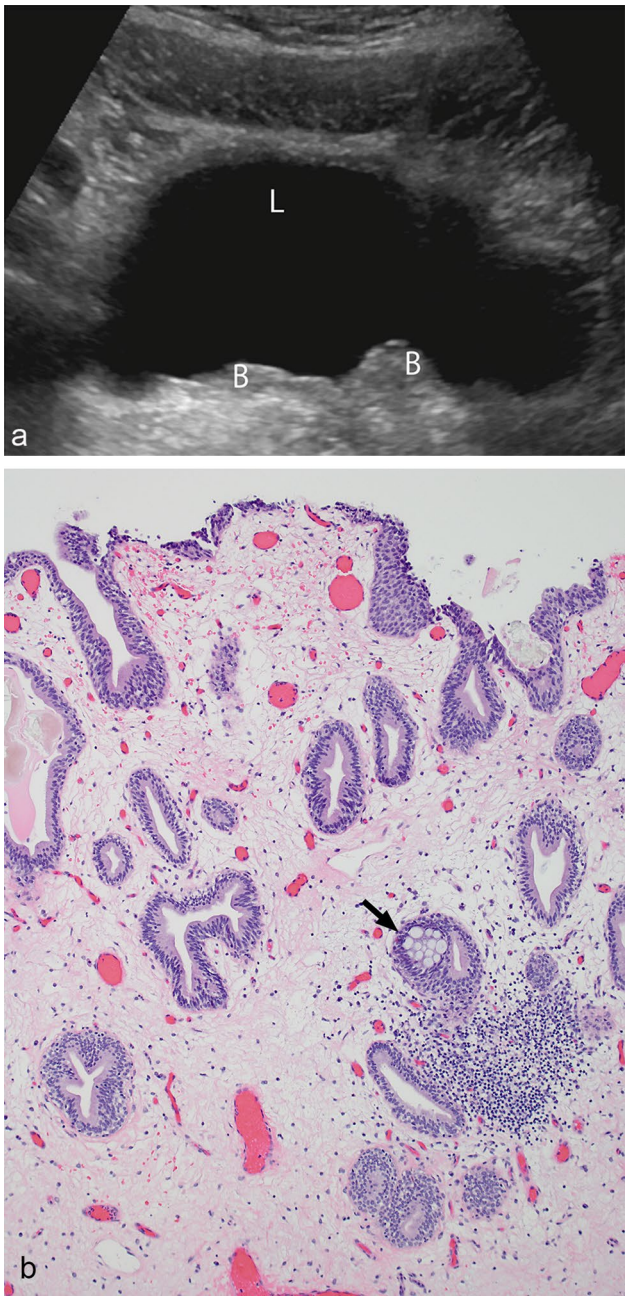

Fig. 10 52-year-old male with cystitis glandularis. **a** Transverse gray-scale ultrasound view of the bladder shows mass-like buds along the posterior bladder wall, which were confirmed via cystoscopy to represent areas of glandular hypertrophy. **b** Histologic sections from a different patient with cystitis glandularis show numerous glandular structures with open lumens below the mucosa. These have columnar cells, rather than urothelial epithelial lining, an example of cystitis glandularis. The arrow denotes a focus of intestinal metaplasia, with mucin-filled goblet cells; small blue nuclei in the lamina propria below are lymphocytes. H&E, original magnification ×100. *L* bladder lumen, *B* buds

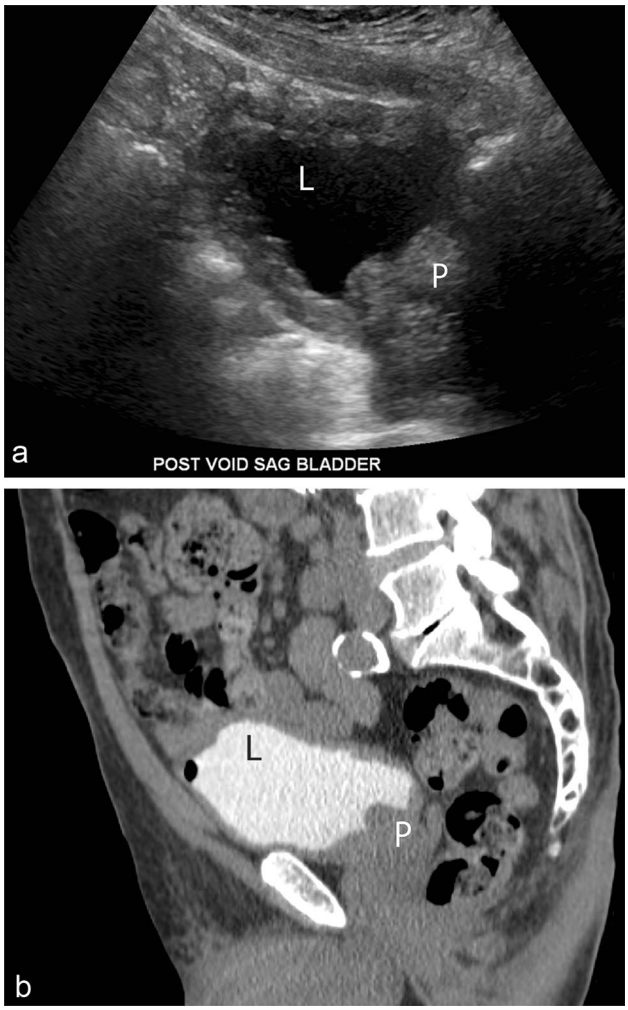

Fig. 11 89-year-old male with chronic bladder outlet obstruction and bladder wall thickening. **a** Longitudinal grayscale ultrasound view of the bladder shows a large prostate, which results in nodular indentation of the inferior bladder margin. Chronic bladder outlet obstruction often leads to bladder wall thickening, trabeculations, and diverticula. **b** Non-contrast sagittal CT of the pelvis shows a corresponding thick-walled bladder and an enlarged prostate, which results in irregularity of the inferior bladder contour. *L* bladder lumen, *P* prostate

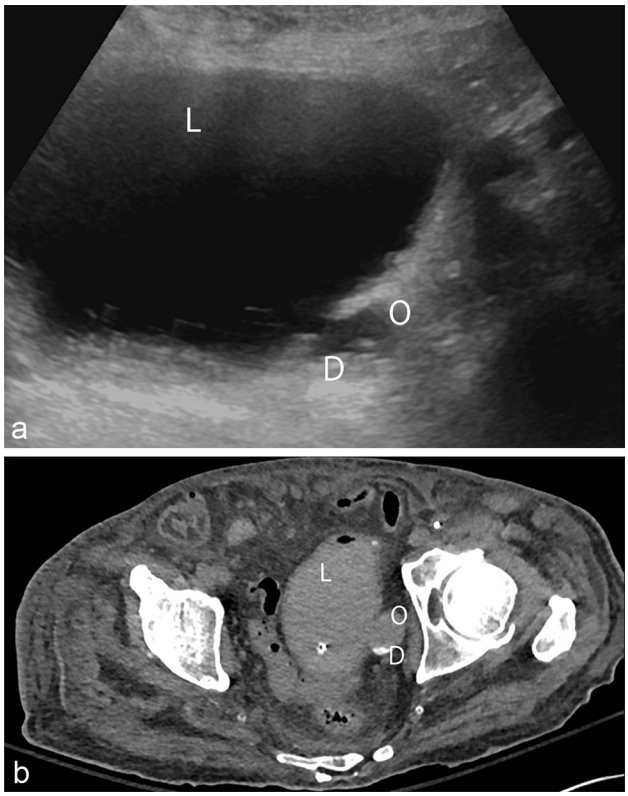

Fig. 12 83-year-old male with chronic bladder outlet obstruction and a bladder diverticulum. **a** Transverse ultrasound view shows a distended bladder with irregular trabeculations along the bladder wall as well as a thin-necked bladder diverticulum containing layering debris. **b** Axial CT in the same patient confirms a diverticular outpouching with layering calcifications. A Foley catheter has now been placed, resulting in partial decompression of the bladder. *D* debris, *O* outpouching, *L* bladder lumen

appear more contracted or irregular on sonography than is seen in acute cystitis. Infrequently, bladder cancer can cause diffuse bladder wall thickening as well as hyperemia, and the imaging appearance may overlap with chronic cystitis. Correlation with symptoms and patient demographics is often helpful in distinguishing cystitis from bladder cancer, particularly favoring the former over the latter when the patient is female, has dysuria, and has an identifiable causative agent, as discussed below.

Infectious cystitis most commonly occurs secondary to bacteria present on the skin entering the bladder in a retrograde fashion via the urethra. In severe cases, phlegmonous tissue or an abscess can develop within the bladder wall and lumen (Fig. 7). On pathology, bacterial cystitis will reveal abundant bacterial overgrowth and the presence of neutrophils. Cystitis can also be secondary to an adjacent inflammatory process, such as prostatitis, diverticulitis, colitis, or salpingitis. In cystitis due to *Schistosomiasis haematobium*, an inflammatory response is elicited by the deposition of ova within the bladder lamina propria. Non-infectious causes of cystitis include chronic irritation from bladder stones or an indwelling catheter or external beam radiation (Fig. 8). On pathology, radiation-induced cystitis is distinguished by the presence of enlarged and atypical stromal and endothelial cells. The chemotherapy agents ifosfamide or cyclophosphamide can also cause cystitis [31] (Fig. 9).

Another iatrogenic source of cystitis is intravesical therapy with bacillus Calmette-Guerin (bCG), used in the treatment of non-muscular invasive bladder cancer. bCG-induced cystitis is a frequent complication of this therapy, seen in up to 91% of patients [32]. Given that bladder wall thickening is seen in the setting of cystitis, it can be difficult to distinguish

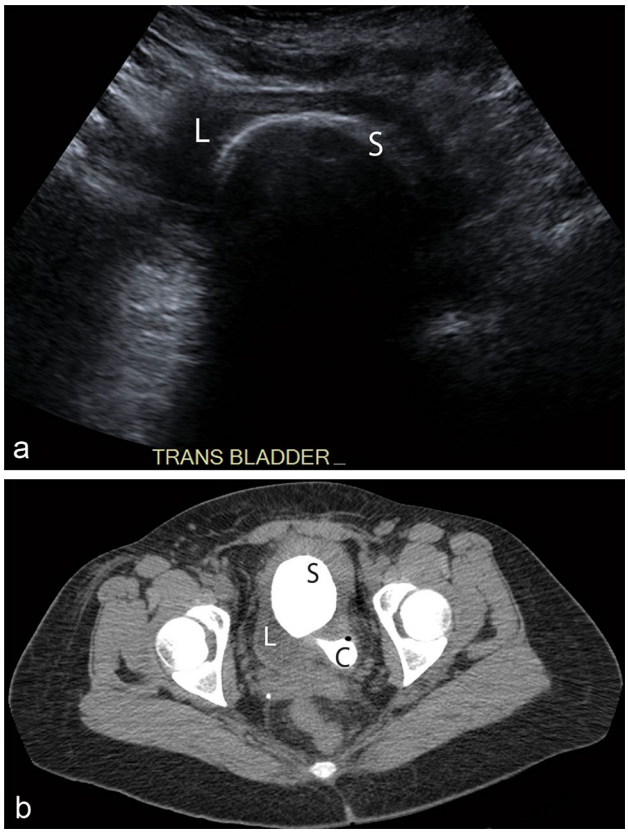

Fig. 13 44-year-old female with a large bladder calculus. **a** Transverse grayscale ultrasound view of the bladder shows the anterior bladder wall and a large round calcified intraluminal mass with marked posterior acoustic shadowing. **b** Axial non-contrast CT shows a large calcified bladder mass, confirmed to represent a large bladder calculus. Note the presence of a left ureteral stent fragment (C) surrounded by calcification. The bladder calculus may have formed secondarily to the presence of this retained distal ureteral stent fragment. *L* bladder lumen, *S* stone, *C* calcified ureteral stent

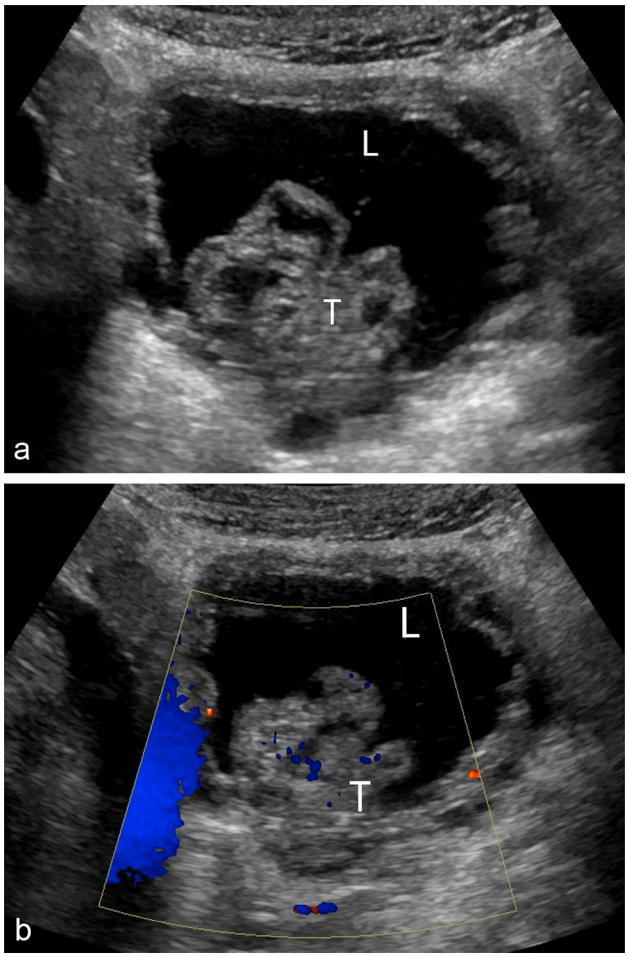

Fig. 14 87-year-old male with large bladder thrombus. **a** Transverse ultrasound view of the bladder shows a heterogeneous lobulated mass, confirmed to represent a thrombus on cystoscopy. **b** Transverse ultrasound view of the bladder with color Doppler overlay. Scattered blue foci over the lesion are artifactual. No vascularity was present within the mass. *L* bladder lumen, *T* thrombus

bCG-induced cystitis from residual/recurrent bladder cancer in follow-up imaging.

Cystitis cystica and cystitis glandularis

Cystitis cystica/glandularis is a non-neoplastic condition that may be a normal variant, or related to chronic infection, bladder calculi, or chronic bladder outlet obstruction [22]. Cystitis cystica/glandularis can occur at any age, although there is a slight male predominance. Patients with cystitis cystica/glandularis typically present with hematuria but can also be asymptomatic.

When florid, cystitis cystica and glandularis may appear radiologically or cystoscopically as polypoidal, mass-like lesions within the bladder. These lesions most often appear at the bladder trigone [33]. Cystitis cystica and glandularis can be indistinguishable from inverted papilloma and/or multifocal bladder cancer [33, 34] (Fig. 10). A biopsy is necessary to differentiate these entities. While cystitis cystica and glandularis are considered non-neoplastic, there is a small risk of degeneration to adenocarcinoma, and follow-up imaging is therefore warranted [35].

Bladder outlet obstruction

Bladder outlet obstruction often presents with urinary retention and discomfort. Outlet obstruction is often secondary to benign prostatic hyperplasia (BPH), and is therefore more common in males, but can also be secondary to urethral strictures or periurethral masses [36].

Chronic bladder outlet obstruction commonly produces diffuse bladder wall thickening without hyperemia as well as bladder wall trabeculations (Fig. 11), which

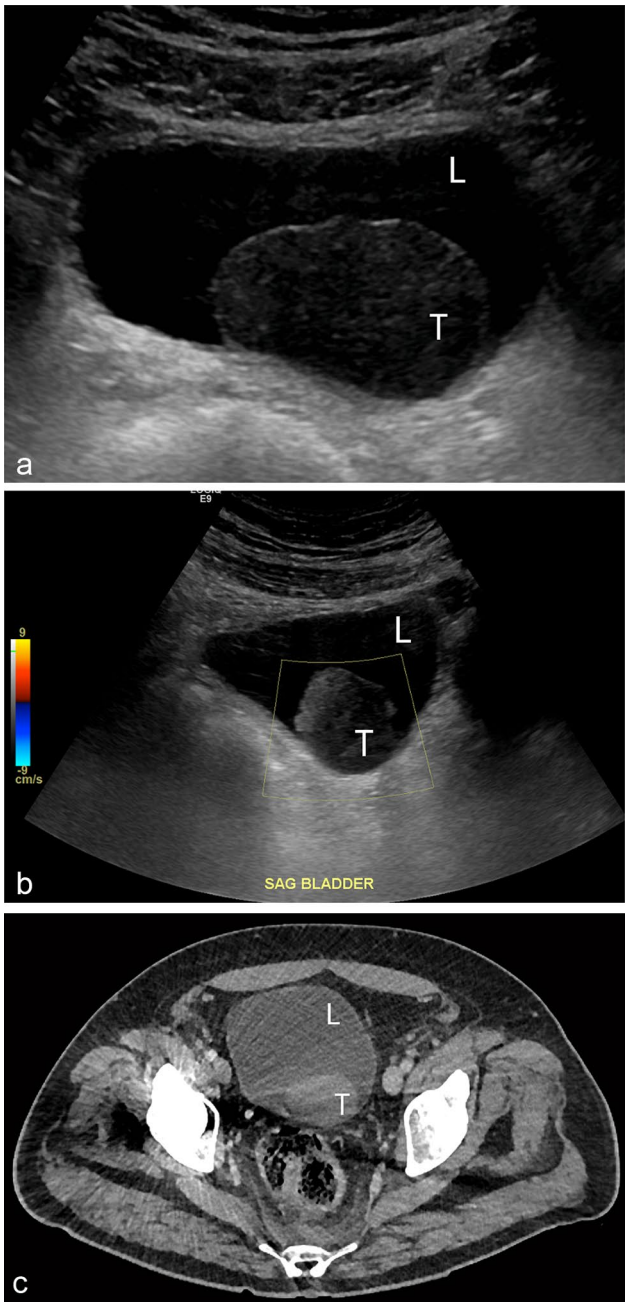

Fig. 15 63-year-old male with large bladder thrombus. **a** Transverse grayscale ultrasound view of the bladder shows a large, hypoechoic, well-circumscribed mass within the bladder. **b** Transverse ultrasound view of the bladder with color Doppler overlay shows no vascularity within the mass. **c** Axial contrast-enhanced CT confirms a large rounded mildly hyperdense intraluminal mass confirmed to represent large thrombus on cystoscopy. The patient had a history of clear cell renal cell carcinoma status post partial nephrectomy complicated by a pseudoaneurysm, which caused hematuria and led to the bladder thrombus. *L* bladder lumen; *T* thrombus

can be appreciated on ultrasound, CT, or MR. A post-void residual volume greater than 200 ml, as measured during sonographic evaluation, is indicative of inadequate emptying of the bladder [37]. Moreover, urinary retention can cause bladder wall irritation and, when chronic, may also lead to cystitis.

Bladder diverticulum

Bladder diverticula are focal outpouchings of the bladder and are often seen in the setting of chronic bladder outlet obstruction. The muscularis propria is either absent or markedly attenuated around the diverticulum. Diverticula are often fluid-filled, clearly communicate with the bladder lumen, and are therefore easily distinguished from bladder cancer. Although bladder diverticula are in communication with the bladder lumen, stasis of urine within the diverticulum may lead to infection, stone formation, or the accumulation of debris (Fig. 12). This in turn can lead to chronic irritation, which is again a risk factor for the development of bladder cancer. Therefore, diverticula should be scrutinized, particularly in exams ordered for the workup of hematuria.

Diverticula are easily identified on ultrasound given the superior spatial resolution, with the ability to identify the communication of the diverticulum with the bladder lumen. Identification of a diverticulum on CT or MRI can be difficult if the neck of the diverticulum is narrow; as a result, the diverticulum can appear as a cystic mass adjacent to the bladder. Filling of the diverticulum with contrast on delayed excretory phase imaging can aid in identification.

The presence of vascularity within the diverticulum, best evaluated with color Doppler, can help distinguish cancer from debris. Well-formed stones within a diverticulum are typically more echogenic than a solid mass, will lack vascularity, and may shadow posteriorly. Twinkling artifact is often seen associated with layering debris and can be a helpful clue to the presence of debris. Twinkling artifact should not be mistaken for true vascularity however and spectral Doppler interrogation may be performed to distinguish between the two entities. Layering debris within a diverticulum may be hyperattenuating on CT; on MRI, the layered debris is best appreciated as hypointense layered material on T2-weighted images. The debris will not enhance on post-contrast CT or MRI.

Bladder stones

Bladder stones, or calculi, are often seen in the setting of bladder outlet obstruction, a neurogenic bladder, or in the presence of a foreign body. The resulting urinary stasis leads to the precipitation of stones. Stones within the bladder lumen can cause irritation and lead to cystitis; such irritation

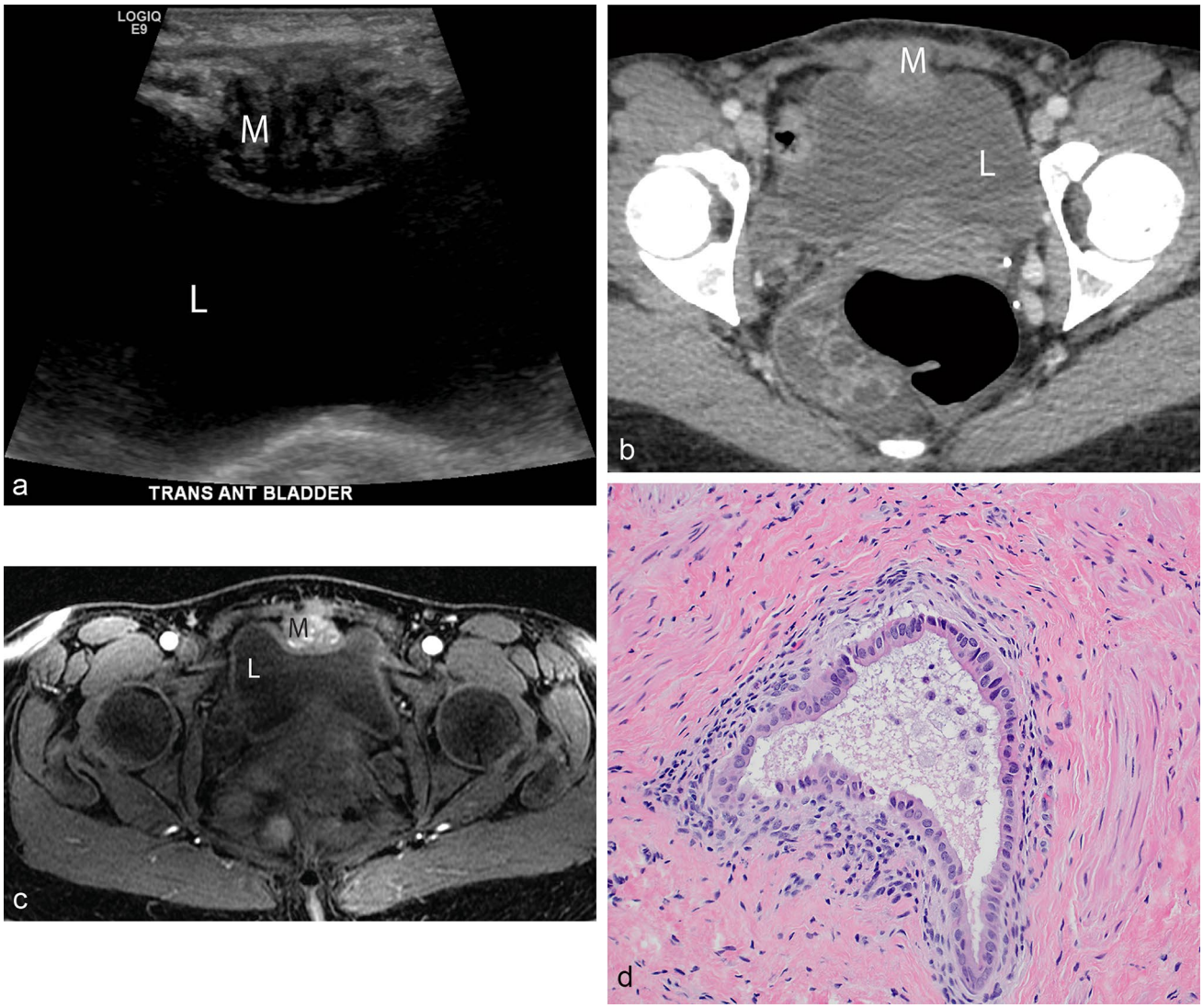

Fig. 16 46-year-old female with an endometriosis implant in the bladder wall. **a** Transverse grayscale ultrasound shows a rounded heterogeneously hypoechoic mass indenting the anterior bladder wall. **b** Axial contrast-enhanced CT and **c** axial contrast-enhanced T1W MR of the bladder similarly show a heterogeneous enhancing mass along the anterior bladder wall. **d** Histologic section shows endometriosis as evidenced by endometrial gland with a cuff of endometrial stroma within the detrusor muscle. Histocytes and acellular debris are seen in the lumen. H&E, original magnification ×200. *L* bladder lumen, *M* mass

and inflammation increase the risk of developing bladder cancer. Patients with bladder stones can be asymptomatic, or may present with pain, urinary tract infections, or hematuria.

Bladder stones are typically highly echogenic in appearance and have associated posterior acoustic shadowing (Fig. 13). On CT, the stones will be hyperattenuating and, on MR, will have very low signal on T1 or GRE sequences. On occasion, bladder stones may be mistaken for a calcified bladder cancer. As previously mentioned, calcifications are present in approximately 5% of bladder cancers [15]. To distinguish bladder stones from bladder cancer, ultrasound is an ideal imaging modality to show the mobility of stones and their migration to a dependent location between supine and lateral decubitus positions.

Thrombus

Thrombus, or blood clot, within the bladder presents with gross hematuria. Bladder thrombus has a myriad of causes. Most commonly patients have a history of anticoagulation use or may present with renal or bladder trauma, such as recent traumatic Foley catheter placement.

Thrombus within the bladder lumen can mimic bladder cancer (Fig. 14), particularly when polypoid in appearance. A chronic bladder thrombus can appear well-circumscribed

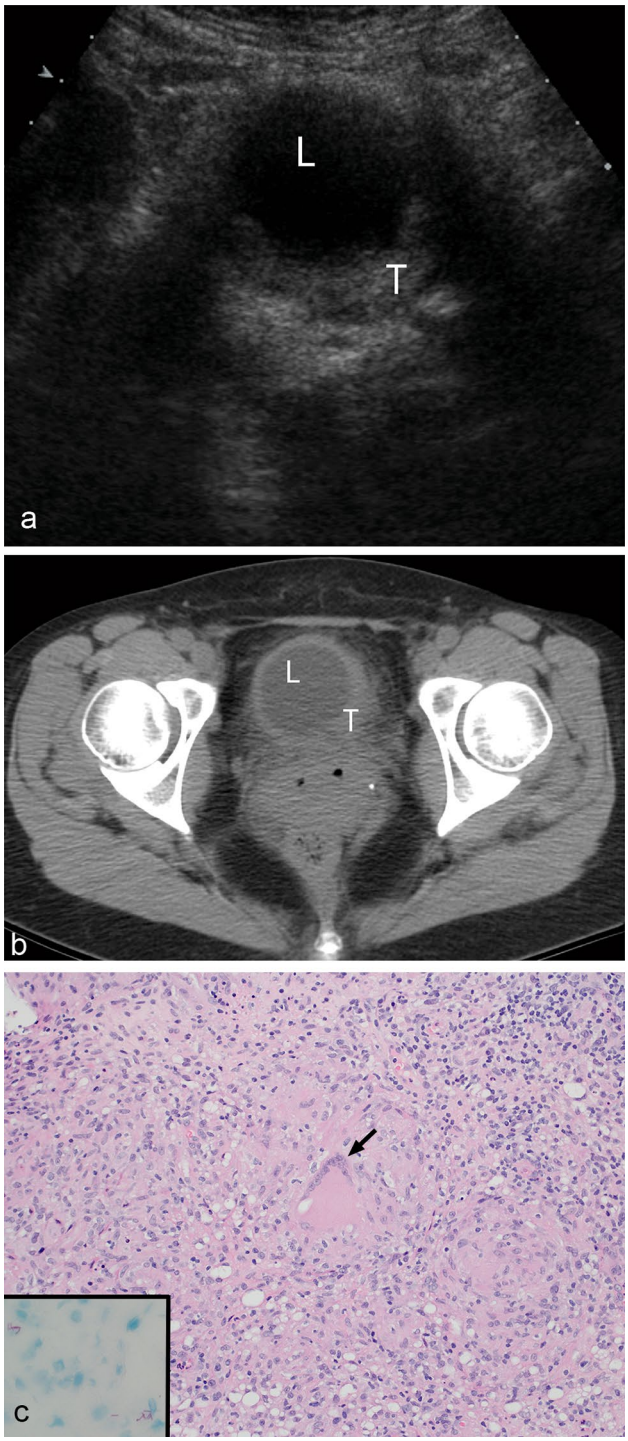

Fig. 17 48-year-old female with bladder tuberculosis. **a** Transverse grayscale ultrasound of the bladder shows asymmetric irregular thickening of the posterior bladder wall. **b** Axial non-contrast CT in the same patient shows irregular thickening of the left posterolateral bladder wall. **c** Pathologic specimen of the bladder confirms bladder tuberculosis, with florid granulomatous inflammation and a central multinucleated giant cell (arrow). Acid-fast stain in inset (bottom left) shows several AFB-positive organisms (red). Original magnification H&E ×200, AFB inset ×630. *L* bladder lumen, *T* thickening of the bladder wall

(Fig. 15). However, unlike bladder cancer, intraluminal thrombus is often mobile and will lack internal blood flow. The lesion will not enhance with contrast on CT or MR imaging. Unlike stones, the thrombus will not exhibit posterior acoustic shadowing.

Endometriosis

Endometriosis is defined as ectopic endometrial glands, located anywhere outside of the uterine cavity. Approximately 10% of reproductive age women have endometriosis, typically between the ages of 30 and 45 years [38]. The urinary tract is involved in 1% of women with endometriosis, and bladder involvement is the most frequent site of urinary tract endometriosis [39]. Women may present with suprapubic pain and a unique clinical presentation of hematuria occurring only during menstruation, also known as "catamenial hematuria."

On ultrasound, a bladder endometrioma can appear as a hypoechoic area of bladder wall thickening but more commonly appears as a hypoechoic spherical or comma-shaped mass [40]. The lesion can have an irregular border and appear similar to bladder cancer. The lesion is often outlined by the echogenic layers of the bladder wall (Fig. 16), whereas bladder cancer often lacks such a boundary. Depending on the time of the patient's menstrual cycle, the degree of vascularity and size of the lesion may fluctuate. On T1-weighted MRI imaging, hyperintense foci within the mass can help confirm chronic blood products, which may help to distinguish an endometrioma from other bladder tumors [41]. Bladder endometriomas are most commonly present along the posterior aspect of the bladder, extending directly from the uterus, but can occur anywhere along the bladder wall (Fig. 16).

On pathology, a bladder endometrioma is evidenced by the presence of endometrial glands. Involvement of the detrusor muscle may be seen.

Tuberculosis

Tuberculosis of the urogenital tract is the third most common form of extrapulmonary tuberculosis after nodal and pleural involvement [42]. Tuberculosis affects the urogenital tract in 2–20% of patients with pulmonary tuberculosis [42, 43], and has a 2:1 male predominance with a mean age of 40 years [44]. Risk factors for bladder tuberculosis are the same as for pulmonary tuberculosis, and includes individuals from developing nations, as well as immunocompromised patients, particularly those inflicted with HIV/AIDS.

Bladder tuberculosis most often causes an irregular asymmetric bladder wall (Fig. 17); in advanced cases, extreme fibrosis of the bladder walls results in marked contraction and small capacity of the bladder lumen, the so-called

"thimble bladder," which results in urinary frequency and urinary incontinence [45] (Fig. 17).

On pathology, tuberculosis of the bladder is denoted by granulomatous inflammation and multinucleated giant cells. Acid-fast stain reveals AFB-positive organisms of *Mycobacterium tuberculosis*.

Conclusion

The detection of bladder cancer can be challenging, since numerous entities can have a similar appearance to bladder cancer. However, correlation with patient history and an optimized ultrasound examination can improve detection and help distinguish bladder cancer from its mimics. In addition, in all ultrasound scans of the pelvis, which require a distended bladder as an acoustic window, care should be taken not to overlook pathology of the bladder itself.

Acknowledgements We would like to acknowledge Jeslyn A. Rumbold for her editorial assistance.

References

1. Tan WS, Sarpong R, Khetrapal P, Rodney S, Mostafid H, Cresswell J, Hicks J, Rane A, Henderson A, Watson D, Cherian J, Williams N, Brew-Graves C, Feber A, Kelly JD, Collaborators DIT (2018) Can Renal and Bladder Ultrasound Replace Computerized Tomography Urogram in Patients Investigated for Microscopic Hematuria? J Urol 200 (5):973-980. https://doi.org/10.1016/j.juro.2018.04.065
2. Horstmann M, Witthuhn R, Falk M, Stenzl A (2008) Gender-specific differences in bladder cancer: a retrospective analysis. Gend Med 5 (4):385-394. https://doi.org/10.1016/j.genm.2008.11.002
3. Shin K, Lim A, Odegaard JI, Honeycutt JD, Kawano S, Hsieh MH, Beachy PA (2014) Cellular origin of bladder neoplasia and tissue dynamics of its progression to invasive carcinoma. Nat Cell Biol 16 (5):469-478. https://doi.org/10.1038/ncb2956
4. Pashos CL, Botteman MF, Laskin BL, Redaelli A (2002) Bladder cancer: epidemiology, diagnosis, and management. Cancer Pract 10 (6):311-322
5. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA (2018) AJCC Cancer Staging Manual. 8th edition edn. Springer, Chicago
6. Pelucchi C, Bosetti C, Negri E, Malvezzi M, La Vecchia C (2006) Mechanisms of disease: The epidemiology of bladder cancer. Nat Clin Pract Urol 3 (6):327-340. https://doi.org/10.1038/ncpuro0510
7. Shinagare AB, Ramaiya NH, Jagannathan JP, Fennessy FM, Taplin ME, Van den Abbeele AD (2011) Metastatic pattern of bladder cancer: correlation with the characteristics of the primary tumor. AJR Am J Roentgenol 196 (1):117-122. https://doi.org/10.2214/ajr.10.5036
8. Malats N, Real FX (2015) Epidemiology of bladder cancer. Hematol Oncol Clin North Am 29 (2):177-189, vii. https://doi.org/10.1016/j.hoc.2014.10.001
9. Bladder cancer: diagnosis and management of bladder cancer: (c) NICE (2015) Bladder cancer: diagnosis and management of bladder cancer (2017). BJU Int 120 (6):755-765. https://doi.org/10.1111/bju.14045
10. Schulz MR, Loomis D (2000) Occupational bladder cancer mortality among racial and ethnic minorities in 21 states. Am J Ind Med 38 (1):90-98
11. Fortuny J, Kogevinas M, Zens MS, Schned A, Andrew AS, Heaney J, Kelsey KT, Karagas MR (2007) Analgesic and anti-inflammatory drug use and risk of bladder cancer: a population based case control study. BMC Urol 7:13. https://doi.org/10.1186/1471-2490-7-13
12. Lopez-Beltran A, Montironi R, Raspollini MR, Cheng L, Netto GJ (2018) Iatrogenic pathology of the urinary bladder. Semin Diagn Pathol 35 (4):218-227. https://doi.org/10.1053/j.semdp.2018.03.001
13. Kleinerman RA, Boice JD, Jr., Storm HH, Sparen P, Andersen A, Pukkala E, Lynch CF, Hankey BF, Flannery JT (1995) Second primary cancer after treatment for cervical cancer. An international cancer registries study. Cancer 76 (3):442-452
14. Travis LB, Curtis RE, Storm H, Hall P, Holowaty E, Van Leeuwen FE, Kohler BA, Pukkala E, Lynch CF, Andersson M, Bergfeldt K, Clarke EA, Wiklund T, Stoter G, Gospodarowicz M, Sturgeon J, Fraumeni JF, Jr., Boice JD, Jr. (1997) Risk of second malignant neoplasms among long-term survivors of testicular cancer. J Natl Cancer Inst 89 (19):1429-1439
15. Wong-You-Cheong JJ, Woodward PJ, Manning MA, Sesterhenn IA (2006) From the Archives of the AFIP: neoplasms of the urinary bladder: radiologic-pathologic correlation. Radiographics 26 (2):553-580. https://doi.org/10.1148/rg.262055172
16. Patel U (2010) Imaging and Urodynamics of the Lower Urinary Tract. 2nd edn. Springer, London
17. Datta SN, Allen GM, Evans R, Vaughton KC, Lucas MG (2002) Urinary tract ultrasonography in the evaluation of haematuria--a report of over 1,000 cases. Ann R Coll Surg Engl 84 (3):203-205
18. Parada Villavicencio C, Adam SZ, Nikolaidis P, Yaghmai V, Miller FH (2016) Imaging of the Urachus: Anomalies, Complications, and Mimics. Radiographics 36 (7):2049-2063. https://doi.org/10.1148/rg.2016160062
19. Gopalan A, Sharp DS, Fine SW, Tickoo SK, Herr HW, Reuter VE, Olgac S (2009) Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. Am J Surg Pathol 33 (5):659-668. https://doi.org/10.1097/pas.0b013e31819aa4ae
20. Quan J, Pan X, Jin L, He T, Hu J, Shi B, Peng J, Chen Z, Yang S, Mao X, Lai Y (2017) Urachal carcinoma: Report of two cases and review of the literature. Mol Clin Oncol 6 (1):101-104. https://doi.org/10.3892/mco.2016.1082
21. Szarvas T, Modos O, Niedworok C, Reis H, Szendroi A, Szasz MA, Nyirady P (2016) Clinical, prognostic, and therapeutic aspects of urachal carcinoma-A comprehensive review with meta-analysis of 1,010 cases. Urol Oncol 34 (9):388-398. https://doi.org/10.1016/j.urolonc.2016.04.012
22. Wong-You-Cheong JJ, Woodward PJ, Manning MA, Davis CJ (2006) From the archives of the AFIP: Inflammatory and non-neoplastic bladder masses: radiologic-pathologic correlation. Radiographics 26 (6):1847-1868. https://doi.org/10.1148/rg.266065126
23. Venyo AK (2014) Lymphoma of the urinary bladder. Adv Urol 2014:327917. https://doi.org/10.1155/2014/327917
24. Iwamoto G, Kawahara T, Tanabe M, Ninomiya S, Takamoto D, Mochizuki T, Kuroda S, Takeshima T, Izumi K, Hattori Y, Teranishi JI, Yumura Y, Miyoshi Y, Uemura H (2017) Paraganglioma in the bladder: a case report. J Med Case Rep 11 (1):306. https://doi.org/10.1186/s13256-017-1473-2
25. Leestma JE, Price EB, Jr. (1971) Paraganglioma of the urinary bladder. Cancer 28 (4):1063-1073

26. Li W, Yang B, Che JP, Yan Y, Liu M, Li QY, Zhang YY, Zheng JH (2013) Diagnosis and treatment of extra-adrenal pheochromocytoma of urinary bladder: case report and literature review. Int J Clin Exp Med 6 (9):832-839
27. Bosserman AJ, Dai D, Lu Y (2019) Imaging Characteristics of a Bladder Wall Paraganglioma. Clin Nucl Med 44 (1):66-67. https://doi.org/10.1097/rlu.0000000000002324
28. Sanguedolce F, Loizzi D, Sollitto F, Di Bisceglie M, Lucarelli G, Carrieri G, Bufo P, Cormio L (2017) Bladder Metastases from Lung Cancer: Clinical and Pathological Implications: A Systematic Review. Oncology 92 (3):125-134. https://doi.org/10.1159/000454731
29. Doo SW, Kim WB, Kim BK, Yang WJ, Yoon JH, Jin SY, Song YS (2013) Metastasis of renal cell carcinoma to the bladder. Korean J Urol 54 (1):69-72. https://doi.org/10.4111/kju.2013.54.1.69
30. Wagenlehner FM, Weidner W, Pilatz A, Naber KG (2014) Urinary tract infections and bacterial prostatitis in men. Curr Opin Infect Dis 27 (1):97-101. https://doi.org/10.1097/qco.0000000000000024
31. Matz EL, Hsieh MH (2017) Review of Advances in Uroprotective Agents for Cyclophosphamide- and Ifosfamide-induced Hemorrhagic Cystitis. Urology 100:16-19. https://doi.org/10.1016/j.urology.2016.07.030
32. Lamm DL, van der Meijden PM, Morales A, Brosman SA, Catalona WJ, Herr HW, Soloway MS, Steg A, Debruyne FM (1992) Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol 147 (3):596-600
33. Singh I, Ansari MS (2001) Cystitis cystica glandularis masquerading as a bladder tumor. Int Urol Nephrol 33 (4):635-636. https://doi.org/10.1023/a:1020511826666
34. Manco LG (1985) Cystitis cystica simulating bladder tumor at sonography. J Clin Ultrasound 13 (1):52-54
35. Chung AD, Schieda N, Flood TA, Cagiannos I, Kielar AZ, McInnes MD, Siegelman ES (2015) Suburothelial and extrinsic lesions of the urinary bladder: radiologic and pathologic features with emphasis on MR imaging. Abdom Imaging 40 (7):2573-2588. https://doi.org/10.1007/s00261-015-0467-z
36. Dmochowski RR (2005) Bladder outlet obstruction: etiology and evaluation. Rev Urol 7 Suppl 6:S3-S13
37. Asimakopoulos AD, De Nunzio C, Kocjancic E, Tubaro A, Rosier PF, Finazzi-Agro E (2016) Measurement of post-void residual urine. Neurourol Urodyn 35 (1):55-57. https://doi.org/10.1002/nau.22671
38. Kinkel K, Frei KA, Balleyguier C, Chapron C (2006) Diagnosis of endometriosis with imaging: a review. Eur Radiol 16 (2):285-298. https://doi.org/10.1007/s00330-005-2882-y
39. Leone Roberti Maggiore U, Ferrero S, Candiani M, Somigliana E, Vigano P, Vercellini P (2017) Reply to Rodolfo Montironi, Silvia Gasparrini, Antonio Lopez-Beltran, et al's Letter to the Editor re: Umberto Leone Roberti Maggiore, Simone Ferrero, Massimo Candiani, et al. Bladder Endometriosis: A Systematic Review of Pathogenesis, Diagnosis, Treatment, Impact on Fertility, and Risk of Malignant Transformation. Eur Urol 2017;71:790-807. Benign Mullerian Lesions in the Urinary Bladder: Endometriosis, Endocervicosis, Endosalpingiosis, and Mullerianosis. Eur Urol 72 (5):e142. https://doi.org/10.1016/j.eururo.2017.05.028
40. Maccagnano C, Pellucchi F, Rocchini L, Ghezzi M, Scattoni V, Montorsi F, Rigatti P, Colombo R (2012) Diagnosis and treatment of bladder endometriosis: state of the art. Urol Int 89 (3):249-258. https://doi.org/10.1159/000339519
41. Beaty SD, Silva AC, De Petris G (2006) Bladder Endometriosis: Ultrasound and MRI Findings. Radiol Case Rep 1 (3):92-95. https://doi.org/10.2484/rcr.v1i3.16
42. Figueiredo AA, Lucon AM, Srougi M (2017) Urogenital Tuberculosis. Microbiol Spectr 5 (1). https://doi.org/10.1128/microbiolspec.tnmi7-0015-2016
43. Abbara A, Davidson RN, Medscape (2011) Etiology and management of genitourinary tuberculosis. Nat Rev Urol 8 (12):678-688. https://doi.org/10.1038/nrurol.2011.172
44. Figueiredo AA, Lucon AM, Junior RF, Srougi M (2008) Epidemiology of urogenital tuberculosis worldwide. Int J Urol 15 (9):827-832. https://doi.org/10.1111/j.1442-2042.2008.02099.x
45. Aswathaman K, Devasia A (2008) Thimble bladder. ANZ J Surg 78 (11):1049. https://doi.org/10.1111/j.1445-2197.2008.04742.x