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REVIEW

Imaging features of immune-mediated genitourinary disease

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Abstract

Purpose Imaging features of immune-mediated genitourinary diseases often overlap, and the same disease may manifest in different ways, so understanding imaging findings in the context of the patient's entire clinical picture is important in providing the correct diagnosis.

Methods In this article, diseases mediated by the immune system which affect the genitourinary system are reviewed. Examples of immune-mediated genitourinary disease including IgG4-related disease, post-transplant lymphoproliferative disorder, immunodeficiency-associated lymphoproliferative disorder due to immunosuppressive and immunomodulatory medications, lymphoma, leukemia, myeloma, amyloidosis, and histiocytosis.

Results Clinical and imaging features will be presented which may help narrow the differential diagnosis for each disease.

Conclusion Recognition of immune-related genitourinary disease is important for appropriate medical management as they may mimic other diseases both by imaging and clinical presentation.

Keywords Genitourinary · Immune-mediated · PTLD · Lymphoma · IgG4 · Leukemia

Introduction

There are a wide variety of immune-mediated diseases that may be encountered on imaging. Imaging features of immune-mediated genitourinary diseases are typically non-specific with a single entity often manifesting in a variety of ways. Furthermore, the clinical presentation may also be non-specific and the initial work up may not guide the clinician to correctly diagnose an immune-related disease. While the majority of these diseases require tissue for definitive diagnosis, imaging is helpful in providing a differential diagnosis that may point the clinician to suspect an immune-mediated disease where they may not have suspected one initially. Nonetheless, interpreting imaging findings in conjunction with the patient's clinical picture is paramount in providing guidance towards reaching the correct diagnosis.

An immune-mediated disease is characterized by dysregulation, either hyper- or hypoactivity, of the immune system leading to deposition of materials in organ parenchyma that may be detected on imaging studies. For example, abnormal type-2 T-helper cells lead to deposition of collagen and fibrotic changes in the renal interstitium in IgG4 nephropathy, leading to imaging features.

In this article, diseases mediated by the immune system which can affect the genitourinary system are reviewed. Entities to be discussed include IgG4-related disease, post-transplant lymphoproliferative disorder (PTLD), immunodeficiency-associated lymphoproliferative disorder due to immunosuppressive and immunomodulatory medications, lymphoma, leukemia, myeloma, amyloidosis, and histiocytosis. While CT remains the workhorse for evaluating these diseases, additional imaging modalities may be helpful to both the radiologist and clinician. MRI may provide a problem-solving tool when a diagnosis remains uncertain, such as using diffusion-weighted imaging (DWI) for evaluation of suspected IgG4-related disease. The use of PET/CT has also been accepted as a staging tool for diseases such as lymphoma and PTLD. A variety of clinical and imaging findings are presented which may help the radiologist narrow the differential diagnosis for these complex diseases.

IgG4-related disease

IgG4-related disease (IgG4-RD) is an entity pathologically characterized by an inflammatory reaction resulting

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in fibrosis and lymphoplasmacytic mass-like collections dense in IgG4-positive cells [1]. IgG4-RD most commonly presents as autoimmune pancreatitis. However, other manifestations in the abdomen include retroperitoneal fibrosis, IgG4-RD sclerosing cholangitis and renal disease. Renal involvement by IgG4-RD usually presents with histologic findings of tubulointerstitial nephritis (TIN) [2]. While the pathophysiology of renal involvement is incompletely understood, it is known that abnormal type-2 T-helper cells are responsible for profibrotic cytokine production, leading to collagen deposition and fibrosis in the renal interstitium [3]. Histologically, there is a spectrum of changes that may take the form of marked inflammation with tubular atrophy or dense fibrosis with tubular damage, leading to the different imaging manifestations [4]. The diagnosis of IgG4-TIN requires specific histological features and one of the following criteria: characteristic radiological findings, elevated serum IgG4 levels, or characteristic findings of IgG4-RD in other organs [2].

Renal involvement by IgG4-RD is usually encountered in middle-aged to elderly patients, with a slight male predominance [5]. Renal function may range from normal to severely impaired [6]. Elevated serum values of IgG4 are helpful, but this finding is neither specific nor sensitive [7]. While definitive diagnosis of IgG4-RD requires tissue sampling, there are radiological signs which may help narrow the differential diagnosis.

In the setting of IgG4-TIN, contrast-enhanced CT evaluation of the kidneys may show hypoenhancing areas which can have one of four different patterns: small peripheral cortical nodules, round lesions, wedge-shaped lesions, or diffuse patchy involvement [8]. Areas of IgG4-TIN involvement are isointense on T1-weighted and hyperintense on T2-weighted MRI sequences. Diffusion-weighted imaging is a powerful tool to detect IgG4-RD lesions with a reported sensitivity of 100% [9]. Subsequent imaging after appropriate steroid therapy can show resolution of the imaging findings (Fig. 1). Additionally, IgG4-RD can affect the renal pelvis leading to pyelitis. There may also be secondary hydronephrosis from IgG related retroperitoneal fibrosis. Renal lesions are difficult, if not impossible, to differentiate from lymphomatous lesions. Thus, it is important for the radiologist to investigate other sites of disease involvement as IgG4 may have more characteristic involvement of the pancreas and biliary tree (Fig. 2).

IgG4-RD has also been reported to involve additional sites of the genitourinary tract, although much less frequently than renal involvement. Involvement of the ovaries has been reported as a large multinodular ovarian mass with iliac lymph node enlargement, mimicking ovarian cancer [10]. Uterine enlargement with heterogeneous enhancement on CECT and with diffuse radiotracer avidity on F18-FDG PET is another reported manifestation of IgG-RD [11].

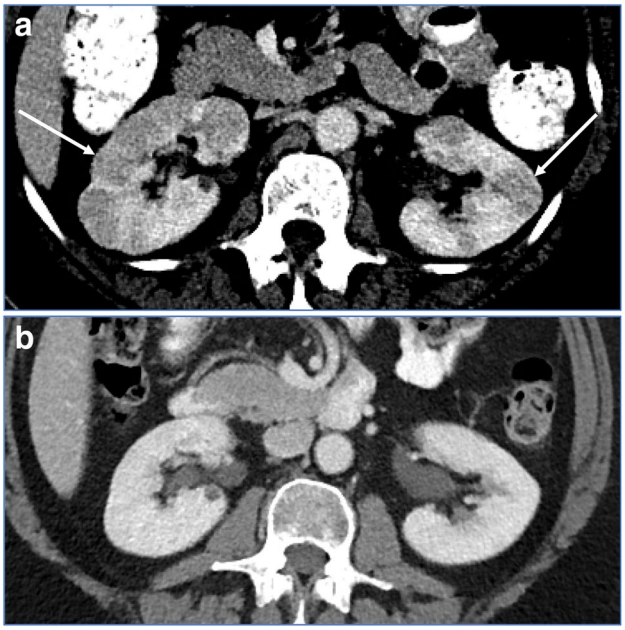

Fig. 1 IgG4 related disease affecting the kidneys in a 50-year-old woman. **a** Post-contrast axial CT demonstrates lobulated kidneys with innumerable hypoenhancing nodules throughout the cortex (arrow). **b** Three-month follow-up contrast-enhanced CT demonstrated resolution of the renal nodules after treatment with steroids

In male patients, IgG4-RD can involve the prostate, seminal vesicles, and scrotum [12–16]. In the prostate, IgG4-RD presents with lower urinary tract symptoms [13], and PET scan demonstrates avid uptake of radiotracer in the prostate gland [12, 16].

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) is a spectrum of lymphoid disease which presents after hematopoietic stem cell transplantation (HSCT) or solid organ transplant (SOT). The highest risk of SOT-PTLD is seen in heart, lung, intestinal, and multi-organ transplant recipients, with reported prevalence as high as 25% [17, 18]. Mortality rates are high in both SOT-PTLD and HSCT-PTLD, ranging from 50–70% and 70–90%, respectively [19, 20]. The majority of cases (55–65%) of PTLD are attributed to Epstein–Barr Virus-induced activation of B-lymphocytes due to use of immunosuppressive agents after transplant. In the setting of augmented T-cell function, these abnormal lymphoid collections, generally of B-cells, accumulate and/or infiltrate into affected organs [21]. Pediatric patients have a higher incidence of PTLD compared to the adult population, as they are more likely to be EBV seronegative and have longer expected lifespans [22, 23]. The transplant grafts with the lowest incidence of PTLD are renal transplants

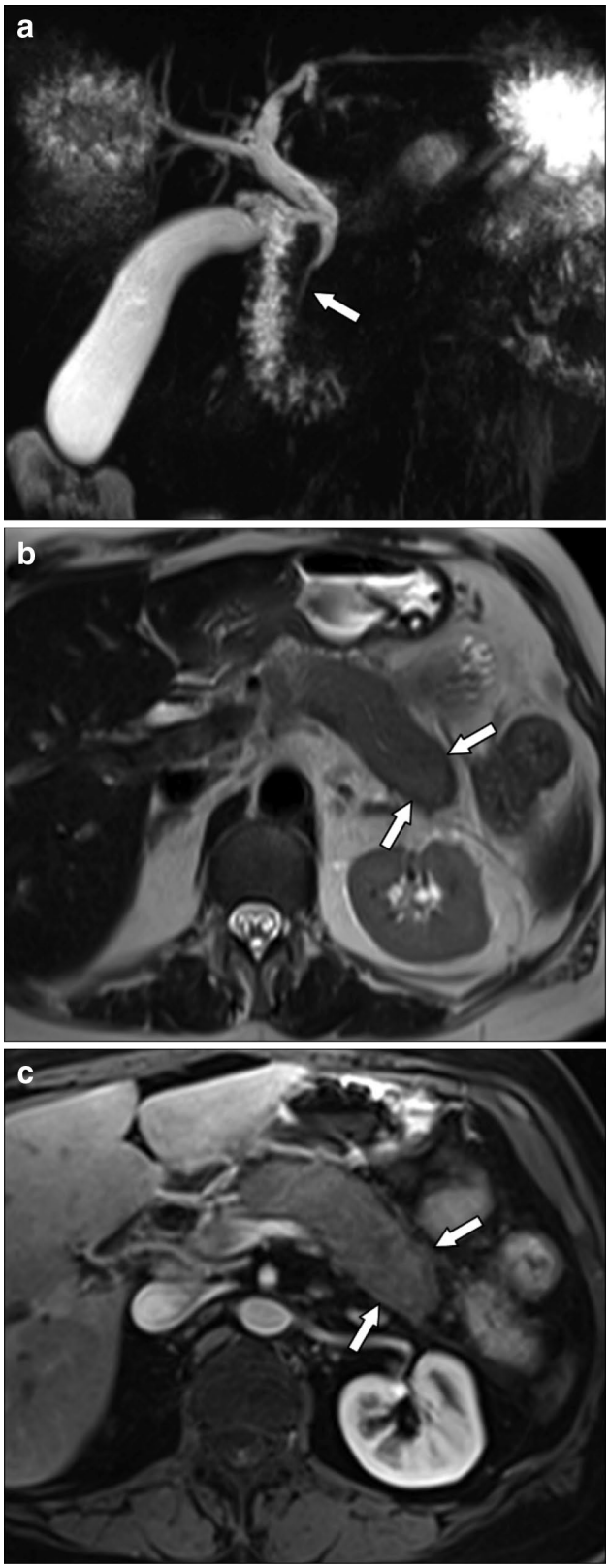

Fig. 2 IgG4 related sclerosing cholangitis and autoimmune pancreatitis in a 55-year-old woman. **a** Smooth 3 cm stricture of the common bile duct is seen on MRCP (arrow). **b** and **c** The pancreas is swollen and "sausage shaped," has a T2 hypointense (**b**, arrows) and hypoenhancing rim (**c**, arrows), and the pancreatic duct is barely visible with decreased caliber

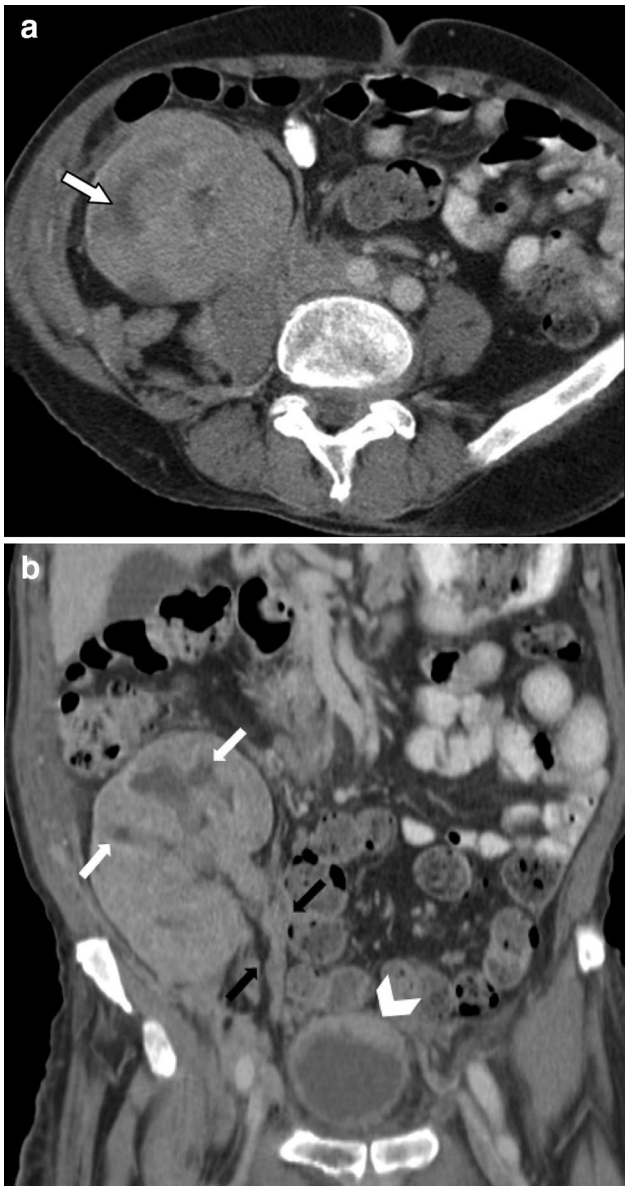

Fig. 3 PTLD affecting a right lower quadrant renal transplant graft in a 65-year-old man 5 years post-transplant. **a**, **b** Axial and coronal CECT demonstrate enlargement of the right lower quadrant transplant graft with areas of collecting system dilatation (white arrows). There is confluent retroperitoneal soft tissue adjacent to the transplant. Additionally, there is ureteral thickening (black arrows) and soft tissue thickening of the superior aspect of the bladder (white arrowhead)

(~ 1%), with the highest risk (up to 33%) encountered with multivisceral transplants [20].

Pathologically, the WHO recognizes four types of PTLD: benign or polyclonal early lesions, polymorphic, monomorphic, and classic Hodgkin lymphoma-like PTLD. Clinically, PTLD may have a variable presentation with non-specific findings such as fever, weight loss, graft dysfunction, and

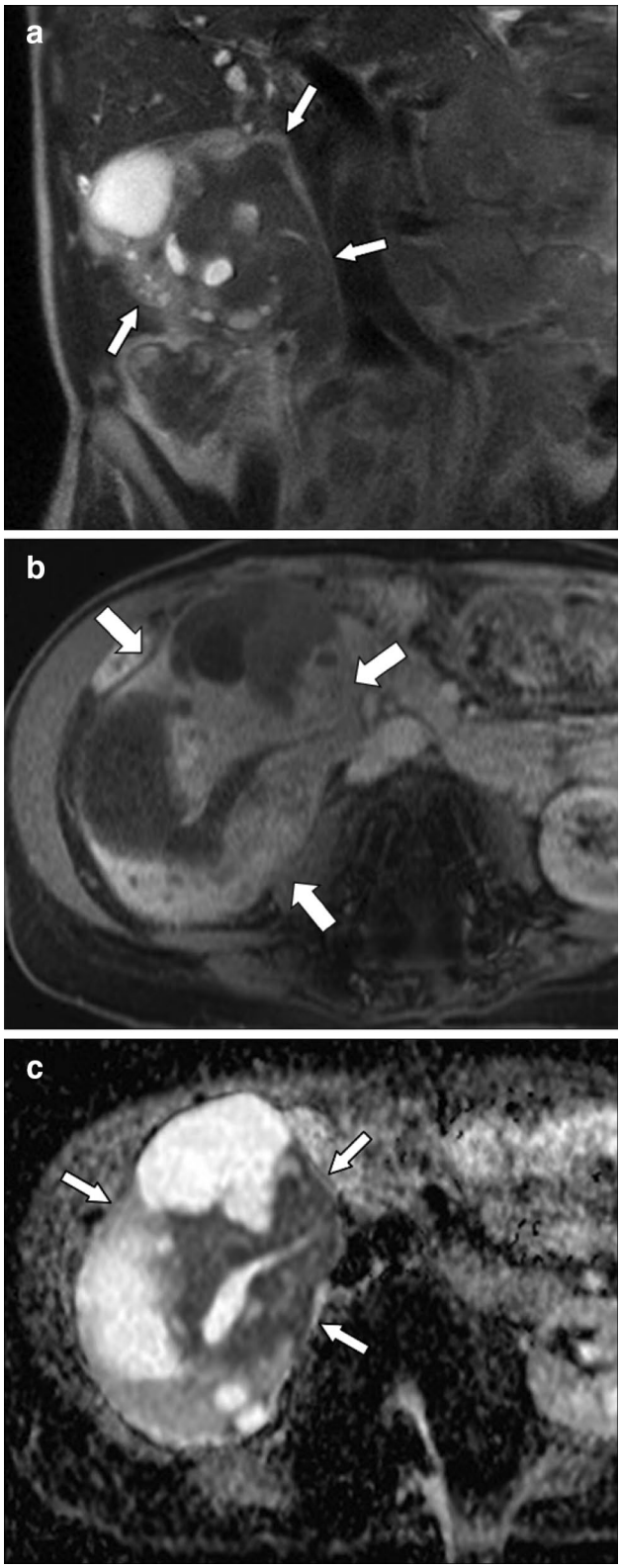

Fig. 4 Other iatrogenic immunodeficiency lymphoproliferative disorder in the right kidney of a 57-year-old woman related to infliximab treatment of rheumatoid arthritis. The right kidney is diffusely enlarged. **a** Coronal HASTE and **b** axial T1 FS contrast-enhanced MRI demonstrate an infiltrative, T2 hypointense, enhancing soft tissue lesion in the right renal collecting system (arrows). **c** Hypointense signal on ADC map demonstrates restricted diffusion within this lesion (arrows)

anemia; it may also present with signs localizing the mass such as lymph node enlargement, and symptoms specific to organ systems such as the gastrointestinal tract, liver, kidney, or brain [24]. The median time to disease onset in HSCT-PTLD is 4-6 months after transplantation [19]. Time to onset for SOT-PTLD is bimodal, with a high incidence immediately after transplantation, a decrease in incidence around 2 years after transplant, then a subsequent rise approximately 4–5 years after transplant. "Early-onset" PTLD from solid organ transplant is less than 2 years, and "late-onset" is greater than 2 years after transplant [25]. Reduction of immunosuppression is the mainstay of treatment, while other options such as immunotherapy, surgery, or radiation may also be considered [26].

Imaging features of PTLD include space-occupying lesions at extranodal sites such as the lungs, bone marrow, CNS, gastrointestinal tract, or bulky lymph node enlargement [27]. The most common body cavity affected is the abdomen [28].

PTLD can affect both transplanted and native kidneys and may manifest as focal renal masses or diffuse infiltration (Fig. 3). CT features in renal involvement are non-specific and may include a non-enhancing or peripherally enhancing hypoattenuating mass or masses due to necrosis which may contain calcifications, a potential differentiator from lymphoma [29]. On MRI, areas of renal involvement are hypointense on both T1- and T2-weighted sequences and demonstrate hypoenhancement after administration of contrast [30].

FDG-PET/CT has become a valuable tool in both staging and monitoring treatment response of PTLD. When undergoing FDG-PET/CT evaluation, upstaging occurs more often than downstaging [31]. The degree of FDG activity in lesions directly correlates with the tumor grade [31]. A consensus document from the International Conference on Malignant Lymphomas Imaging Working Group defines indications for PET in staging of FDG-avid lymphomas for patient follow-up and evaluation for remission [32]. Initial data of PET/CT in confirming PTLD remission are promising, however must be taken with caution as little prospective data exist [31]. More PTLD lesions are seen with FDG-PET/CT than diagnostic CT alone, although using both can help with initial staging and guiding biopsy [33]. Therefore, is reasonable to use a diagnostic CT for initial diagnosis and anatomical evaluation, then subsequently follow disease with PET/CT.

In addition to PTLD involving the native and transplant kidneys, PTLD can occur throughout the genitourinary

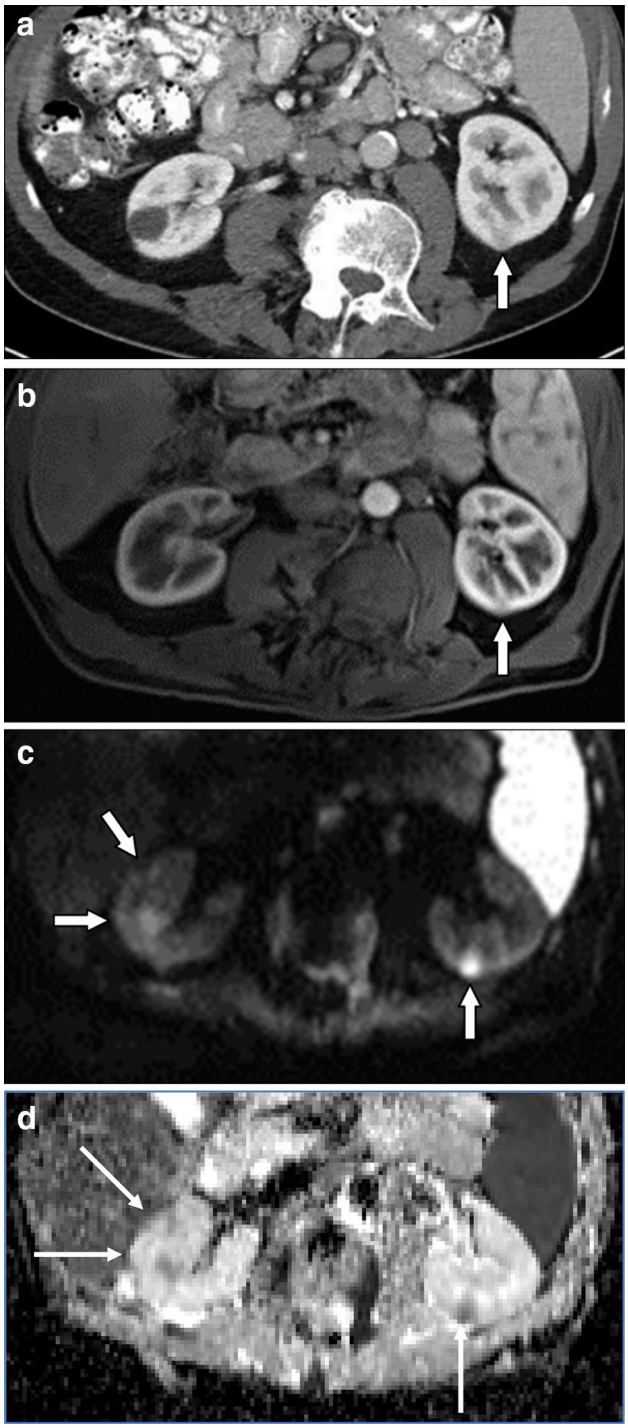

Fig. 5 Lymphomatous involvement of the kidney in a 68-year-old man, best seen on DWI. **a** CECT demonstrates a 1.2 cm lesion in the posterior aspect of the left kidney suspicious for solid mass (arrow). MRI redemonstrates this solid lesion in the posterior left kidney on axial contrast-enhanced T1 FS (**b**, arrow). Numerous additional small renal parenchymal lymphomatous lesions are better seen on DWI than on conventional sequences (arrows), hyperintense on B800 (**c**), hypointense on ADC (**d**)

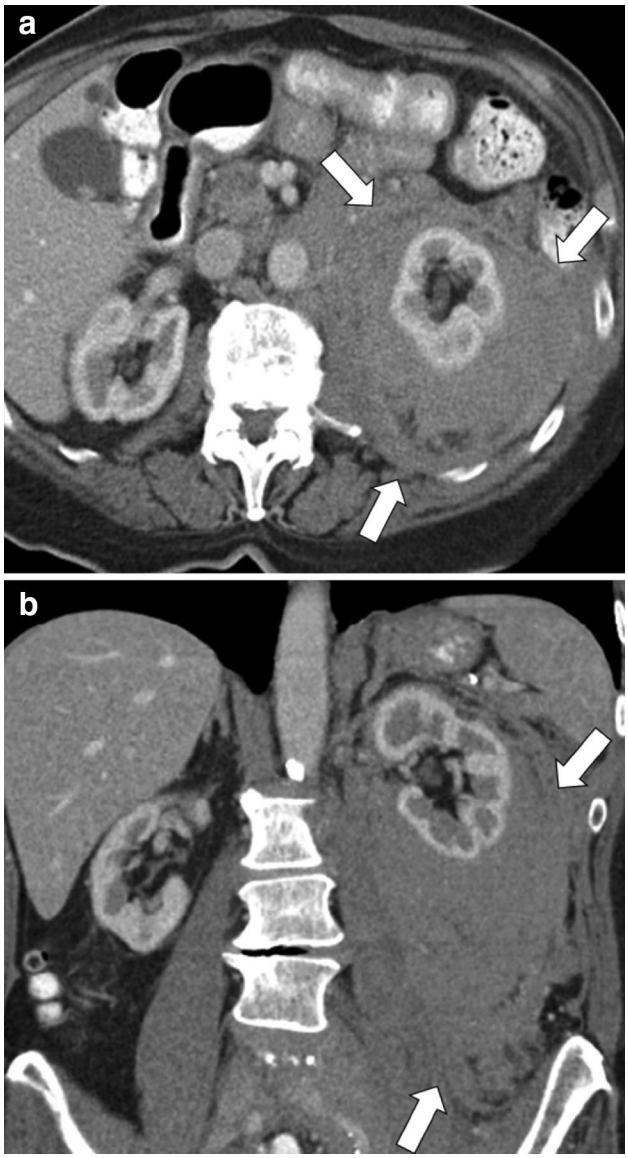

Fig. 6 Perirenal lymphoma surrounding the left kidney. **a** Axial CECT demonstrates ill-defined confluent perineprhric soft tissue encasing the left kidney (arrows). **b** The coronal CECT image demonstrates extension of this soft tissue into the pelvis, tracking along the course of the ureter. This patient had intact renal function and no hydronephrosis

tract. Donor-derived PTLD involving the donor ureter has also been encountered in kidney transplant recipients [34]. PTLD has also been reported to involve the ovary as the primary site with subsequent metastatic disease to the liver in a patient with living renal transplantation [35].

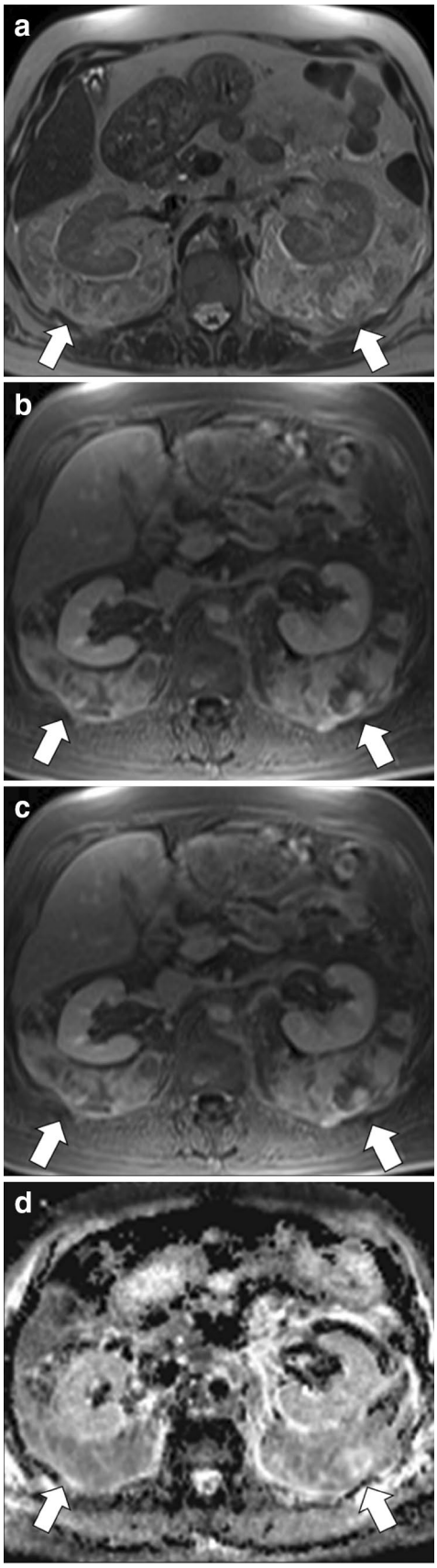

Fig. 7 Perirenal lymphoma involving the bilateral kidneys. (**a**) Axial ▶ T2 HASTE sequence demonstrates ill-defined retroperitoneal soft tissue bilaterally (arrows). (**b**) Contrast-enhanced axial T1 FS VIBE sequence demonstrates heterogenous enhancement. The perirenal lymphoma demonstrates restricted diffusion, hyperintense on B1000 image (**c**) and hypointense on the ADC map (arrows) (**d**)

Other iatrogenic immunodeficiency lymphoproliferative disorders (non-transplant associated)

Other iatrogenic immunodeficiency lymphoproliferative disorders (OIIA-LPDs) comprise a group of lymphoid neoplasms that occur in the setting of the use of immunosuppressant agents in non-transplant settings. There is a strong association of iatrogenic immunodeficiency LPDs with Epstein Barr virus [36]. Medications implicated in iatrogenic immunodeficiency LPDs include but are not limited to methotrexate, azathioprine, cyclosporine, fludarabine, infliximab, and combinations of therapies [37]. Iatrogenic immunodeficiency LPDs exhibit a wide range of morphology including atypical polymorphous LPDs, diffuse aggressive non-Hodgkin's lymphomas, Hodgkin's disease, and lymphoproliferations resembling Hodgkin's disease. In some cases, other iatrogenic immunodeficiency LPDs may regress with discontinuation of therapy but may subsequently recur [38].

OIIA-LPDs can present as a wide range of lesions. Literature regarding the radiologic presentation is limited and predominantly consists of case reports. For example, a case of primary adrenal lymphoma in a 70-year-old man related to EBV reactivation due to methotrexate therapy showed hypointensity on T1-weighted images, hyperintensity on T2-weighted images and hypoenhancement on contrast-enhanced MRI sequences [39]. A case of other iatrogenic immunodeficiency-associated LPD (OIIA-LPD) involvement of the kidney in a 57-year-old woman related to infliximab treatment for rheumatoid arthritis demonstrated enlargement of the kidney by an infiltrative mass (Fig. 4). Initial differential diagnosis included lymphoproliferative disorders such as lymphoma and infiltrative carcinoma. Tissue sampling was required to make the diagnosis as no specific imaging findings were identified. This is a relatively uncommon diagnosis without unique imaging findings, so it is important for the radiologist to be aware of this entity given the increased use of immune-modulating biologic drugs.

Lymphoma

Lymphoma represents a wide spectrum of neoplasms resulting in uncontrolled division and spread of lymphoid cells, broadly divided into Hodgkin's and non-Hodgkin's subtypes

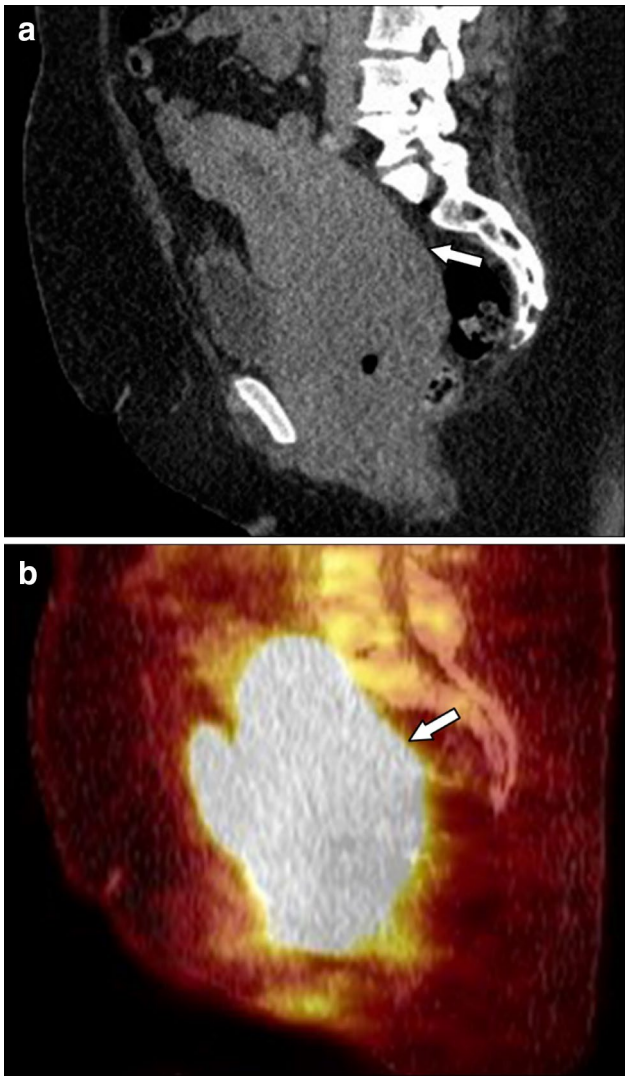

Fig. 8 A 52-year-old patient with diffuse large B-cell lymphoma of the uterus, cervix, and vagina on contrast-enhanced CT (**a**, arrow) and increased uptake on PET/CT scan (**b**, arrow)

depending on the presence or absence of mature B-cells called Reed-Sternberg cells, respectively. We focus on the manifestations of Non-Hodgkin's lymphoma (NHL). NHL is one of the most common cancers in the US, comprising about 4% of all cancers. NHL affects the entire spectrum of age, being one of the more common cancers in children and young adults, while those above the age of 65 comprise more than half of the NHL patients [40]. The renal parenchyma features relatively scant innate lymphoid tissue, and thus the kidney is an infrequent primary site of lymphoma, comprising less than 1% of extranodal disease [41]. However, the kidney is the second most commonly involved secondary site of extranodal lymphomatous involvement, after the spleen [42]. Although lymphomatous involvement of the kidneys is seen in 30-60% of patients at autopsy, there is only radiologic evidence of involvement in 1-8% of lymphoma patients due to the microscopic nature of lymphomatous invasion [43].

Lymphomatous involvement of the kidneys may manifest in multiple forms with imaging. The most common manifestation is multiple parenchymal masses (Fig. 5). Less common appearances include a solitary renal mass followed by multiple perinephric masses [44]. Non-Hodgkin's Lymphoma should be strongly considered in the differential for a perinephric mass (Figs. 6-7). Renal collecting system involvement is uncommon. There are additional findings to help narrow the differential between lymphoma and primary renal cell carcinoma (RCC). On contrast-enhanced CT and MRI, renal lymphoma is typically a hypoenhancing mass relative to the surrounding renal parenchyma, which is a crucial differentiating factor from clear cell renal carcinoma which is hyperenhancing. It is important to note, however, that certain subtypes of primary RCC, notably papillary and chromophobe, do not exhibit the hyperenhancement of the more common clear cell RCC, and thus biopsy is usually required to distinguish these diagnoses from lymphoma. The presence of extensive retroperitoneal lymphadenopathy surrounding vasculature should lead one to suspect lymphoma. The presence of venous invasion is unusual for lymphoma, and should thus lead one to suspect RCC [44]. On MRI, lymphoma is typically hypointense on T1-weighted images and hyperintense on T2-weighted images and demonstrates restricted diffusion on DWI sequences [42]. Lymphoma has been shown to restrict diffusion to a greater degree compared to RCC [45].

Lymphoma may involve any part of the genitourinary tract (primary or secondary involvement). Typical imaging features are similar to those in the kidney, including hypoattenuating tissue on non-enhanced CT similar to muscle, hypointense T1 and hyperintense T2 signal, and PET-avidity [46–48]. Examples of genitourinary involvement in lymphoma in the uterus and testes are shown in Figs. 8 and 9. Lymphoma involvement of the adrenal gland also demonstrates similar imaging patterns: hypoattenuating soft tissue on CT, hypointense T1 and hyperintense T2 signal on MRI (Fig. 10). These lesions are often bilateral and infiltrate adjacent structures [49].

Leukemia

Leukemia is a hematologic malignancy characterized by unregulated proliferation of myeloid or lymphoid precursor cells which can affect any age group. Acute lymphocytic leukemia is the most common malignancy in the pediatric population [50]. The clinical manifestations of renal involvement are broad and include acute kidney injury, chronic kidney disease, renal vascular disease, and electrolyte and acid-base abnormalities [51]. Acute kidney injury is common in

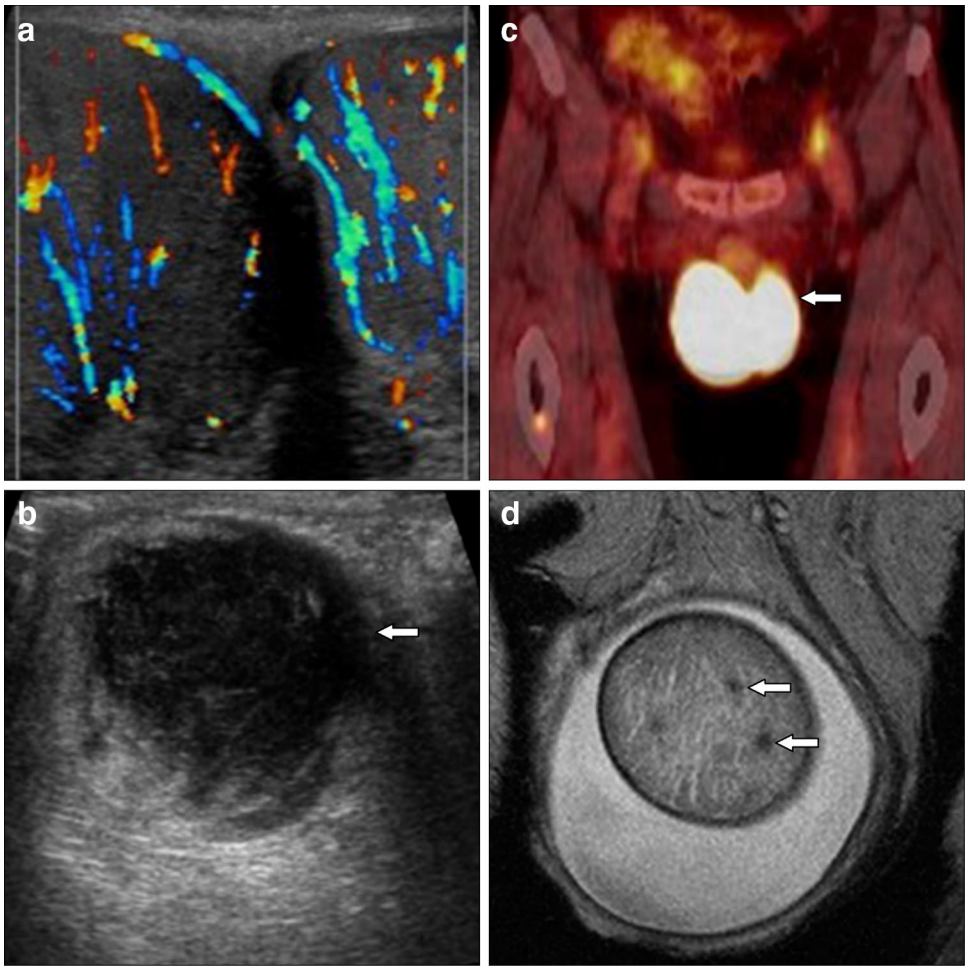

Fig. 9 Diffuse large B-cell lymphoma of the testes in a 61-year-old man. Ultrasound shows enlarged hypervascular heterogenous testes on color doppler (**a**) and gray scale (**b**, arrow). Staging FDG-PET (**c**) demonstrates marked diffuse uptake in the scrotum (arrow). Testicular lymphoma in another patient (**d**) shows multiple small T2 hypointense lesions on MRI (arrows)

patients with leukemia; a study evaluating intensive care unit admissions showed 43% of patients with hematologic malignancy presented with acute kidney injury [52].

On autopsy series, up to 90% of patients with leukemia demonstrate renal involvement. However, it has been reported that only approximately 5% of those with renal involvement manifest findings on imaging [43, 53]. Leukemic involvement is typically bilateral and most commonly manifests as diffuse renal enlargement; less commonly, bilateral renal masses or unilateral renal enlargement may occur (Fig. 11) [43, 54].

Ureteric involvement may also be seen in patients with leukemia and may result in ureteric obstruction [55]. Leukemia has been reported to involve the male reproductive tract including the prostate and testes [56, 57]. Leukemic involvement of the female reproductive system, including involvement of the uterus, cervix, and ovaries, has been reported [58, 59]. Imaging findings of leukemic involvement at these sites is often non-specific, and clinical history is necessary to lead to a correct diagnosis.

Acute myeloid leukemia can be associated with a 3–5% incidence of granulocytic sarcoma, a neoplasm composed of immature and mature granulocytes that involves an extramedullary anatomic site [60] . The testicle is a rare site for involvement and is associated with a poor prognosis (Fig. 12) [61]. As older men typically lie outside the age range for primary testicular malignancy, one should consider leukemia or lymphoma for testicular masses in this age group.

Multiple myeloma

Multiple myeloma (MM) is a malignant proliferation of a single clone of plasma cells which produces a monoclonal set of immunoglobulins. Diagnosis of multiple myeloma is confirmed with end-organ damage attributed to the clonal process, colloquially known as "CRAB" features: hypercalcemia, renal failure, anemia, and bone lesions. The International Myeloma Working Group's diagnostic criteria allow CT, PET/CT, and MRI to diagnose bone lesions. Additionally, hematologic biomarkers were included in the diagnostic criteria to facilitate earlier diagnosis [62].

Extra-osseous disease is common and has been reported in up to one-third of patients [63]. The kidneys are the

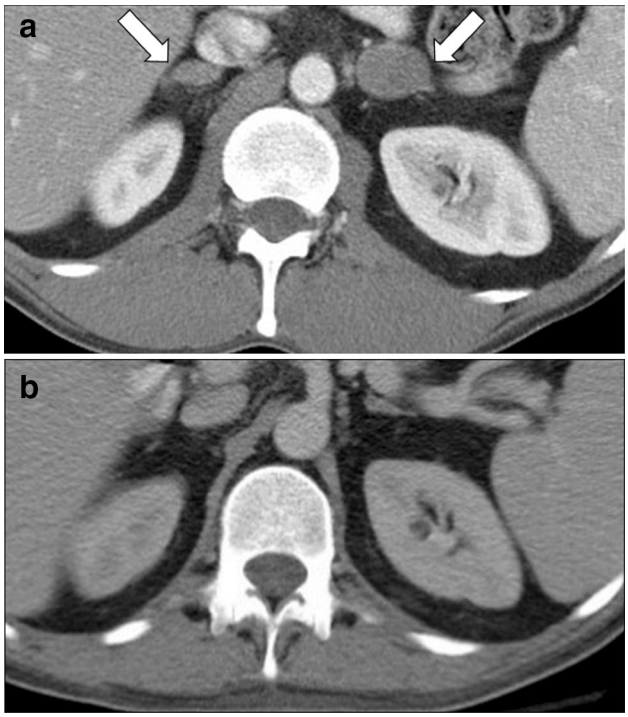

Fig. 10 Lymphomatous involvement of the adrenal glands in a 40-year-old man. **a** CECT demonstrate bilateral hypoattenuating adrenal lesions (arrows). **b** After initiation of chemotherapy, lymphomatous foci in the adrenal glands have resolved

second most common site of extra-osseous involvement after the spleen [64]. Autopsy series demonstrate renal involvement in approximately one-third of patients, although renal involvement is less commonly seen on imaging [63, 65, 66]. Renal involvement can present radiologically as either discrete masses or diffuse infiltration. Renal masses from multiple myeloma are indistinguishable from other malignant renal masses based on imaging alone, and tissue diagnosis is often needed to differentiate the lesions [67, 68]. Perinephric MM lesions cannot be distinguished from lymphoma radiologically, and consideration should usually be given to the latter given its more frequent occurrence. The presence of the other constellation of findings in MM, such as hypercalcemia, renal failure, anemia, and bone lesions, could point the radiologist to raise this diagnosis. Also, perirenal multiple myeloma can have a more aggressive appearance with venous invasion and/or urinary tract obstruction (Fig. 13).

Plasmacytomas are masses composed of extramedullary malignant proliferation of plasma cells which may be solitary or multiple lesions (as in multiple myeloma) [69]. As with multiple myeloma, the imaging characteristics of solitary plasmacytomas are non-specific and may mimic other malignancies, such as RCC and lymphoma [70]. Plasmacytomas are intensely PET-avid [69]. Biopsy is usually indicated for differentiation between plasmacytoma versus other primary renal neoplasms.

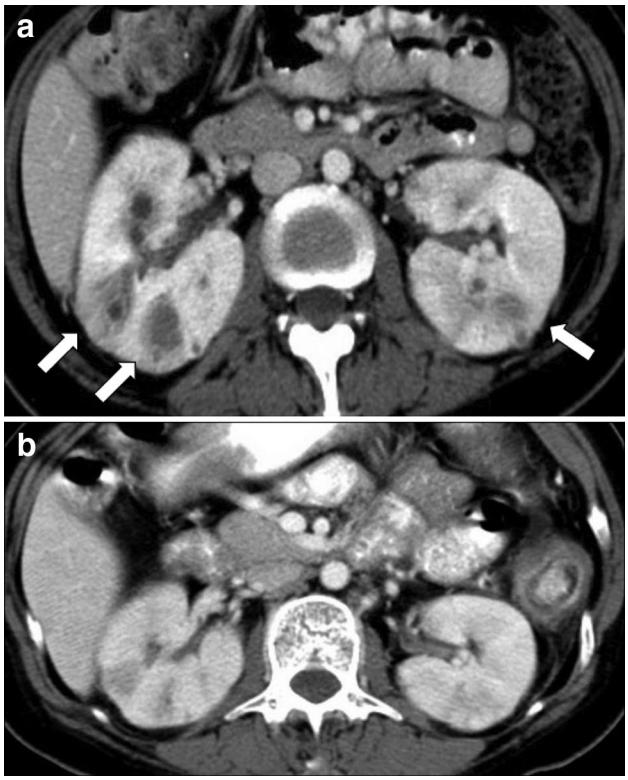

Fig. 11 Acute leukemic involvement of the kidneys before (**a**) and after (**b**) treatment. Case courtesy of Kate Maturen, MD, University of Michigan

Amyloidosis

Amyloidosis is characterized by deposition of extracellular beta-sheet fibrils in organs or tissues. It is usually classified as either primary amyloidosis (amyloid immunoglobulin light-chain [AL amyloidosis] disease) or secondary to a co-existent inflammatory disease (amyloid-associated [AA amyloidosis] disease) [42]. Other types of amyloidosis include organ-specific, heritable, dialysis-related, and senile forms [42]. Localized amyloidosis affecting only a single organ system is rare [71]. Amyloid deposits demonstrate a characteristic "apple green" coloration when examined under polarized light with Congo red staining. When localized amyloidosis is diagnosed, patients frequently undergo testing for systemic disease, such as multiple myeloma or Waldenström macroglobulinemia [71].

The most common imaging feature of renal amyloidosis is bilateral renal atrophy, seen in up to 50% of patients. Bilateral diffuse enlargement is less common [42]. Corticomedullary differentiation is maintained. Hydronephrosis is typically absent. Retroperitoneal or perinephric masses can extend into the kidneys which can calcify over time [42, 72]. Renal vein thrombosis may occur as a complication of amyloidosis [42].

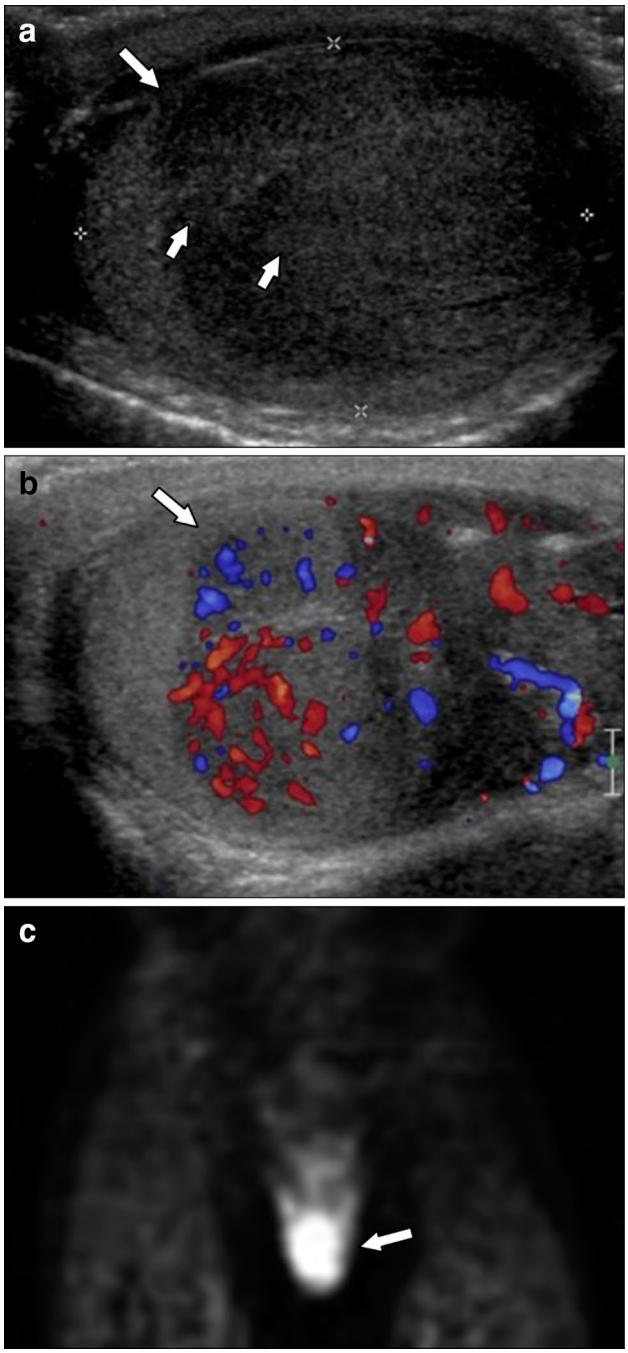

Fig. 12 Acute myelogenous leukemia with testicular involvement in a 31-year-old man. Gray scale (**a**) and color Doppler (**b**) US images show a hypoechoic, hypervascular mass in the right testis with extratesticular extension (arrows). Coronal FDG-PET image (**c**) shows focal hypermetabolic uptake in the testis (arrow). Orchiectomy with subsequent pathology revealed granulocytic sarcoma

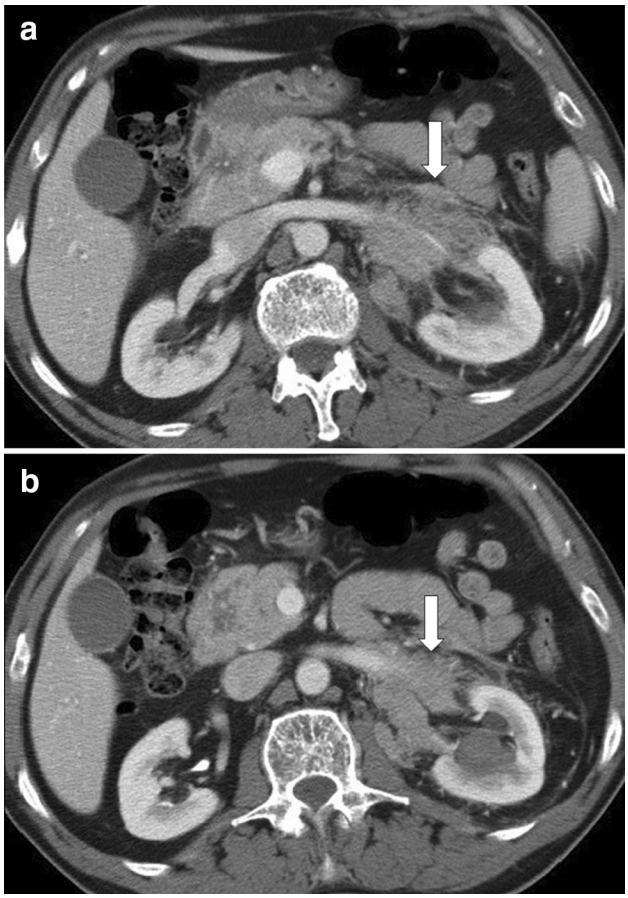

Fig. 13 53-year-old man with multiple myeloma and a perirenal plasmacytoma (arrows). **a** CECT demonstrates a hyperattenuating perirenal mass with invasion into the left renal vein. **b** There is mild left hydronephrosis. Contrast this image to previously provided cases of lymphoma. This has a more aggressive appearance given invasion into the vein and urinary tract obstruction

Amyloidosis in the ureter is rare but may present as a long segment of thickened ureteral wall with mild enhancement, without severe hydronephrosis [73]. Imaging findings of bladder involvement include asymmetric wall thickening mimicking the appearance of a primary bladder neoplasm [74], and calcification can occur in areas of primary or secondary amyloidosis (Fig. 14) [75]. Therefore, a high level of suspicion and tissue sampling is required to differentiate amyloid from bladder neoplasm.

The localized form of amyloidosis in the seminal vesicles is relatively common in elderly men. Amyloidosis in the seminal vesicles may mimic tumor invasion by prostate cancer [76]. Amyloidosis in the seminal vesicles also shows increased uptake on Ga-prostate-specific membrane antigen (PSMA) PET/CT [77], similar to extension of prostate cancer and is a false positive for this examination. However, prostatic amyloidosis does not demonstrate the restricted diffusion or enhancement pattern typical of prostate cancer [71,

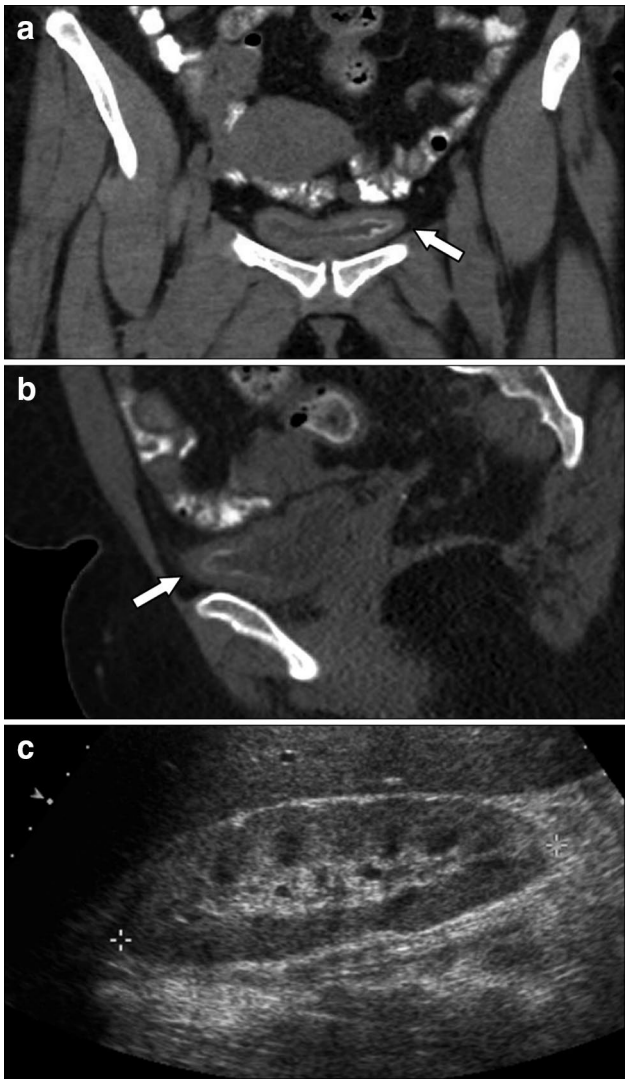

Fig. 14 51-year-old woman with amyloidosis of the bladder. Coronal (**a**) and sagittal (**b**) non-contrast CT images demonstrates asymmetric bladder wall thickening and calcification (arrows). Case courtesy of Victoria Chernyak, MD, Montefiore Medical Center. **c** 55-year-old man with amyloidosis of the kidney. Ultrasound demonstrates renal enlargement, increased echogenicity in the renal cortex and prominent medullary pyramids. Case courtesy of Hebert Alberto Vargas MD, Memorial-Sloan Kettering Cancer Center

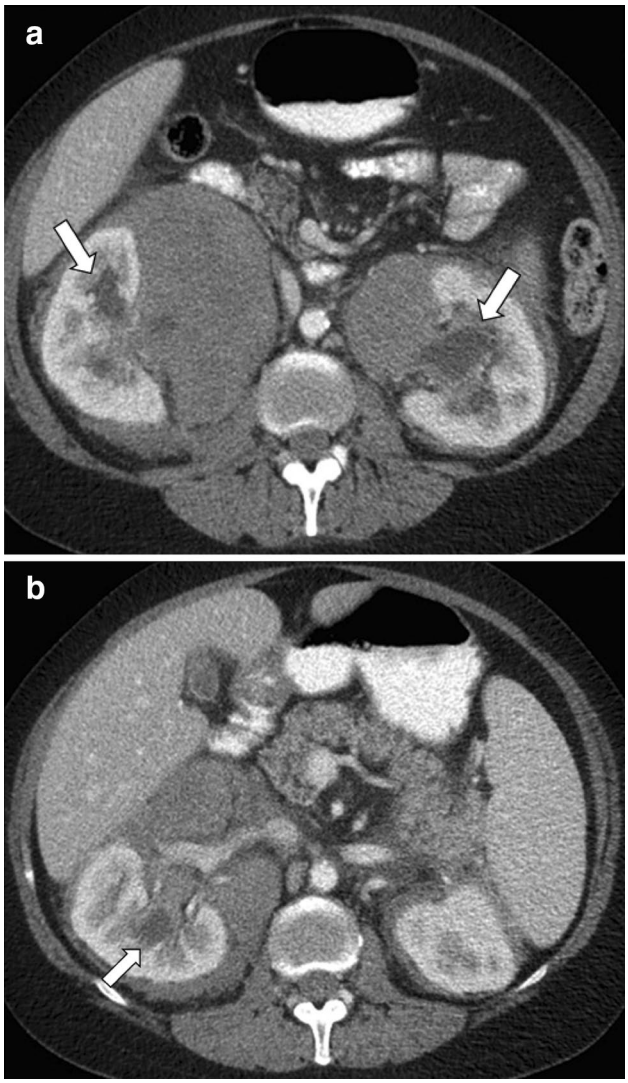

Fig. 15 Rosai–Dorman disease. **a**, **b** CECT demonstrates bilateral infiltrative perihilar masses with regions of hydronephrosis (arrows). Collecting system dilatation is indicative of the more aggressive nature of these lesions. Contrast this to the previously Fig. 4, lymphoma, which did not show collecting system dilatation. Case courtesy of Erick Remer, MD, Cleveland Clinic

78]. In the testis, amyloidosis is a low T2 signal, enhancing mass, mimicking a tumor [79]. In women, systemic amyloidosis can involve the endometrium. Endometrial involvement may be asymptomatic or cause abnormal uterine bleeding [80].

Histiocytosis

Rosai–Dorfman disease (RDD) is an uncommon histiocytic disease which typically presents with cervical lymphadenopathy in young adults. The cause is uncertain, but autoimmune or viral etiologies have been proposed. Pathologically, the disease is characterized by bone marrow monocytes being recruited into lymph node sinuses with transformation into immunologically distinct RDD histiocytes. These histiocytes release cytokines which result in systemic symptoms such as fever and fatigue [81]. Extranodal sites in the breast, thorax, abdomen, pelvis, and osseous structures may be involved. Eighty percent of patients with extranodal RDD have concomitant lymphadenopathy [81].

The kidneys are the most common intra-abdominal extranodal site of RDD, seen in approximately 2% of patients. On cross sectional imaging these typically appear as bilateral infiltrative perihilar masses (Fig. 15). Given

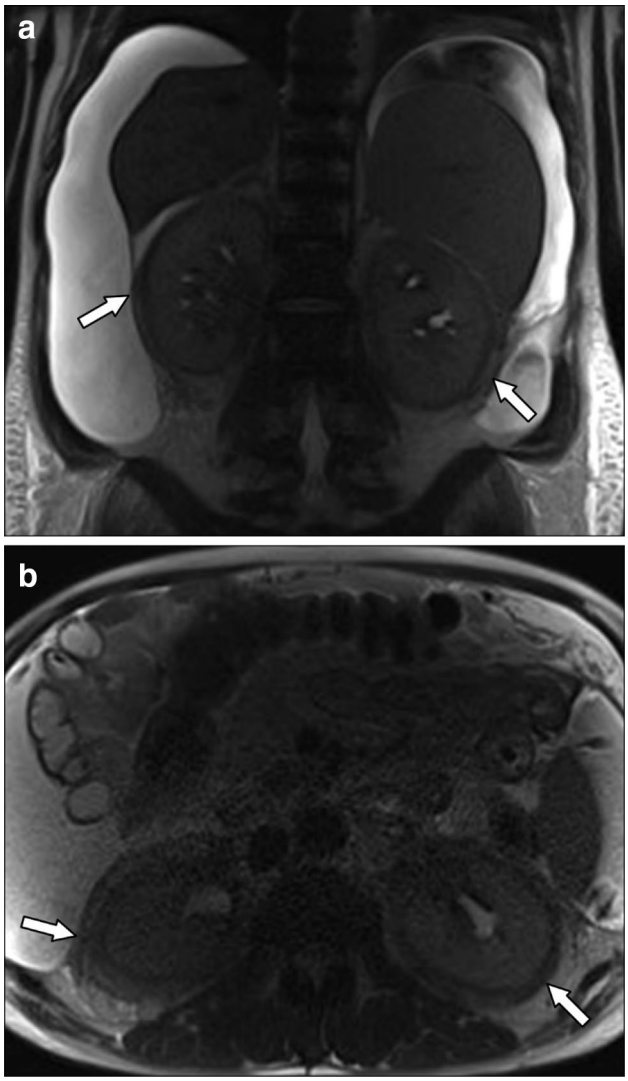

Fig. 16 51-year-old with Erdheim–Chester Disease. **a**, **b** Axial and coronal T2-weighted images demonstrate confluent T2-hypointense tissue encasing the bilateral kidneys (arrows). There is extensive abdominal and pelvic ascites due to liver dysfunction as part of Erdheim–Chester disease. Case courtesy of Erick Remer, MD, Cleveland Clinic

this similar appearance to additional disease entities discussed thus far, correlation with additional clinical and radiologist findings, namely a young adult with lymph node enlargement in the neck, may lead the radiologist to suggest this diagnosis. Lesions can also have a mass-like appearance and be subcapsular. Masses typically demonstrate mild enhancement. Extranodal lesions in RDD are usually T1 hypo/isointense, T2 iso/hyperintense, and show restricted diffusion [81]. After response to treatment, the restricted diffusion and FDG-PET/CT uptake will decrease [81]. Subcapsular and perinephric RDD is thought to be due to renal lymphatic involvement [82]. Renal dysfunction may be present due to the infiltrative nature of the disease [81].

RDD involvement of the reproductive organs is rare but can occur. In women, RDD can involve the uterus or ovaries and presents as masses. In men, less than 1% of patients have involvement of the reproductive organs, which can be seen as an epididymal or testicular mass which shows increased flow on Doppler sonography [81, 83].

Erdheim–Chester Disease (ECD) is a rare non-Langerhans cell histiocytosis with multi-organ infiltration by foamy histiocytes, more common in men in their 4th and 5th decades [84]. Serum analysis of ECD patients demonstrate a unique inflammatory marker profile with elevated levels of interferon-α, interleukin-12, and monocyte chemotactic protein-1 with decreased levels of interleukin-4 and interleukin-7 [85]. ECD can have multi-organ involvement and may be seen in the bones, brain, lungs, kidneys, and heart [86]. The most common presenting symptom of ECD is non-specific bone pain, usually around the knees. Other signs can include diabetes insipidus, exophthalmos, interstitial lung disease, retroperitoneal fibrosis, renal dysfunction, and cardiac dysfunction.

ECD commonly causes retroperitoneal fibrosis which may lead to renal dysfunction secondary to collecting system obstruction. Associated symptoms reported in ECD include dysuria, frequency and urgency [87]. CT and MRI show enhancing retroperitoneal infiltration with thickened perinephric soft tissue bands surrounding the kidneys, leading to an appearance of "hairy" kidneys (Fig. 16) [84]. As with most entities discussed in this review, there is significant overlap of radiographic features with other diseases. Lymphoma may have confluent perinephric and/or retroperitoneal soft tissue. Thus, additional features of this disease including osteosclerosis of long bones, peri-aortic infiltration, pulmonary, CNS, and pericardial involvement may lead to the radiologist suggesting this diagnosis.

Elsewhere in the genitourinary tract, testicular infiltration can occur and is typically bilateral. Adrenal gland infiltration can also occur in ECD [88].

Conclusion

Immune-mediated diseases can involve the genitourinary system in a variety of ways, and their imaging features should be recognized by radiologists in order to prevent a delay in diagnosis. Some characteristic imaging features of these diseases include bilateral renal nodules in IgG4 disease, new masses in post-transplant patients in PTLD, hypoenhancing renal masses in lymphoma, T2 hypointense masses and renal atrophy in amyloidosis, and "hairy" kidneys in Erdheim Chester Disease, to name a few. Table 1 summarizes key imaging findings and distinguishing

Table 1 Summary of key imaging findings and distinguishing features of immune-mediated diseases seen in the genitourinary system on CT and MRI

Pathology	PTLD	IgG4	Lymphoma	Leukemia	Amyloidosis	Myeloma	Erdheim–Chester	Rosai–Dorfman disease
Imaging features CT	Focal masses or diffuse infiltration. Low-attenuation mass which is non- or peripherally enhancing. May contain calcifications	Hypodense mass on early phase with mild enhancement on delayed phase	Most common pattern is multiple unilateral or bilateral parenchymal lesions. Do not enhance as avidly as surrounding renal parenchyma (vs enhancement for clear cell RCC)	If there are imaging abnormalities, the most common pattern is bilateral diffuse enlargement of the kidneys	Most common pattern is atrophic kidneys. May also see enlarged hypodense kidneys, calcified calyceal masses, and increased perirenal fat density	Most common pattern is perinephric nodules and masses mimicking metastases and lymphoma. Intrarenal masses may also occur	Most common urologic pattern is retroperitoneal fibrosis, which may cause ureteral obstruction. Solid renal masses may occur, mimicking primary RCC	Most common pattern is bilateral infiltrative perihilar masses with mild homogenous enhancement
Imaging features MR	Mildly enhancing, T1- and T2-hypointense	DWI is 100% sensitive. Iso- to hypointense on T1, hypointense on T2. Mildly enhancing	Hypointense to renal parenchyma on T1, slightly hyperintense on T2. Do not enhance as avidly as renal parenchyma (vs hyperenhancement for clear cell RCC). Restricts diffusion to greater degree than RCC	Same anatomic appearance as CT. No specific imaging characteristics on MRI	Same anatomic appearance as CT. ADC mapping recently showed to differentiate amyloid renal lesions from CKD patients	Same anatomic appearance as CT. No specific imaging characteristics on MRI	Same anatomic appearance as CT. No specific imaging characteristics on MRI	Same anatomic appearance as CT. No specific imaging characteristics on MRI
Comments	New mass in a transplant patient, think PTLD. FDG-PET/CT can upstage or detect occult disease and can monitor treatment response	In kidneys and also reported in reproductive organs—ovaries, uterus, testicles, and prostate	Avid FDG-PET uptake. May be indistinguishable from chromophobe and papillary subtypes of renal cell carcinoma based on enhancement. Does not usually invade vascular structures. May be accompanied by retroperitoneal LAD	While 90% of patients with leukemia show renal involvement at biopsy, imaging abnormalities detected in 5%. Does not usually obstruct collecting system	Usually does not cause hydronephrosis, even in advanced cases. Potential complication of renal vein thrombosis	Generally seen in context of disease in other organs. Avid FDG-PET uptake, unlike RCC. Impairs renal function, unlike lymphoma and leukemia	Associated with disease involvement in long bones, CNS, and lungs. Classically associated with ILD and osteosclerosis of long bones	Young adult with neck lymphadenopathy. Kidney is most common intra-abdominal extranodal site of disease

features of immune-mediated diseases seen in the genitourinary system on CT and MRI discussed in this review. With a better understanding of these immune-mediated diseases and how they manifest in the genitourinary system, differential diagnosis may be narrowed, leading to quicker diagnosis and treatment.

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