Clinical and Translational Imaging
https://doi.org/10.1007/s40336-026-00752-0

REVIEW

Expecting the unexpected: diagnostic imaging of side effects due to cancer treatment in children

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Received: 15 October 2025 / Accepted: 30 January 2026

Abstract
Pediatric oncological treatments significantly improved in the last decades with a significant positive impact on survival rates. Despite these achievements, cancer therapy is affected by side effects which may represent a diagnostic challenge and influence the overall management of children with tumors. Diagnostic imaging plays a crucial role in diagnosing adverse events, distinguishing them also from potential mimickers like infections or recurrences. Radiologists and nuclear medicine physicians are expected to have a deep knowledge of the common therapeutic schemes, their potential side effects, and features at imaging. Therefore, the aim of this review is to provide a comprehensive overview of the role of imaging, including hybrid techniques, in correctly identifying and characterizing the side effects of cancer treatment in children, including a brief overview of the main therapeutic options in pediatric oncology.

Keywords Children · Oncology · Chemotherapy · Immunotherapy · Side effects

Introduction

In the last decades, the research community has made significant strides in understanding the molecular and cellular mechanisms of pediatric cancer, leading to the development of novel targeted therapies and immunotherapies. Unlike traditional treatments such as chemotherapy and radiotherapy, which are directed against cancer cells, immunotherapy activates the immune system to cure cancer with a significant improvement in survival rates [1]. However, current treatments—whether involving chemotherapy, radiotherapy, or the innovative frontier of immunotherapy—still carry significant acute and long-term side effects in various organs, and diagnostic imaging plays a significant role in their identification and characterization. Therefore, radiologists and nuclear medicine physicians dealing with pediatric cancer are expected to have a deep knowledge of the therapeutic options and their potential adverse reactions avoiding misinterpretation of the findings at imaging and assuring timely and correct management.

Thus, the aim of this review is to provide a comprehensive overview of the therapeutic options in pediatric oncology and the typical signs at imaging of potential side effects, emphasizing the appropriate diagnostic approaches. Even if infectious complications are an indirect effect of oncological treatment, given their clinical importance and the significant role in the differential diagnostic workflow of this group of patients, we have also addressed this type of complication in a paragraph.

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Published online: 16 February 2026

Main therapeutic options in pediatric oncology: a brief overview

A brief overview of the main category of drugs/therapeutic options in pediatric oncology, their mechanism of action, and common applications has been summarized in Table 1.

Imaging of cancer treatment side effects in children

The range of side effects associated with pediatric cancer treatments is broad, including direct toxicities, susceptibility to infections by external pathogens, and complex, multifactorial syndromes. Here we summarize the main side effects detectable by diagnostic imaging subdivided according to the affected system. A graphic representation is also provided in Fig. 1.

Neurological side effects

Neurotoxic symptoms may stem from multiple mechanisms, including direct cytotoxicity, indirect free radical generation, and vascular alterations, all contributing to neural damage and functional impairment. In children with non-central nervous system solid tumors, neurological side effects are observed in approximately 33% of the cases, emerging either during active treatment or in a delayed phase [2].

Leukoencephalopathy

Leukoencephalopathy includes a group of clinical conditions of the white matter, primarily affecting the myelin sheath and leading to various neurological symptoms. In children, it may cause cognitive impairments, motor weakness, seizures, and behavioral changes [3]. Vincristine, ifosfamide, cyclosporine, cisplatin, and methotrexate are commonly associated with this side effect, the latter especially when administered at high doses or intrathecally.

MR plays a main role in diagnosing leukoencephalopathy, and the common findings are hyperintense areas on T2-weighted and FLAIR sequences, reflecting demyelination or white matter injury (Fig. 2). Methotrexate-induced leukoencephalopathy typically causes symmetrical periventricular lesions. In advanced cases, diffusion-weighted imaging (DWI) may show restricted diffusion [4]. CT is less

Table 1 Summary of the main therapeutic options in pediatric oncology

Drug Class	Examples of molecules	Main mechanism of action	Type of cancer
Alkylating agents	Cyclophosphamide, ifosfamide, busulfan, cisplatin, carboplatin	Disrupts DNA replication through alkylation or covalent binding	Leukemias, lymphomas, neuroblastoma, sarcomas
Antimetabolites	Methotrexate, 6-mercaptopurine, cytarabine, gemcitabine, 5-fluorouracil	Blocks DNA/RNA synthesis by inhibiting key enzymes or incorporating faulty nucleotides	ALL, AML, Non-Hodgkin's lymphoma, osteosarcomas
Antitumor antibiotics	Bleomycin, dactinomycin, doxorubicin	Interferes with DNA transcription via free radicals or intercalation	Rhabdomyosarcoma, Wilms' tumor, Ewing's sarcoma, Hodgkin's lymphoma
Bacterial Enzymes	L-asparaginase	Depletes asparagine, impairing leukemic cell survival	ALL, lymphoblastic lymphoma
CAR T-Cell Therapy	Tisagenlecleucel	Genetically modifies T-cells to target CD19 + cancer cells	B-ALL (relapsed/refractory)
Hematopoietic Stem Cell Transplantation (HSCT)	-	Replaces diseased bone marrow with healthy stem cells	High-risk or relapsed ALL, AML, neuroblastoma, lymphomas
Microtubule agents	Vincristine, vinblastine	Binds tubulin, inhibiting mitotic spindle formation.	ALL, Wilms' tumor, neuroblastoma
Monoclonal antibodies	Blinatumomab, rituximab, brentuximab vedotin, nivolumab, ipilimumab	Targets cancer-specific antigens, enhancing immune response	AML, neuroblastoma, Hodgkin's lymphoma
Protein kinase inhibitors	Crizotinib, dasatinib, imatinib, larotrectinib	Blocks phosphorylation in cancer cell pathways, preventing tumor growth	ALK^+ cancers, CML, Ph^+ALL
Radiotherapy	External beam, proton therapy, brachytherapy	Uses ionizing radiation to damage cancer cell DNA	Brain tumors, Wilms tumor, rhabdomyosarcoma, lymphomas
Steroids	Prednisone, dexamethasone	Anti-inflammatory, immunosuppressive, and anticancer effects	ALL, lymphomas, brain tumors
Topoisomerase inhibitors	Etoposide, teniposide, irinotecan	Inhibits topoisomerases, leading to DNA strand breaks	ALL, lymphomas, neuroblastoma, brain tumors

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ALK^+: anaplastic lymphoma kinase; B-ALL: B-cell acute lymphoblastic leukemia; CML: chronic myelogeneous leukemia; Ph^+ ALL: Philadelphia chromosome positive acute lymphoblastic leukemia

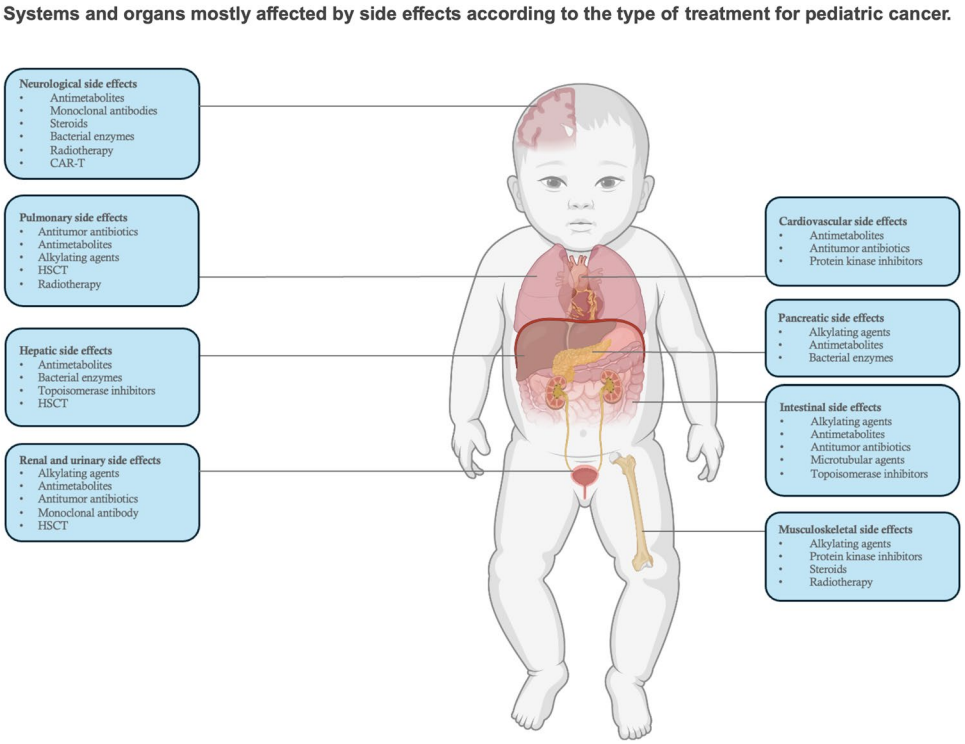

Fig. 1 Representation of the systems and organs mostly affected by side effects according to the type of treatment for pediatric cancer. Created in BioRender. Giraudo, C. (2025) https://BioRender.com/4ypv5p8

sensitive, but in severe cases it may show hypodense areas in the white matter.

Progressive multifocal leukoencephalopathy (PML)

PML is a severe, often fatal demyelinating disease with subacute and insidious onset, caused by the John Cunningham virus that infects oligodendrocytes, leading to a widespread white matter injury. It mainly occurs in patients with a compromised immune system, also as a result of immunosuppressive treatments, for instance, with monoclonal antibodies (e.g., brentuximab vedotin and rituximab) [5]. The clinical symptoms of PML include cognitive impairment, motor weakness, and vision changes.

On CT, the demyelinating lesions appear as subcortical hypodensities, often with a predilection for the parieto-occipital lobes. MRI shows multifocal, confluent white matter T2 hyperintensities without mass effect or contrast enhancement, especially in the subcortical areas of the cerebral hemispheres [6]. PML lesions are usually asymmetric.

Posterior reversible encephalopathy syndrome (PRES)

PRES is characterized by vasogenic cerebral edema and patients may experience seizures, headache, vomiting, vision disturbances, and altered consciousness. Although PRES is generally reversible, delayed diagnosis and/or treatment can lead to severe and sometimes irreversible complications, including massive cerebral hemorrhage or cerebellar herniation. It may occur after the administration of immunosuppressive agents (e.g., cyclosporine, tacrolimus, and corticosteroids) or after allogenic hematopoietic stem cell transplantation (HSCT) with an incidence of 1–10%. Regarding its pathophysiology, two main hypotheses have been proposed: (i) the hypertension acts as the initial trigger of the cascade of events, ultimately resulting in vasogenic cerebral edema; (ii) the endothelial cell activation acts as a primary factor.

CT is usually applied as a first-line tool, but it might be negative or show unspecific findings, like white matter hypodensities in the posterior cerebral region. MRI is the gold standard, demonstrating hyperintense areas on T2w and FLAIR sequences in the subcortical white matter and sometimes in the cortex, with a posterior predominance. Indeed, the parietal and occipital lobes are commonly involved. DWI is crucial to distinguish PRES from cerebrovascular events. In fact, DWI is usually normal in PRES, while in the case of cytotoxic edema due to ischemic stroke, there is restricted diffusion with low ADC values. Even if gadolinium-based contrast is sometimes used to rule out differential diagnoses, rarely there is contrast enhancement in PRES [7].

Central venous thrombosis (CVT)

CVT is a relatively common complication in oncological children treated with L-asparaginase and corticosteroids, with incidence rates ranging from 2% to 10% in pediatric

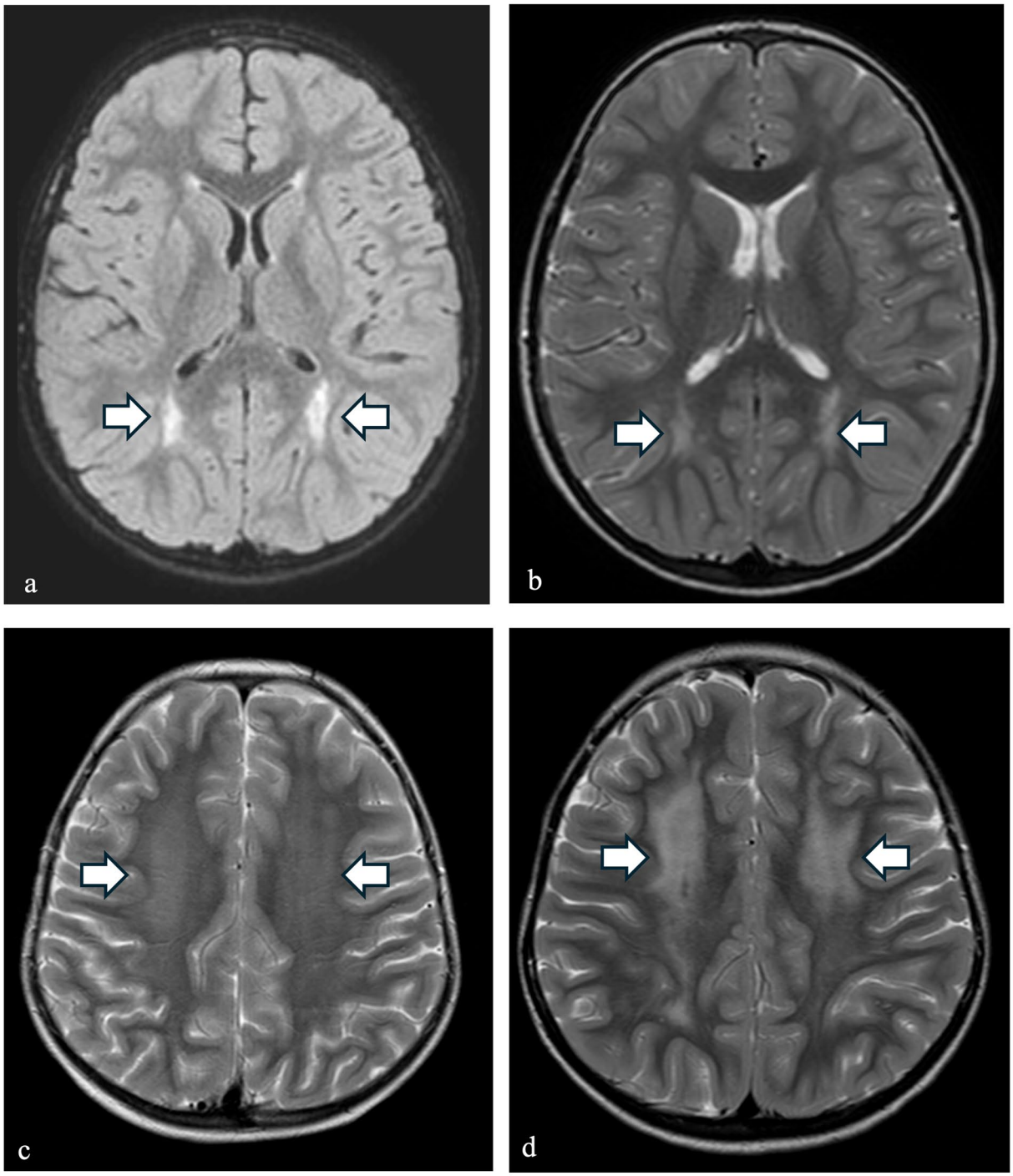

Fig. 2 Axial FLAIR (**a**) and T2 TSE (**b**) images of the MR performed on a six-year-old boy six months after the end of treatment with methotrexate for acute lymphoblastic leukemia showing hyperintense areas in the posterior periventricular regions (white arrows in a and b). In **c**, the axial T2 TSE of a six-year-old girl affected by acute lymphoblastic leukemia with multiple episodes of aphasia, dysphagia, sialorrhea, and short-term loss of consciousness during treatment with methotrexate, showing symmetric hyperintense areas in the centrum semiovale (white arrows in **c**). The MR performed six months later demonstrated a worsening of the findings (white arrows in **d**) suggesting the persistence of the demyelination

patients undergoing treatment for acute lymphoblastic leukemia [8]. It is also associated with monoclonal antibodies like blinatumomab. If not promptly diagnosed it might be life-threatening due to the risk of severe complications, including cerebral edema and hemorrhage. Patients with CVT are often affected by persistent headache, nausea, visual disturbances, and, in severe cases, seizures or altered mental status [7].The initial imaging modality is often a non-contrast enhanced CT scan, which may reveal hyperdensities in the venous sinuses suggestive of thrombosis (Fig. 3a and b). However, the gold standard is MRI. In the acute phase the clot is isointense on T1-weighted (T1w) and hypointense on T2-w images, while in the subacute phase the clots tend to be hyperintense on T1w sequences (Fig. 3c). Moreover, MR venography with or without contrast medium is very useful, allowing a proper characterization of the veins and the identification of flow voids due to the clots [9]. In particular, 3D gradient echo post-contrast sequences are insensitive to slow flow, reducing false positives, and allow a precise anatomical characterization [10].

Stroke-like migraine attacks after radiation therapy syndrome (SMART)

The SMART syndrome is a delayed complication associated with cranial irradiation in patients treated for intracranial malignancies. This syndrome manifests with migraine-like headaches and stroke-like neurological symptoms, which may include nausea, vomiting, photophobia, and temporary deficits. Although often reversible, the SMART syndrome may be long lasting or leave permanent sequelae. The exact pathophysiology of SMART is still unclear, but it is thought to be multifactorial, including white matter necrosis, vascular endothelial damage, demyelination, and gliosis due to the radiation injury. MRI is the primary diagnostic tool, typically revealing unilateral, gyriform cortical enhancement with T2 and FLAIR hyperintensity in areas not corresponding to vascular territories. These findings are often unilateral, likely corresponding to the radiation field [11].

Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS is a well-recognized and potentially severe adverse event associated with Chimeric Antigens Receptor Cells-T (CAR-T) therapy with an incidence ranging from 7% to 72% [12]. ICANS typically occurs within the first week after treatment and it is often preceded by cytokine release syndrome, which shares inflammatory pathways that can amplify the neurotoxicity risk. The clinical manifestations of ICANS vary but commonly include reduced levels of consciousness, confusion, headaches, tremors, language impairments, and seizures. Neuroimaging is often normal in mild to moderate cases. However, in severe cases, CT and MR imaging may reveal diffuse cerebral edema. MR signs include reversible T2 hyperintensities and swelling in the thalami, pons, and medulla, often accompanied by symmetric T2 hyperintensities in the subcortical white matter or the external and extreme capsule (Fig. 4) [13]. In adults with ICANS, brain positron emission tomography with 18 F-Fluorodeoxyglucose ([18 F] FDG-PET) is characterized by a fronto-lateral hypometabolic signature which reflects the more prominent susceptibility of frontal lobes to cytokine-induced inflammation and therefore the predominant frontal distribution of the syndrome [14].

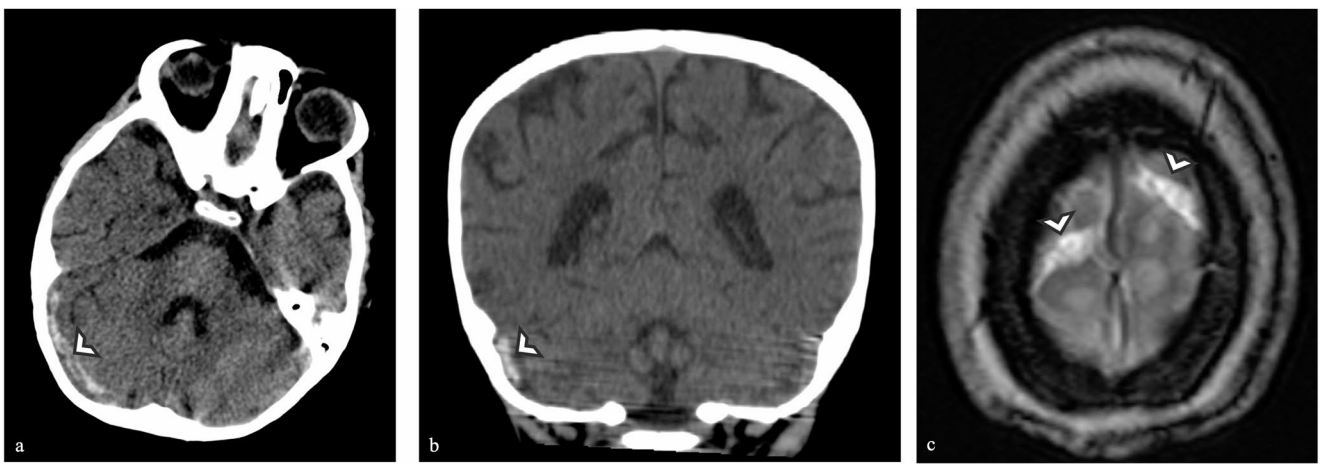

Fig. 3 Four-year-old boy with B-cell acute lymphoblastic leukemia under treatment with blinatumomab who had an episode of reduced responsiveness accompanied by upward eye deviation. The axial and coronal plain CT demonstrated hyperdense areas in the right transverse sinus (white arrows in **a** and **b**) suggestive of thrombosis. In **c**, a fourteen-year-old girl with B-cell acute lymphoblastic leukemia with severe headache and photophobia during the induction phase. The T1 axial MR showed hyperintense areas due to subacute bilateral thrombosis in two cortical veins at the vertex (white arrows in c)

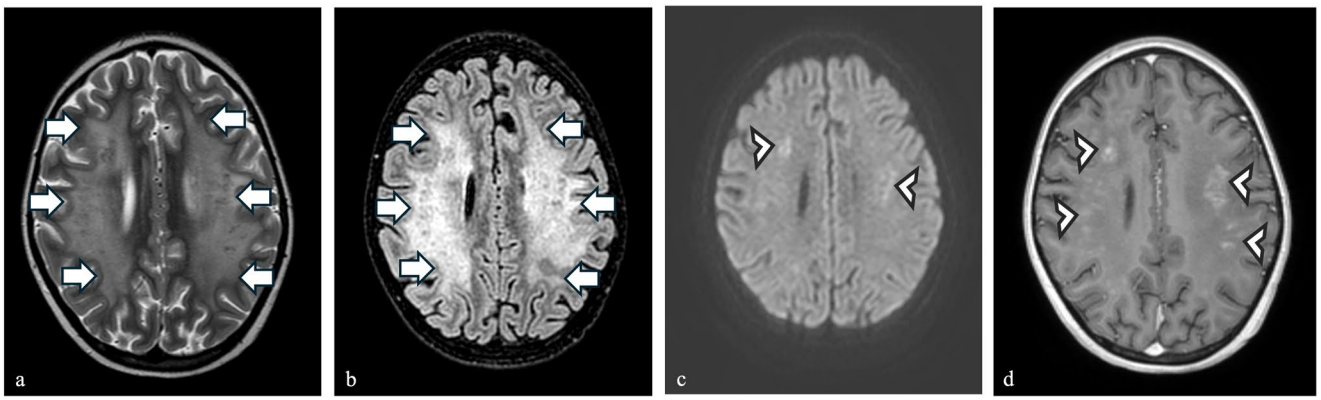

Fig. 4 Ten-year-old boy with acute lymphoblastic leukemia under treatment with Chimeric Antigens Receptor Cells-T (CAR-T) therapy who developed psychomotor impairment. The MRI revealed large signal abnormalities in the white matter of the cerebral hemispheres (white arrows in the T2 TSE in **a** and in the FLAIR in **b**). Within these regions, multiple focal lesions characterized by restricted diffusion (white arrowheads in the DWI image in **c**), hemorrhagic components, and blood-brain barrier disruption with contrast enhancement (white arrowheads in the post-contrast T1w sequence in **d**) were visible. The findings were suggestive of immune effector cell-associated neurotoxicity syndrome (ICANS)

Pulmonary side effects

Pulmonary disease is the third leading cause of non-recurrence-related mortality in pediatric cancer survivors. Therefore, it is essential to promptly recognize any sign of respiratory injury related to the treatment, whether acute or delayed, although often the symptoms are unspecific. Pulmonary complications due to cancer treatment are multifactorial, resulting from complex interactions among therapy-induced lung damage, immune suppression, and an increased risk of infections. Aiming to avoid progressive and even irreversible lung injury, early detection and treatment are crucial. Although HRCT represents the preferred technique to detect many of the typical signs of pulmonary side effects, the radiation exposure associated with this technique cannot be overlooked especially in children and the ALARA (*As Low As Reasonably Achievable*) principle should always be respected [15]. Therefore, given the tremendous technological progress in CT scanners, low-dose protocols should always be favored [16, 17].

Pulmonary inflammation

Bleomycin, alkylating agents, nitrosoureas, and radiotherapy may cause pulmonary inflammation [18]. Chest imaging especially via HRCT is the gold standard for detecting this side effect.

Bleomycin is associated with a high risk of pulmonary toxicity because it is poorly metabolized in the lungs due to the low levels of bleomycin hydrolase, the enzyme responsible for its detoxification. Bleomycin-induced pneumonitis is a serious and potentially fatal complication, often occurring during or soon after treatment. Symptoms include nonproductive cough and exertional dyspnea, which can progress to dyspnea at rest and cyanosis if untreated. At CT, it may show different patterns, including diffuse alveolar damage, organizing pneumonia, non-specific interstitial pneumonia, and bronchiolitis obliterans organizing pneumonia with poorly marginated subpleural nodules. Methotrexate has been linked to hypersensitivity pneumonitis, characterized by the rapid onset of nonspecific symptoms like dyspnea, cough, and fever. At imaging, areas of ground glass, poorly defined centrilobular nodules, reticular opacities, and in the late phase, fibrosis and traction bronchiectasis can be seen [19].Radiation therapy to the chest may cause radiation pneumonitis, typically presenting with localized areas of consolidation, atelectasis, and lung volume loss. At HRCT, symmetric ground-glass opacities and consolidations in the mid and upper lung zones, aligning with irradiated regions can be detected [20]. Overall, according to the literature, the incidence of pediatric radiation pneumonitis is lower than in adults. This difference could be due to the lower radiation dose typically used in children.

Idiopathic pneumonia syndrome (IPS)

IPS is a severe and rapidly progressing complication following HSCT. It is characterized by the acute onset of non-infectious, diffuse lung injury leading to respiratory failure. It typically occurs within weeks to months after HSCT and patients present with cough, hypoxia, and worsening dyspnea. The incidence is around 5–10%, and the prognosis is poor, with reported mortality rates between 50% and 80% [21]. The pathogenesis of IPS is complex, likely involving multiple lung insults, including direct toxicity from conditioning regimens, inflammatory cytokine release, and immunologic factors. HRCT features include ground-glass opacities, air-space consolidations, and intralobular

reticulation, often forming a "crazy-paving" pattern (Fig. 5a). A mosaic pattern of lung attenuation may also occur, frequently with a basal or posterior predominance [22]. These imaging findings, while indicative, are non-specific and may resemble pulmonary infections; therefore, it is necessary to rule out any potential infection even via bronchoalveolar lavage.

Cavitations/Pneumothorax

Recent studies have investigated the occurrence of pneumothorax associated with cavitations during treatment with vascular endothelial growth factor (VEGF)–inhibitors, in particular pazopanib. Although these studies are limited in sample size due to the off-label use of this drug in children (mainly for relapsed solid tumors), the current evidence suggests a significant association between antiangiogenic therapies, cavitations and pneumothorax, especially in patients with lung metastases. These complications seem to be linked to the drug's mechanism, which inhibits the VEGF, leading to tumor necrosis and alterations in the lung parenchyma. The cavitation occurring in solid pulmonary lesions can be easily diagnosed with CT. In children treated with pazopanib, cavitations are often observed in lung metastases responding to therapy, indicating tumor reduction (Fig. 5b and c) [23]. Some studies have also investigated the occurrence of spontaneous pneumothorax associated with other chemotherapeutic agents such as doxorubicin and adriamycin; nevertheless, further research is needed to fully understand the mechanisms and frequency of this complication [24].

Bronchiolitis obliterans

It often occurs after HSCT, especially after conditioning regimens including cyclophosphamide or total body irradiation. It is considered a manifestation of chronic graft-versus-host disease (GVHD) in the lungs, presenting as irreversible airflow obstruction. Clinically, it is defined by a decline in forced expiratory volume in one second (FEV1) of at least 20% from the baseline. On HRCT, air trapping, bronchiectasis, bronchial wall thickening and ground glass opacities can be detected [25].

Pulmonary fibrosis

Pulmonary fibrosis is a late complication associated with radiotherapy and some chemotherapeutic agents, such as bleomycin. It is characterized by progressive scarring and stiffening of the lungs due to collagen deposition, resulting in persistent dyspnea. Pulmonary fibrosis related to bleomycin is well known in adults and this complication has been addressed also in children [26]. The typical findings associated with fibrosis, including reticulations and bronchiectasis, can be easily detected by HRCT. In cases of fibrosis due to radiotherapy, the fibrotic changes are usually confined to the radiation field.

Pulmonary venous occlusive disease (PVOD)

Is a rare but severe complication after HSCT due to the obliteration of the pulmonary venules then causing pulmonary hypertension, usually not responsive to vasodilators [27]. It typically occurs weeks after the transplant and the main symptom is dyspnea. CT is crucial in the diagnostic workflow and usually shows centrilobular ground-glass opacities and interlobular septal thickening. Mediastinal lymph nodes enlargement, pleural and/or pericardial effusion and dilatation of the pulmonary trunk can also be detected [27].

Cardiovascular side effects

The risk of cardiac injury from antineoplastic therapy is increasing due to an association of various factors such

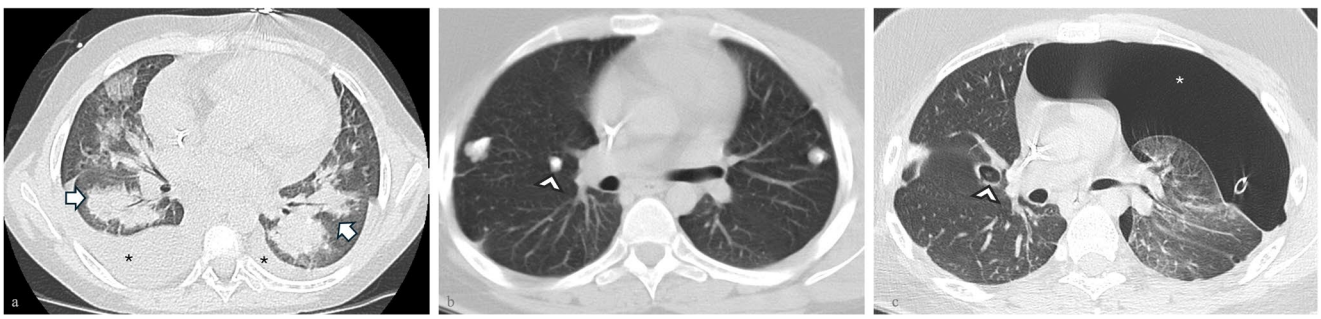

Fig. 5 In **a**, axial chest CT image demonstrating bilateral para-hilar consolidations (white arrows) and pleural effusion (black asterisks) in an eleven-year-old girl with B-cell acute lymphoblastic leukemia who shortly after hematopoietic stem cell transplantation developed cough and fever. The findings were suggestive of idiopathic pneumonia syndrome; no clinical or laboratory signs of infection were detected. In **b** and **c**, axial chest images of a 17-year-old boy with bilateral pulmonary metastases due to right humeral osteosarcoma; during the treatment with pazopanib the lesions reduced in size but some of the nodules cavitated (arrowhead in **c**) and one of the cavitations even caused a massive left pneumothorax (white asterisk in **c**) treated with the placement of a thoracic drainage

as the rising incidence of cancer, the application of more aggressive treatment protocols, and the extended survival of patients following treatment [28]. The range of symptoms due to cardiotoxicity is broad and it includes symptomatic or asymptomatic heart failure, arrhythmias, hypertension, coronary artery disease, valvular disease, pericardial disease, and peripheral vascular diseases. Cardiotoxicity may occur during or after treatment. The current guidelines emphasize the importance of regular cardiac monitoring with electrocardiography, radiograph, and echocardiography for an early diagnosis in patients at high and moderate risk [29].

Cardiomyopathy

Anthracyclines, like doxorubicin, are frequently associated with cardiotoxicity. This type of drug generates reactive oxygen species in the cardiomyocytes, leading to oxidative stress and cellular injury. In the acute stage, arrhythmias or myocarditis may occur, while in the long run patients may suffer from congestive cardiomyopathy, which in turn may result in heart failure. Echocardiography is typically the first-line imaging method allowing a rapid, non-invasive assessment of the left ventricular function. Nevertheless, MRI is more sensitive. Indeed, it may show wall motion abnormalities, and the late gadolinium enhancement may reveal subtle changes due to myocardial fibrosis [30].

Pericarditis

The most common side effect of oncological treatments on the pericardium is represented by pericarditis. Antimetabolites, like 5-fluorouracil, and tyrosine kinase inhibitors have been associated with this side effect [31]. Patients may report sudden pleuritic chest pain, dyspnea, and fever, although they may also be asymptomatic. In case of chest radiotherapy, acute inflammatory pericarditis with effusion, which may evolve into chronic exudative pericarditis or, over time, progress to constrictive pericarditis, may occur [28](Fig. 6a). Echocardiography is often the first-line imaging modality for pericarditis allowing the detection of fluid and the dynamic assessment of cardiac contractility as well as the identification of pericardial thickening in chronic cases. Cardiac MRI is applied for a better characterization of fibrotic changes like pericardial thickening and stiffness [32] (Fig. 6b).

Gastrointestinal side effects

Gastrointestinal side effects are common in pediatric oncological patients and the entire gastrointestinal tract can be affected with a wide spectrum of symptoms.

Hepatic steatosis

Hepatic steatosis, commonly known as fatty liver, is due to fat accumulation within the hepatocytes. While often

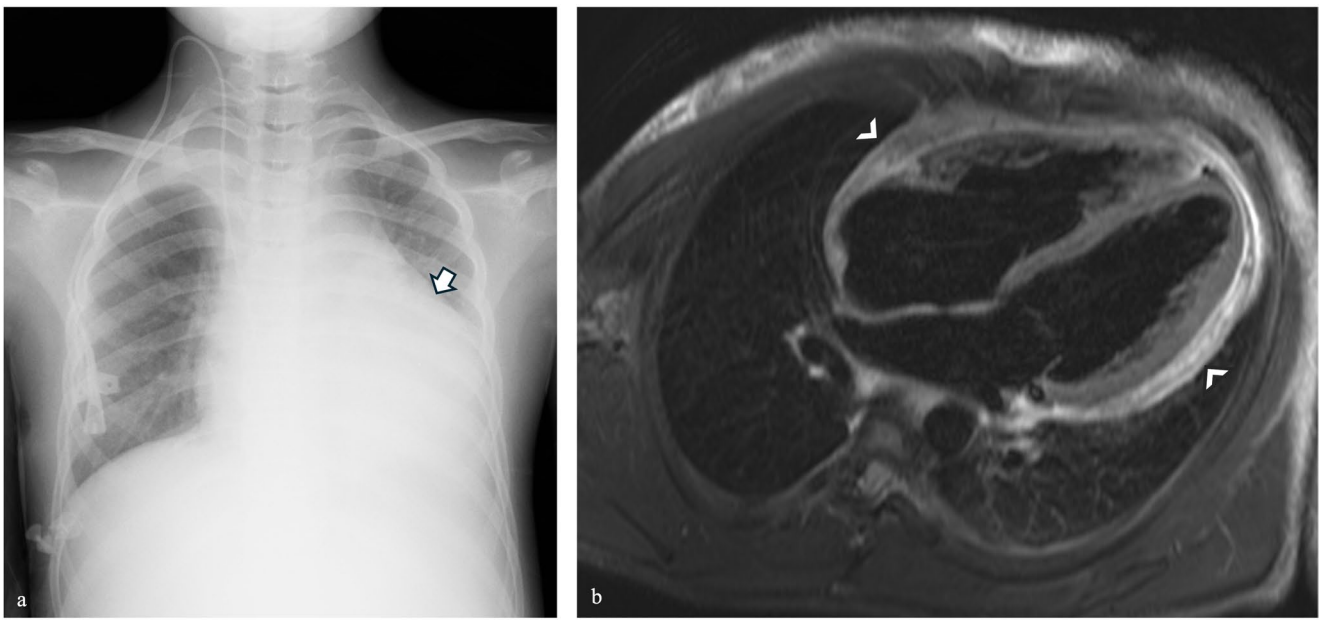

Fig. 6 In **a**, chest X-ray of a nine-year-old girl under treatment with idarubicin for acute myelogenous leukemia who showed dyspnea and desaturation. The radiograph indirectly shows a pericardial effusion with a widened cardiac silhouette and flattening of the cardiac waist (white arrow). In **b**, axial T2 fat-sat showing thickening of the pericardium which is suggestive of chronic pericarditis in a 17-year-old boy treated with methotrexate for non-Hodgkin's lymphoma

asymptomatic, it may evolve to steatohepatitis, which is characterized by inflammation and hepatocyte degeneration. Various agents may induce steatosis including irinotecan, L-asparaginase, and methotrexate. It can be easily diagnosed by ultrasound (US) which reveals focal or diffuse areas of increased echogenicity (Fig. 7a). Moreover, the application of quantitative techniques, such as transient elastography allows the quantification of fatty liver disease by the collection of Controlled Attenuation Parameter (CAP) [33]. Steatosis is easily seen also on second level imaging performed for cancer monitoring, and it is expressed by areas of decreased parenchymal attenuation or a drop in signal intensity on opposed-phase images compared to in-phase images, respectively on CT and MR. Identifying and reporting fatty changes in chemotherapy patients is crucial since such side effect is often reversible with the discontinuation of therapy [34].

Sinusoidal obstruction syndrome (SOS)

Previously known as hepatic veno-occlusive disease, SOS is a well-recognized complication of high-dose chemotherapy in patients undergoing HSCT with an incidence ranging from 2 to 20%. It may also occur with dactinomycin, alkylating agents like busulfan, cyclophosphamide, and platinum-based complexes such as carboplatin and cisplatin [35]. SOS is characterized by the activation of sinusoidal endothelial cells and subsequent liver injury, leading to a cascade that may result in hepatocellular necrosis, fibrosis, vascular occlusion, and ultimately liver failure, hepatorenal syndrome, and multi-organ dysfunction. Often the symptoms are unspecific, and they may mimic other complications due to the treatment. For the diagnosis, three diagnostic criteria have been proposed over time (i.e., the Baltimore criteria, the modified Seattle criteria, and the European Society for Blood and Marrow Transplantation -EBMT- pediatric criteria), each incorporating, to varying extents, bilirubin levels, ascites, unexplained weight gain exceeding 5%, and hepatomegaly [36]. In terms of imaging, color-Doppler US is the main imaging modality, easily revealing decreased portal flow, increased resistive index of the hepatic artery, and the presence of collateral veins [37]. In the early phase, hepatic vein peak systolic velocity may increase while reversed portal venous flow usually occurs in late-stage disease [37] (Fig. 7b). Additional findings include gallbladder wall thickening, ascites, splenomegaly, and dilatation of the portal vein [37].

Acute pancreatitis

Acute pancreatitis is a common and severe side effect of treatment with L-asparaginase, frequently used for ALL. Also, cisplatin, ifosfamide, cyclophosphamide, and 6-mercaptopurine may cause this type of toxicity [34].The diagnosis is achieved via clinical findings, laboratory tests (high serum amylase and lipase levels), and imaging. US is

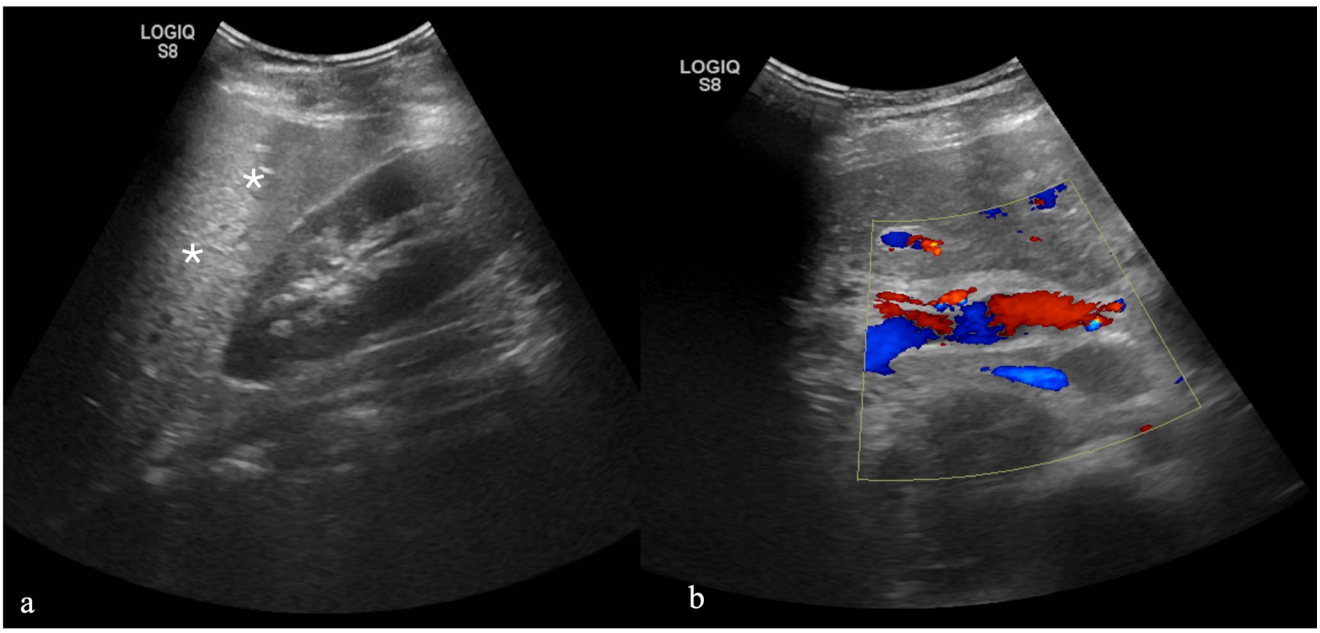

Fig. 7 In **a**, ultrasound of a sixteen-year-old girl undergoing chemotherapy with methotrexate for acute lymphoblastic leukemia, showing the increased liver echogenicity (white asterisks) consistent with hepatic steatosis. In **b**, Color-Doppler showing the initial inversion of the flow in the portal vein which is suggestive of sinusoidal obstruction syndrome, related to actinomycin-D in an eleven-year-old girl with Wilms' tumor of the right kidney under treatment with actinomycin-D, vancomycin, and doxorubicin. The patient reported diffuse abdominal pain, and laboratory findings showed increased hepatocytolysis and cholestasis indices

often the first-line imaging modality, and it may reveal an enlarged, edematous pancreas with reduced echogenicity. Peripancreatic or abdominal fluid may occur. To assess the severity and the potential complications of pancreatitis, contrast-enhanced CT is the gold standard. Indeed, not only does it allow a better characterization of the pancreatic enlargement and abdominal fluid collections, but it also easily reveals necrosis, hemorrhage, pseudocysts, or abscesses [34] (Fig. 8). MR cholangiopancreatography can be used for a detailed characterization of ductal abnormalities.

Enteritis

Chemotherapy-induced enteritis, commonly presenting with abdominal pain, bloating, and diarrhea, is one of the most frequent toxicities linked to traditional cytotoxic agents. It is due to a non-specific targeting of rapidly dividing cells of the gastrointestinal mucosa. Irinotecan, for example, is associated with a high incidence of diarrhea and neutropenia. Abdominal radiographs may represent the initial diagnostic approach, showing dilated bowel loops and air-fluid levels. US may add information about concomitant bowel wall thickening. Especially for severe cases, contrast-enhanced CT is suggested, and it shows submucosal edema and hyperemia of the mucosa and serosa, with the typical 'target sign' [38].

Neutropenic Enterocolitis

Neutropenic enterocolitis, or typhlitis, is not directly caused by chemotherapy, but its pathogenesis is closely associated with the immunosuppression induced by certain types of treatment. It is an acute transmural inflammation affecting the ileum, cecum, and ascending colon in patients with severe neutropenia, which can progress to segmental ulceration, perforation, and sepsis [39].Cytarabine, gemcitabine, vincristine, cyclophosphamide, and doxorubicin as well as HSCT are among the common causes of this side effect. The clinical symptoms include fever, abdominal pain, and diarrhea. In terms of imaging, US is often the initial imaging modality, showing bowel wall thickening (> 4 mm) and fluid collections and/or free abdominal fluid (Fig. 9a and b). If the US is inconclusive or the clinical symptoms are very severe, a contrast-enhanced CT scan is recommended. Typical CT findings include bowel wall thickening, pericolonic fat stranding, portal venous gas, pneumatosis intestinalis, and/or free air due to perforation [40] (Fig. 9c and d).

Renal and urinary side effects

Nephrotoxicity is a well-established side effect of several pediatric cancer treatments, including cisplatin, carboplatin, ifosfamide, and radiation therapy. Although most nephrological and urinary side effects of oncological therapies are typically diagnosed through clinical evaluation and laboratory findings, imaging may represent a valuable support in reaching the proper diagnosis.

Interstitial nephritis

It is an inflammation of the renal interstitium. Patients may present oliguria or, sometimes, hematuria. Ipilimumab and sorafenib are common agents inducing this type of side effect, which can cause kidney enlargement at US and/or low-attenuation areas at CT. 99mTc-dimercaptosuccinic acid ([99mTc] DMSA) renal scan has been proposed as a

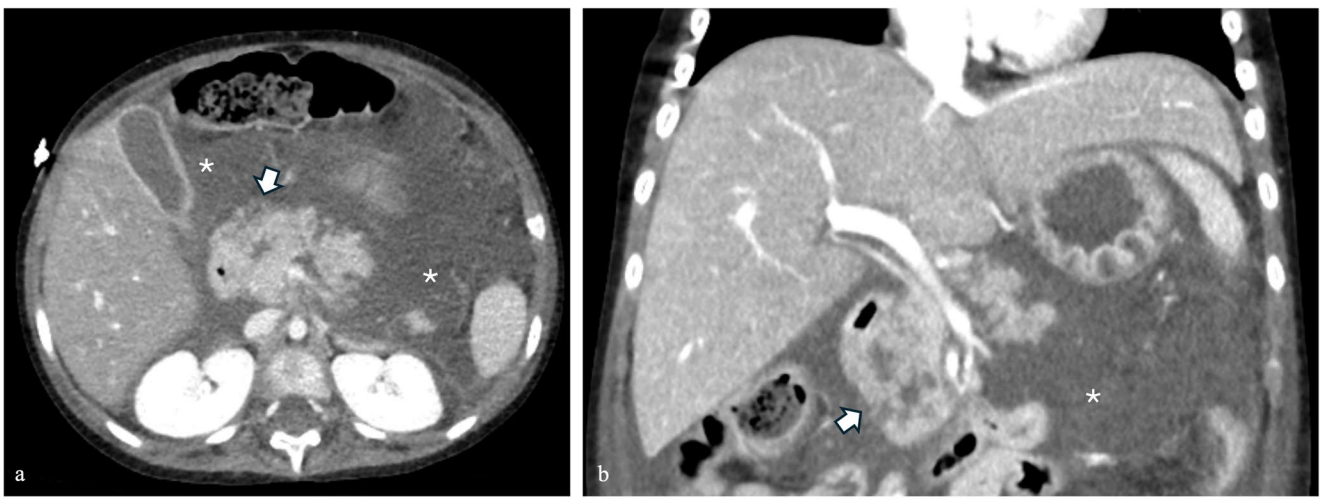

Fig. 8 Axial (**a**) and coronal (**b**) images of the abdominal CT scan after contrast medium injection of a six-year-old girl treated with PEG-asparaginase for B-cell acute lymphoblastic leukemia. The CT was performed because of diffuse abdominal pain with elevated levels of amylase and lipase and revealed acute necrotizing hemorrhagic pancreatitis. Indeed, the pancreas appeared enlarged with fuzzy margins and hypodense necrotic areas (white arrows in a and b); in addition, the patient had severe ascites (white asterisks in a and b)

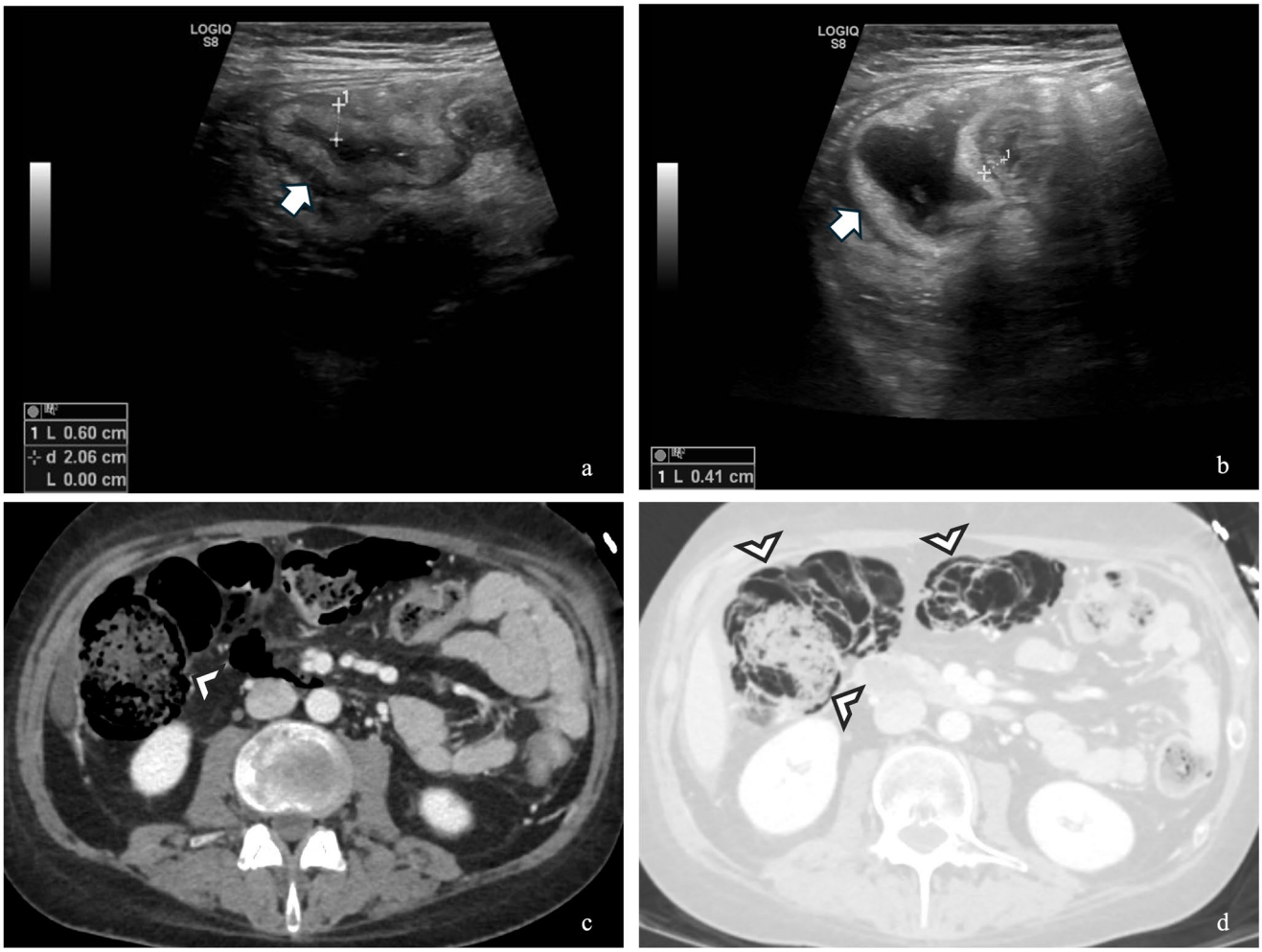

Fig. 9 Four-year-old boy with B-cell acute lymphoblastic leukemia undergoing induction therapy admitted to the emergency room for fever, irritability, diarrhea, and abdominal pain. The US revealed walls of the caecum (6 mm; white arrow in **a**) and of the terminal ileum (4 mm; white arrow in **b**), with a substenotic appearance proximal to the ileocecal valve. Blood and stool cultures were negative. The clinical and radiological findings were suggestive of typhlitis. In **c** and **d**, axial images of the contrast-enhanced CT performed for acute abdominal pain in an 18-year-old boy with acute lymphoblastic leukemia, who underwent allogenic hematopoietic stem cell transplantation. The CT demonstrated cecal distension with parietal thinning and air in the wall, suggestive of pneumatosis intestinalis (white arrowheads in c and d)

valid tool for the diagnosis and follow-up of acute tubulointerstitial nephritis in children, showing diffuse reduction of the renal uptake of radionuclide and the presence of 'cold' focal corticomedullary areas [41] (Fig. 10). Despite the low radiation dose associated with ([99mTc] DMSA, considering the above mentioned ALARA principle, it should not be overlooked that also MR imaging, including DWI as demonstrated in recent case reports, can be a useful tool for interstitial nephritis [42, 43].

Renal papillary necrosis

It is secondary to ischemia and it has been described as a side effect of analgesic and platinum-based agents (e.g., cisplatin and nedaplatin). Symptoms are quite unspecific, including fever, hematuria, and flank pain. US usually shows multiple medullary cystic spaces around the renal sinus, while at CT urography, a collection of contrast medium in the papillary regions peripheral to the calyces can be seen (aka, ball on tee sign).

Renal infarction

It is an ischemic event hampering the blood supply to the whole kidney or part of it. Methotrexate and combination schemes including cisplatin and gemcitabine have been associated with its occurrence. In the case of acute renal infarct, CT is the investigation of choice, showing the reduction or lack of perfusion, but at ultrasound, the lack of vascularization can be detected using the Color-Doppler. Chronic infarcts typically present as wedge-shaped, hypoechoic areas with cortical scarring. Similarly, on CT,

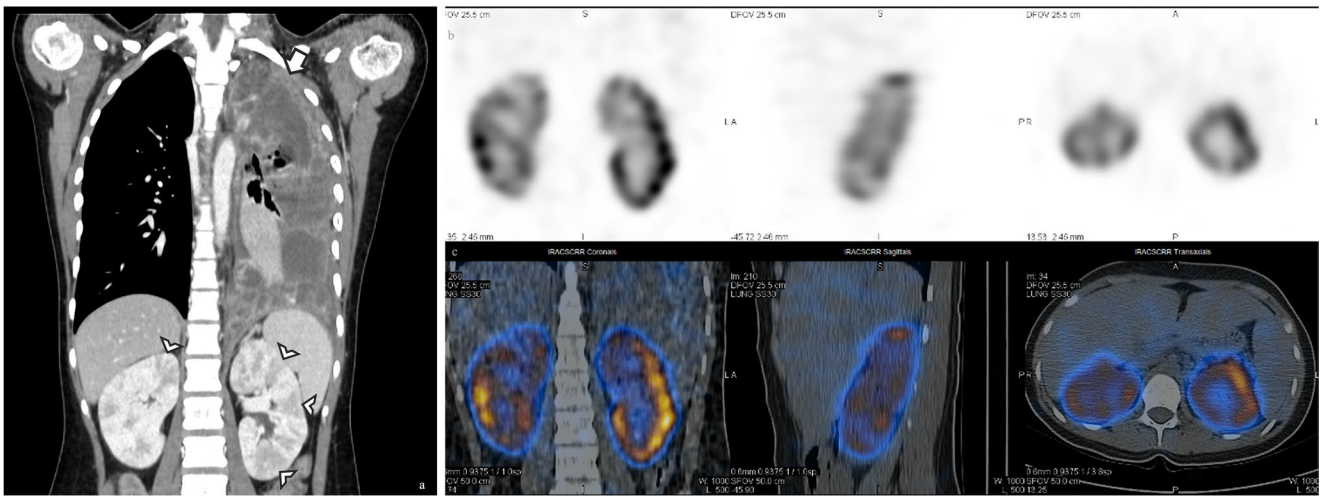

Fig. 10 Coronal reconstruction of the contrast-enhanced CT of a 13-year-old girl with thoracic Ewing's sarcoma (white arrow in **a**) showing low-attenuation areas in the kidneys at CT (white arrowheads in a) which are suggestive of interstitial nephritis related to the monoclonal antibodies treatment. The 99mTc-dimercaptosuccinic acid ([99mTc]Tc-DMSA) scan performed one week later showed areas of diffuse reduction of the renal uptake of the radionuclide (**b** and **c**)

wedge-shaped parenchymal defects affecting the cortex and medulla and reaching the capsular surface can be seen. At [99mTc] DMSA scintigraphy, infarcts appear as photopenic areas [44].

Acute tubular necrosis

It is due to an insult to the tubular epithelial cells commonly induced by cisplatin and ifosfamide.

The diagnosis is mainly based on laboratory findings (e.g., decreased GFR and urine osmolality). At imaging, the kidneys may appear enlarged and with increased cortical echogenicity at US as well as with increased and prolonged renal density especially in the pyramids at CT-urography. Dynamic renal scintigraphy with 99 m-technetium mercaptoacetyltriglycine ([99mTc] MAG3) is useful for diagnosis, showing severe cortical retention and a plateauing renogram, and follow-up [45].

Hemorrhagic cystitis

Hemorrhagic cystitis is due to an injury to the transitional epithelium and blood vessels of the bladder causing hematuria. When non-infectious, it is associated with drugs or irradiation. It is typically painless. Nevertheless, patients may experience urinary urgency, dysuria, and bladder spasms [46]. It has been described as a short and long-term side effect of HSCT, either as a consequence of the conditioning regimen (chemotherapy and/or radiation) or of the myelosuppression-induced thrombocytopenia, which increases the risk of bleeding. The most common chemotherapeutic agents causing this side effect include alkylating agents, such as cyclophosphamide, ifosfamide, and busulfan. US is the most common imaging modality for its diagnosis, revealing focal or diffuse bladder wall thickening (≥ 3 mm when distended and ≥ 5 mm when non-distended), intraluminal echogenic debris, and focal or diffuse hypervascularity as well as areas of active bleeding at Color-Doppler [46].

Musculoskeletal side effects

Musculoskeletal side effects are of particular concern in children given the potential impact on skeletal growth.

Hypoplasia and growth interference

Radiation therapy can have a severe impact on growth plates, even inducing skeletal deformities in the long run. The severity of growth arrest and deformity is usually dose-dependent and inversely related to patients' age, with younger patients facing higher risks. Similarly, some chemotherapy drugs, such as doxorubicin, methotrexate, cisplatin, cabozantinib, and corticosteroids, may affect growth plates, potentially causing premature closure that could result in limb length discrepancies or angular deformities [47, 48]. Regarding the role of imaging, radiographs easily show asymmetrical growth patterns or deformities, while MRI favors the detection of premature physeal closure and of potential changes on the soft tissues like edema and/or fibrosis due to radiotherapy [49].

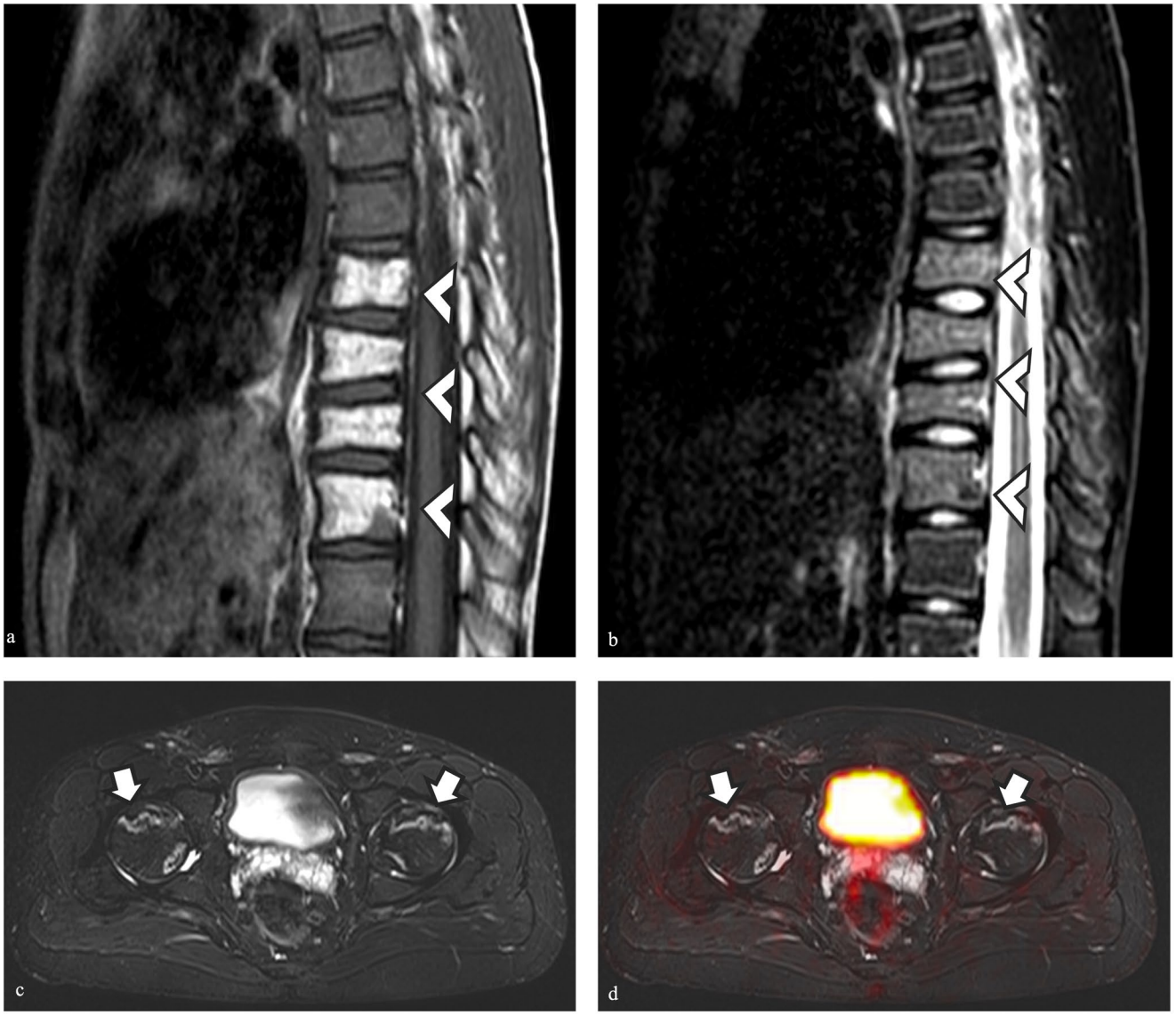

Fig. 11 Eight-year-old girl with spinal/paraspinal kaposiform hemangioendothelioma. The spinal MR performed after radiotherapy showed hyperintensity on T1 (**a**) and hypointensity on T2 fat sat (**b**) of the bone marrow in the area treated with radiotherapy. In c, axial TIRM of a 17-year-old boy with Hodgkin's lymphoma who underwent an [18 F]-FDG PET/MR scan after treatment (i.e., EuroNet-PHL-C2 protocol), showing areas of avascular necrosis in the femoral heads (white arrows in **c** and **d**). The areas did not show any pathological FDG uptake (fused TIRM and PET in **d**)

Osteoporosis/osteopenia

Osteopenia and osteoporosis are common side effects of methotrexate and steroids which accelerate bone loss by impairing osteoblast function and increasing bone resorption [50]. Cranial irradiation may induce changes in bone turnover by reducing growth hormone secretion and causing hypogonadotropic hypogonadism. This in turn increases bone resorption and reduces osteoblast function, leading to bone frailty and fracture risk. Patients may be asymptomatic or report bone pain. Dual-energy X-ray absorptiometry (DEXA) is the main tool for assessing bone mineral density. However, its use is limited in children because it does not adjust for rapid skeletal changes [51].

Avascular osteonecrosis

The exact pathogenesis of avascular osteonecrosis has not yet been fully clarified. So far it is known that there is an alteration of the blood flow in the bone, which leads to cell death with potential articular consequences such as joint collapse. There is usually a multifocal, bilateral involvement with hips and knees being mostly affected. The clinical spectrum is broad, ranging from asymptomatic patients to

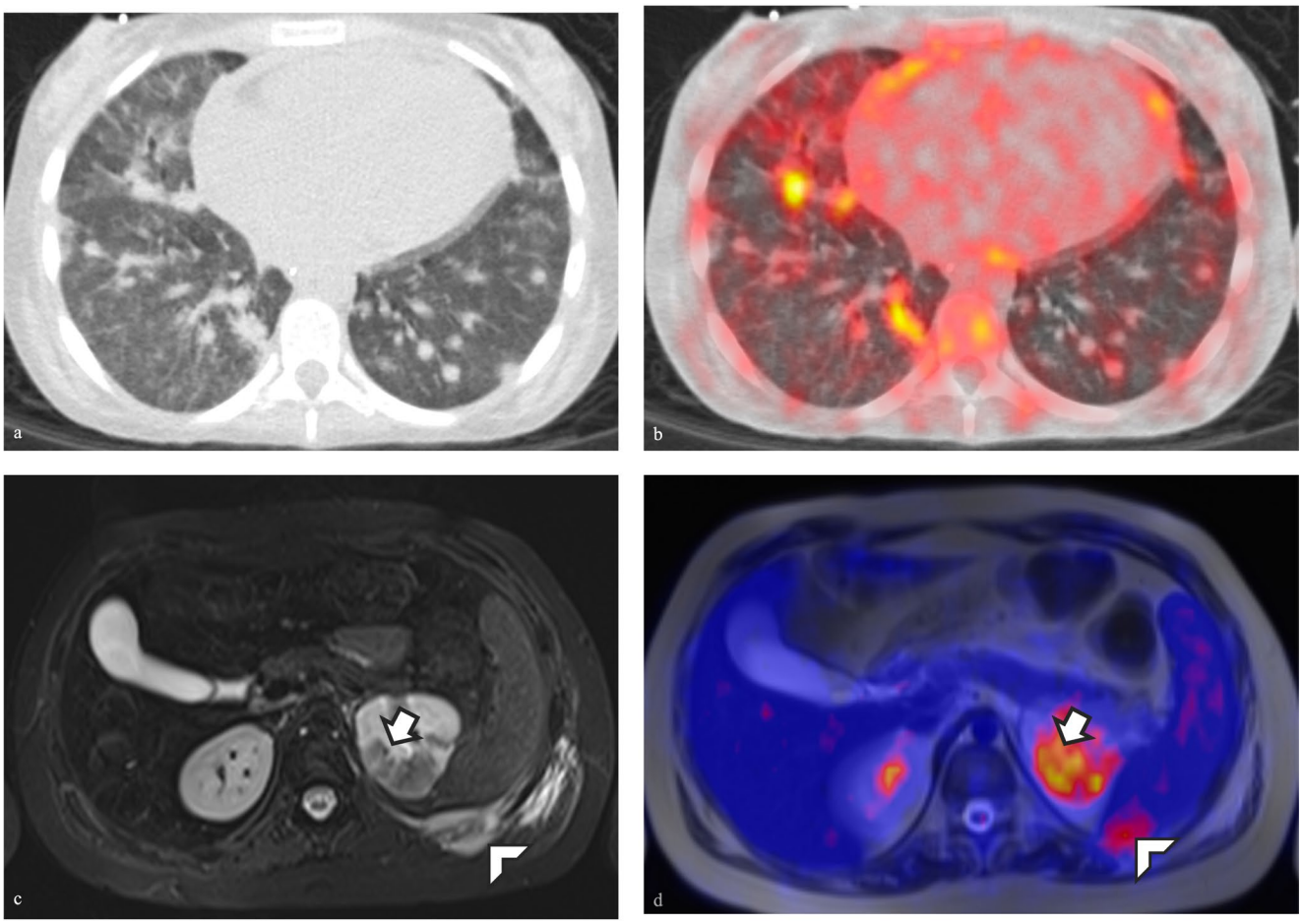

Fig. 12 Twelve-year-old girl who underwent hematopoietic stem cell transplantation for acute lymphoblastic leukemia and developed fever, cough, and shortness of breath. She underwent [18]-FDG-PET/CT to search for infectious foci and it revealed bilateral pulmonary nodules (**a**) with FDG uptake (**b**) suggestive of fungal infection. The further laboratory assessment confirmed an infection due to Aspergillus fumigatus. In **c**and **d**, axial TIRM and fused PET and HASTE, of a 10-year-old girl with costal recurrence of Ewing's sarcoma (white arrowhead in **c** and **d**) and hypointense areas in the left kidney (white arrows in **c**) with mild FDG uptake (white arrow in **d**) more suggestive of pyelonephritis, given also the tracer uptake, rather than renal infarcts. The renal color-Doppler performed afterwards excluded the renal infarcts and the laboratory test confirmed the urinary tract infection, which was then treated with antibiotics

children with significant pain and loss of function, sometimes even in need of joint replacement. Therefore, an early and accurate diagnosis is critical to prevent long-term disabilities. It is a common and debilitating therapy-related side effect of anti-leukemic treatment, with steroids playing a significant role. Some studies have shown that asparaginase, high-dose methotrexate, and cyclophosphamide may also cause this side effect [52]. MRI is the gold standard due to its high sensitivity in identifying bone marrow changes even in early phases. Typically, serpiginous areas with low T1 and high T2 signal are identified. A recent PET/MR study on children with lymphoma demonstrated that these lesions rarely show FDG uptake and are not associated with fractures/disability [53] (Fig. 11). In advanced stages, radiographs and CT can be useful to assess structural injuries, including bone collapse, joint space narrowing, and subchondral fractures.

Infectious complications

Oncological children are at high risk of infections because of the compromised immune system. The neutropenia occurring in hematological diseases and/or due to the treatment with drugs with cytotoxic effects or associated with HSCT, represents one of the main risks. Infectious complications commonly affect the lungs, urinary tract, and bowel although the soft tissue can also be involved. In particular in children with febrile neutropenia (single temperature ≥ 38.3 °C or two consecutive temperatures > 38.0 °C in a 12-h period for at least 1 h in patients with an absolute neutrophilic count of less than 1500 cells/microliter), pulmonary infections can be very severe and rapidly disseminate [54]. Multiple bacterial, viral and fungal agents may cause pulmonary infections in patients treated with HSCT, with higher morbidity and mortality than in immunocompetent subjects

[55]. Although radiographs may represent a first line diagnostic tool to assess pulmonary infections, CT represents the gold standard, revealing the typical patterns related to the infectious agents, like segmental or lobar consolidations in bacterial infections, nodules with or without the halo sign in the case of fungal spread, especially due to aspergillosis, and extensive areas of ground-glass in the case of viral etiology [55]. Hybrid imaging like PET/CT may support the diagnostic workflow of pulmonary infections in oncological children, especially contributing to the early diagnosis and the assessment of response to therapy of invasive fungal infections [56] (Fig. 12a and b). UTIs are common in oncological children under chemotherapy [57]. Although the US would represent the first line of investigation for UTI in general, it might be negative, for instance in the acute phase of pyelonephritis, and often the UTI is detected by CT performed as part of oncological disease monitoring [58]. On contrast-enhanced CT, pyelonephritis is characterized by hypodense focal wedge-like regions, even extending to the cortex during the venous phase. If the urinary phase is acquired, a striated appearance can be seen. It can be distinguished by renal infarction that usually spares the cortex. MR findings, mimic those of CT. Renal scintigraphy with [99mTc] DMSA may be useful also to rule out other side effects such as renal infarction. [18 F]FDG PET/CT and PET/MR usually have a limited role because of the excretion of tracer that hampers the renal assessment (Fig. 12c and d). Last, the neutropenic enterocolitis mentioned above (see the section about gastrointestinal side effects) may also be associated with infections.

Conclusions

While advancements in pediatric oncology - particularly through targeted therapies and immunotherapy -have substantially improved survival rates, the broad spectrum of acute and long-term side effects remains a critical challenge. The early detection and management of such side effects is essential, and diagnostic imaging plays a crucial role also in monitoring their course. Radiologists and nuclear medicine physicians should be aware of the typical features of each potential complication and the association with specific types of treatment.

Author contributions Author Contributions: All authors significantly contributed to manuscript preparation, editing, and reviewing.

Funding Open access funding provided by Università degli Studi di Padova within the CRUI-CARE Agreement. This study did not receive any fundings.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethical Committee Approval It doesn't apply.

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