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PICTORIAL ESSAY

What the emergency radiologist needs to know about treatment-related complications from conventional chemotherapy and newer molecular targeted agents

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Abstract Emergency departments (ED) are increasingly utilized by oncology patients for disease- and treatment-related issues. With the increased use of new molecular targeted therapy (MTT) and conventional chemotherapeutic regimens, oncology patients present with a range of adverse treatment effects, some of which reveal characteristic injury patterns and imaging appearances. Knowledge of these imaging findings is critically important for early detection and prompt management in oncology patients. In this article, we present a brief review of conventional chemotherapeutic and new MTT regimens as well as address adverse reactions that bring oncology patients to the ED.

Keywords Emergency · Oncology · Chemotherapy · Molecular targeted therapy · Complications

Introduction

Common cytotoxic chemotherapeutic agents have been in use as early as the 1940s and 1950s and target RNA and DNA synthesis of highly mitotic cells via varying mechanisms (Table 1) [1]. Inadvertently, these agents are often toxic to non-neoplastic rapidly dividing cells, such as those in the gastrointestinal (GI) tract and bone marrow, therefore predisposing patients to a multitude of adverse reactions [1, 2].

With the increased understanding of cancer biology, molecular targeted therapies (MTT) have been developed and utilized, starting in the early 2000s with the FDA approval of imatinib mesylate (Gleevac) for the treatment of chronic myeloid leukemia (CML). The mechanisms of MTT agents include targeting cell surface growth factor receptors and signal transduction proteins that are responsible for the transmission of signals to the cancer cell nucleus for growth and survival. Imatinib, for example, turns off the BCR-ABL transgene, the product of the Philadelphia translocation. MTTs are classified by their mechanism of action such as monoclonal antibodies, tyrosine kinase inhibitors, and agents that target other small molecules (e.g., mammalian target of rapamycin [mTor]) (Table 2). Adverse reactions secondary to MTT regimens are most often noninfectious in etiology.

Using an organ-based approach, this paper will discuss treatment-related noninfectious adverse reactions that bring oncology patients to the emergency room, addressing clinical presentation and imaging findings of neurological, pulmonary, hepatobiliary, GI, and musculoskeletal/soft tissue complications (Table 3).

Complications

Central nervous system

Symptoms of patients presenting to the emergency department (ED) with treatment-related complications of the central nervous system may be acute or subacute and vary in

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Table 1 Names, indications, and properties of common chemotherapy agents

Class Drugs	Indication	Primary target
Alkylating agents		DNA
Cyclophosphamide	Breast, lung, ovary, testis, bladder, lymphoma, leukemia	
Ifosfamide	Testicular, lung, sarcoma, lymphoma	
Melphalan	Multiple myeloma	
Carmustine (nitrosourea)	Brain, lymphoma, melanoma	
Platinum analogs		DNA, platinum coordination
Cisplatin	Testis, ovarian, endometrial, cervical, bladder, sarcoma, NHL	
Carboplatin	Ovarian, endometrial, breast, bladder, lung	
Oxaliplatin	Colon, rectum, stomach, nonsmall cell lung	
Antimetabolites		
Methotrexate	Bladder, breast, head and neck, osteosarcoma, ALL, NHL	Folic acid analog
Mercaptopurine	ALL	Purine analog
5-FU	Breast, colorectal, anal, stomach, pancreas, esophagus, liver, bladder	Pyrimidine analog
Gemcitabine	Pancreas, nonsmall cell lung, NHL	
Antitumor antibiotics		DNA, intercalation
Doxorubicin	Breast, bladder, liver, lung, and other solid tumors; lymphoma and leukemia	
Bleomycin	Testis, head and neck, penis, cervix, anus, skin, lymphoma	
Daunorubicin	Acute leukemias	
Topoisomerase inhibitors		
Etoposide	Small cell anaplastic, nonsmall cell lung, stomach, germ cell, lymphoma	Topoisomerase II, inhibits reconnection of DNA
Teniposide	ALL, neuroblastoma, NHL	
Topotecan	Ovarian, cervix, small/nonsmall cell lung	Topoisomerase I, inhibits reconnection of DNA
Irinotecan	Colon, rectum, esophagus, stomach, lung	
Vinca alkaloids		Microtubules, inhibits tubule assembly
Vincristine	Hodgkin's and NHL, ALL, breast	
Vinblastine	Hodgkin's and NHL, testicular, kidney, breast	
Taxanes		Microtubules, inhibits tubule depolymerization
Paclitaxel	Ovarian, breast, lung, cervix, melanoma	
Docetaxel	Breast, stomach, lung, ovarian, prostate	

NHL non-Hodgkin's lymphoma, *ALL* acute lymphoblastic leukemia

severity from a mild focal neurological deficit to seizure or coma.

Known neurotoxic complications of certain chemotherapeutic agents include transient toxic leukoencephalopathy. Although the exact etiology is unknown, the pathological mechanism is likely multifactorial, involving direct injury to microvasculature [3, 4]. Initial head computed tomography (CT) is often unremarkable, while magnetic resonance imaging (MRI) demonstrates non-enhancing periventricular white matter T2 prolongation with restricted diffusion (Fig. 1). Methotrexate, an antifolate chemotherapeutic agent often used intrathecally for the treatment of leukemia, has been associated with toxic leukoencephalopathy. It often presents with behavioral disturbances and sensorimotor abnormalities, approximately 7–10 days after the second or third course of chemotherapy [3–5]. Other treatment agents that have been associated with toxic leukoencephalopathy include carmustine (nitrosourea), cisplatin (platinum analog), and thiotepa (alkylating agent) [4]. Treatment includes discontinuation of the relevant chemotherapeutic agent, although findings may be irreversible and lead to patient death.

Toxic leukoencephalopathy should be distinguished from another treatment-related complication, posterior reversible encephalopathy syndrome (PRES), which is often associated with similar medications. PRES clinically manifests as

Table 2 Common MTT

Generic name	Trade name	Indications	Type	Target
Rituximab	Rituxan	Non-Hodgkin's lymphoma	Monoclonal Ab	CD20 (mature B cells)
Imatinib	Gleevac	CML, GIST, ALL	Small molecule	BCR-ABL
Gefitinib	Iressa	NSCLC	Small molecule	Tyrosine kinases, including EGFR
Erlotinib	Tarceva	Metastatic NSCLC	Small molecule	EGFR
Sorafenib	Nexavar	Advanced RCC	Small molecule	RAF kinase, c-*kit*, Flt 3, VEGFR
Panitumumab	Vectibix	Metastatic colorectal caner	Monoclonal Ab	EGFR
Sunitinib	Sutent	GIST, metastatic RCC	Small molecule	VEGFR2, c-*kit*, Flt 3
Bevacizumab	Avastin	Metastatic colorectal, NSCLC	Monoclonal Ab	VEGF
Cetuximab	Erbutix	Metastatic colorectal, squamous head and neck	Monoclonal Ab	EGFR
Dasatinib	Sprycel	CML, ALL	Small molecule	Tyrosine kinases
Temsirolimus	Torisel	Advanced RCC	Small molecule	mTOR inhibitor

CML chronic myelogenous leukemia, *ALL* acute lymphoblastic leukemia, *NSCLC* nonsmall cell lung cancer, *EGFR* epidermal growth factor receptor, *VEGF* vascular endothelial growth factor, *RCC* renal cell carcinoma

headache, nausea, and visual loss. PRES is often associated with hypertensive encephalopathy and preeclampsia [6]. It is a toxicity in patients receiving cytotoxic drugs such as bevacizumab (monoclonal antibody to vascular endothelial growth factor [VEGF]) and tyrosine kinase inhibitors targeting the VEGF pathway (sorafenib

Table 3 Treatment-related complications by drug and toxicity (non-inclusive)

Organ system and toxicity	Agent
Central nervous system	
Toxic leukoencephalopathy	Methotrexate, carmustine, cisplatin, thiotepa
PRES	Bevacizumab, sorafenib, sunitinib
Pulmonary	
Acute interstitial lung disease	Gemcitabine, oxaliplatin, methotrexate, EGFR, small molecule tyrosine kinase inhibitors [gefitinib, erlotinib], rituximab
Interstitial pneumonitis	mTor inhibitors
Pleural effusions	Imatinib, dasatinib
Pneumothorax	VEGF inhibitors
Thromboembolic (including pulmonary embolism, arterial and venous embolism in mesenteric, pelvic vessels)	Cisplatin, gemcitabine, bevacizumab, sorafenib, sunitinib
Hepatobiliary/pancreatic	
Hepatic steatosis	Irinotecan, oxaliplatin, FOLFIRI (5-FU, leucovorin, irinotecan) or FOLFOX (5-FU, leucovorin, oxaliplatin) with or without bevacizumab
Cholecystitis	Sorafenib, everolimus
Pancreatitis	L-asparaginase, sorafenib
GI	
Bowel perforation	Taxols, cytosine arabinoside, bevacizumab
Pneumatosis intestinalis	Cyclophosphamide, vincristine, bevacizumab, sunitinib, and sorafenib
Colitis	5-FU, floxuridine, irinotecan, EGFR and VEGF inhibitors
Intratumoral hemorrhage	Imatinib
MSK/soft tissue	
Subtrochanteric femoral insufficiency fractures	Bisphosphonates
Fluid retention	Docetaxel, imatinib

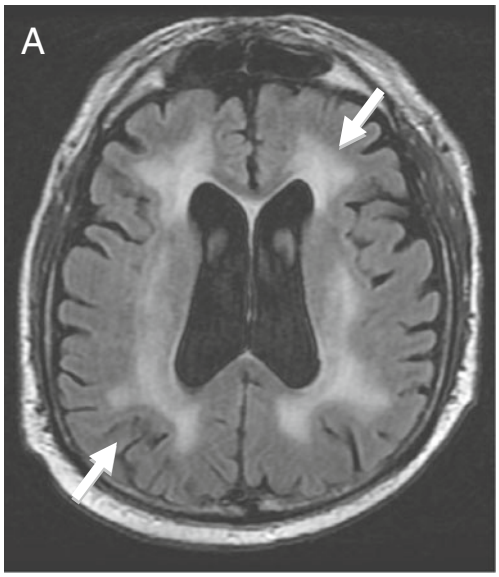

Fig. 1 A 68-year-old male with acute lymphoblastic leukemia on intrathecal methotrexate presented to the emergency room with cognitive decline and gait instability. Initial noncontrast head CT was normal (not shown). **a** Axial FLAIR T2 sequences from MRI of the brain demonstrates non-enhancing, moderate to severe diffuse periventricular white matter disease (*arrows*) consistent with acute toxic leukoencephalopathy

and sunitinib) [4, 7]. Other causative agents include tacrolimus, cyclosporine, and cisplatin. The median time to onset of PRES has been reported as 61 days with tacrolimus [7]. Brain MRI and CT will demonstrate white matter abnormalities predominately in the cortex and subcortical white matter of the occipital, posterior temporal, and parietal lobes of the brain, best appreciated on T2 fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 2) [6]. Symptoms and imaging findings may resolve spontaneously or after cessation of the treatment.

Pulmonary

Oncology patients may present to the emergency room with pulmonary symptoms such as shortness of breath, chest pain, and hypoxia. The diagnosis of drug-induced etiology is one of exclusion wherein other causes of acute lung injury such as pneumonia, alveolar hemorrhage, pulmonary edema, and metastatic disease have been excluded. A combination of clinical symptoms, radiological findings, cultures, serology, and in selected cases, bronchoalveolar lavage or open lung biopsy may be necessary to exclude alternate diagnosis. Acute interstitial lung disease and acute respiratory distress syndrome manifest on imaging as diffuse bilateral pulmonary infiltrates and may be seen in a variety of conventional chemotherapy agents and newer MTTs, such as the monoclonal antibody rituximab which is used to treat large B cell lymphoma (Fig. 3) [8].

Interstitial pneumonitis associated with mTOR inhibitors such as everolimus and temsirolimus is reported in up to 40 % of patients, although half of them are asymptomatic [9]. In rare acute cases of interstitial pneumonitis, patients present with acute shortness of breath and desaturation (Fig. 4) after initiation of treatment. Imaging findings on chest CT include ground glass and reticular pulmonary opacities. Discontinuation of the putative drug with or without treatment with steroids (after excluding infection) usually results in rapid improvement.

BCR-ABL tyrosine kinase inhibitors, namely, imatinib and dasatinib, can cause significant pleural effusions, sometimes in the absence of anasarca, which may be mistaken for progression of metastatic disease (Fig. 5) [10]. Treatment options include symptomatic relief or discontinuation of therapy and, in resistant effusions, thoracentesis may be necessary.

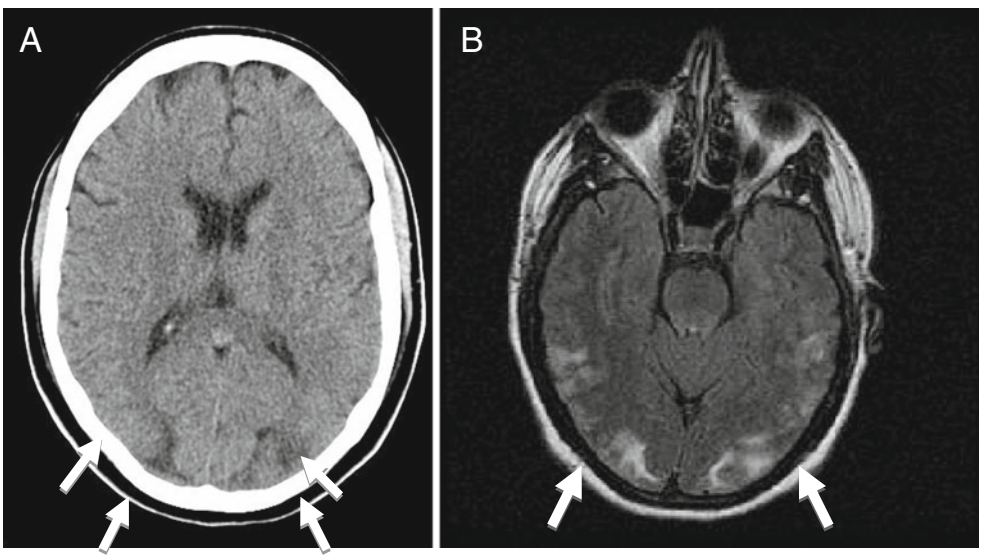

Fig. 2 A 35-year-old female with colorectal cancer on bevacizumab (Avastin) presented with altered mental status and profound occipital headache. **a** Noncontrast CT of head demonstrates hypodensities in bilateral occipital lobes (*arrows*). **b** Axial FLAIR T2 sequence from MRI of the brain shows patchy T2 hyperintense signal change within the bilateral occipitoparietal regions (*arrows*), suggestive of PRES. Symptoms spontaneously resolved

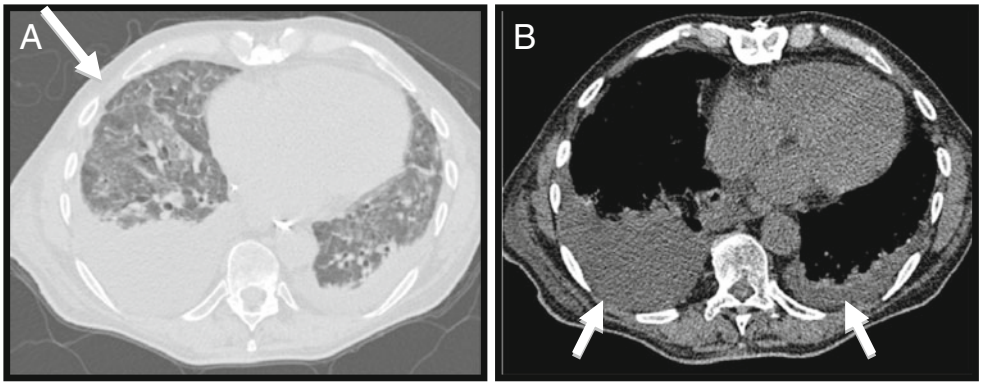

Fig. 3 A 65-year-old male with large B-cell lymphoma was admitted through the ED with respiratory failure. Infectious workup was negative. Noncontrast CT of the chest demonstrates bilateral heterogeneous ground glass opacities (**a**, *long arrow*) and bilateral pleural effusions (**b**, *shorter arrows*), suggestive of rituximab-associated acute interstitial lung disease

Spontaneous pneumothorax can occur secondary to treatment-related cavitation of subpleural pulmonary metastases, especially after anti-VEGF therapy (Fig. 6). The mechanism was thought to be secondary to central necrosis of lesions after the inhibition of angiogenesis [11, 12].

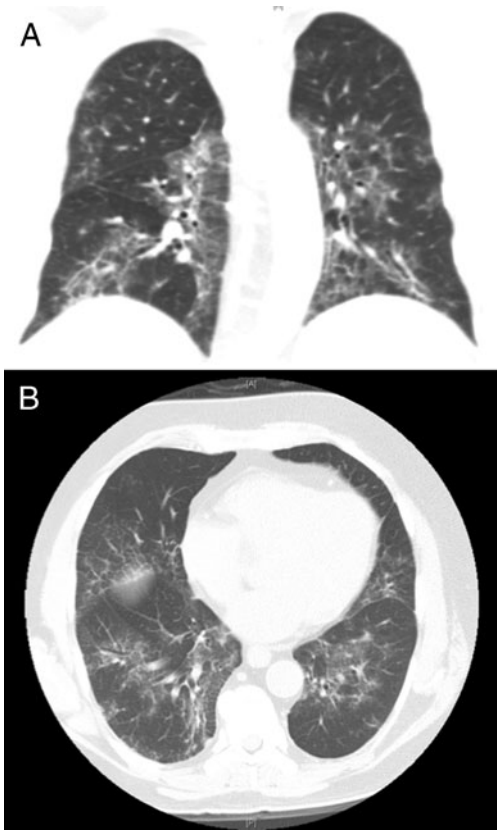

Fig. 4 A 69-year-old female with metastatic renal cell carcinoma on mTOR inhibitor therapy (temsirolimus) presented to the ED with shortness of breath, cough, and low-grade fever. Coronal (**a**) and axial (**b**) CT images demonstrate patchy ground glass and reticular opacities in a peribronchial and subpleural distribution, most striking on the coronal images. Serology, cytology, and cultures were negative for infectious process. Symptoms improved significantly following discontinuation of the drug and short course of steroids

Thromboembolic

Both venous and arterial thrombosis and thromboembolic events occur in patients treated with common chemotherapeutic and MTT regimens [13, 14]. Patients may present to the emergency room with acute symptoms corresponding with the thromboembolic event (i.e., shortness of breath with pulmonary embolism). Arterial events are of great clinical concern as they can result in end-organ infarction. The exact etiology of

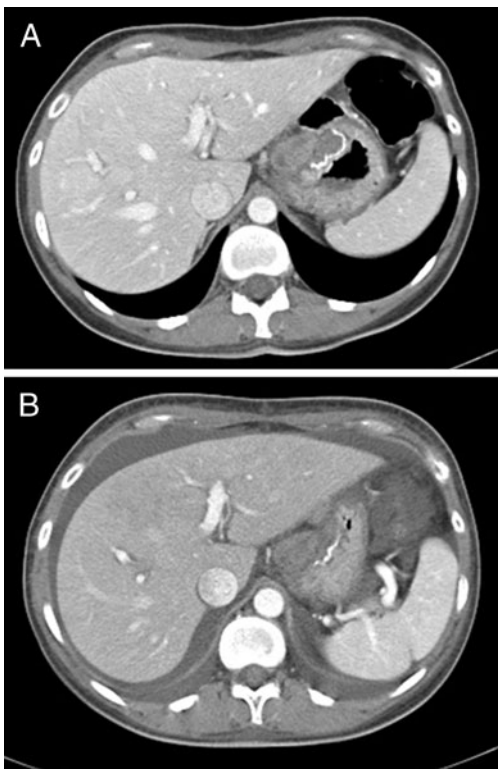

Fig. 5 A 30-year-old female with GIST who initiated treatment with sunitinib. **a** Axial contrast-enhanced CT image prior to treatment shows a soft tissue mass along the lesser curvature of the stomach representing known GIST. **b** Approximately 1 month after initiating treatment with sunitinib, repeat axial contrast-enhanced CT demonstrates new pleural effusions and small-volume perihepatic ascites. Patient was treated symptomatically with furosemide

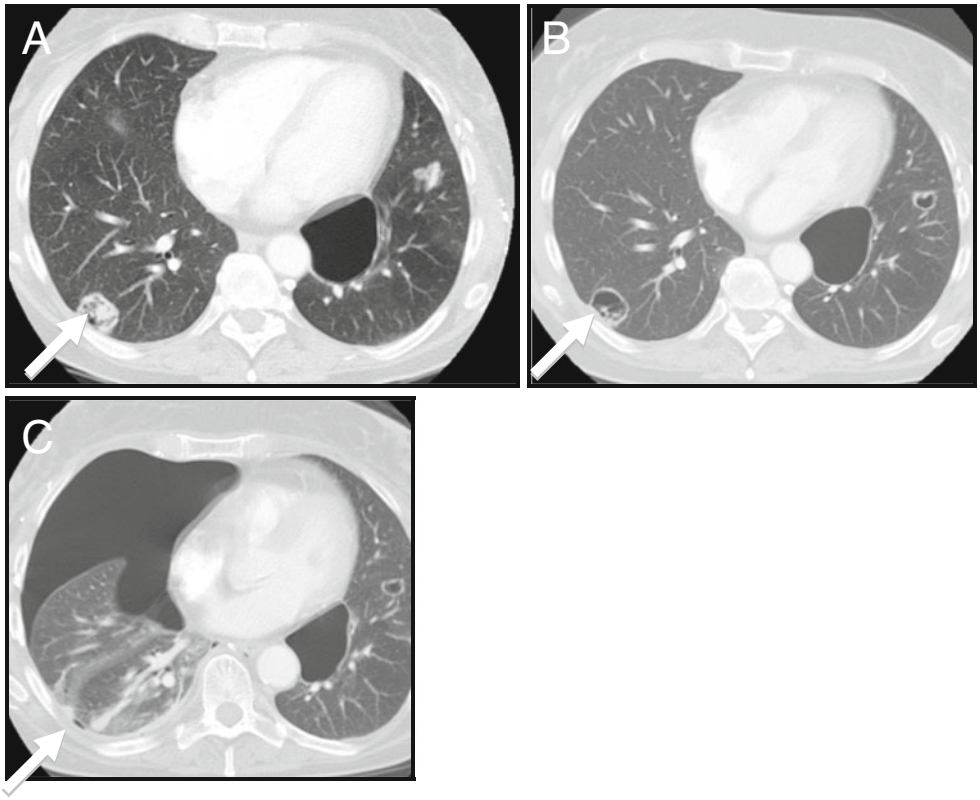

Fig. 6 A 74-year-old male with metastatic colorectal cancer on VEGF inhibitor presented to the ED in December 2010 with acute shortness of breath and chest pain. Axial CTs of the chest were obtained. In August 2010, the patient was asymptomatic, with right lower lobe subpleural nodule (**a**, *arrow*); follow-up imaging in October 2010 demonstrates slight internal cavitation of the lesion (**b**, *arrow*) In December 2010, there is a new right-sided pneumothorax (**c**, *arrow*) secondary to rupture of the peripheral metastatic cavitary pulmonary lesion after treatment. Management included chest tube placement (not shown)

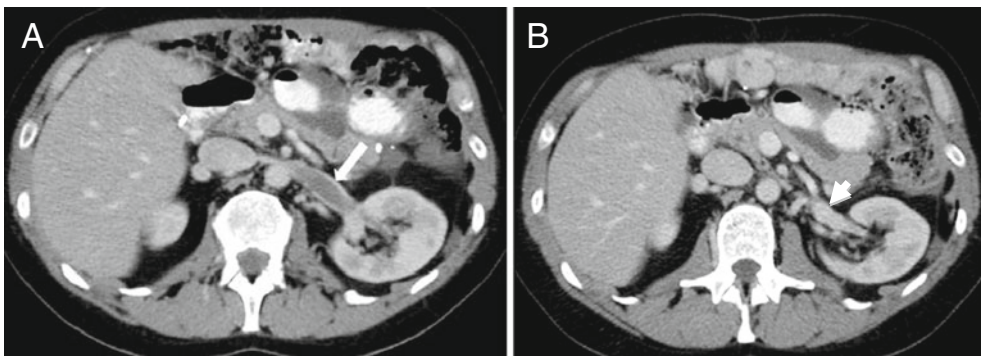

Fig. 7 A 45-year-old man with metastatic well-differentiated mucinous appendiceal adenocarcinoma on FOLFIRI and bevacizumab developed mild dull left upper quadrant pain. Contrast-enhanced CT of the abdomen was performed, demonstrating left renal vein thrombosis (**a**, *arrow*). The left kidney was well-perfused with no delayed nephrogram. The patient was anticoagulated and bevacizumab was discontinued. Three-month follow-up CT demonstrates near resolution of renal vein thrombosis (**b**, *arrowhead*)

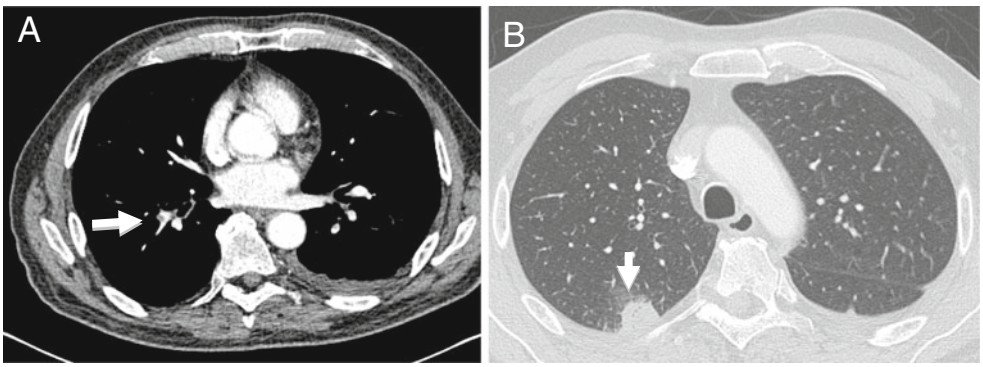

Fig. 8 A 73-year-old male with metastatic renal cell cancer on bevacizumab presented with shortness of breath and chest pain to the ED. Contrast-enhanced chest CT demonstrates segmental right upper lobe pulmonary embolism (**a**, *arrow*) with associated pulmonary infarct (**b**, *shorter arrow*). Bevacizumab was discontinued and patient was treated with low molecular weight heparin

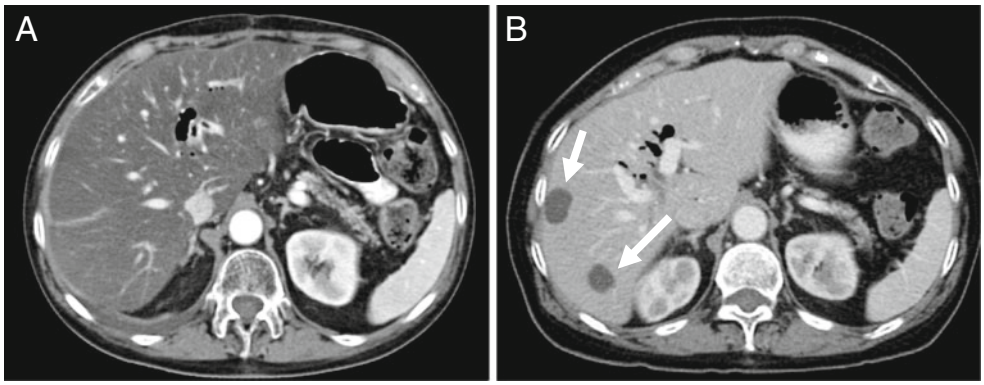

Fig. 9 A 77-year-old female with metastatic pancreatic cancer on oxaliplatin presented to the ED with right upper quadrant pain; patient has prior history of sphincterotomy with expected pneumobilia. Contrast-enhanced CT of the abdomen at the time of presentation reveals severe hepatic steatosis (**a**). After discontinuation of oxaliplatin, hepatic steatosis has resolved. Decreased liver attenuation of steatosis made lower attenuation liver metastases difficult to evaluate (**b**, *arrows*)

these thromboembolic events is unknown, but is likely multifactorial given the patient's underlying hypercoagulable state in malignancy, immobility, indwelling lines, as well as vascular and endothelial damage from antineoplastic agents [8]. In particular, cisplatin and gemcitabine have been associated with thromboembolic events [15, 16]. Anti-VEGF therapy, given VEGF's role in integrity of vascular endothelium, has been shown to increase the frequency of thromboembolic events including pulmonary embolism and thrombus formation in the aorta, arteries, and veins of the pelvis, mesentery, and extremities (Figs. 7 and 8) [14]. Management includes discontinuation of the agent and treatment as per accepted medical guidelines. Follow-up surveillance imaging has been recommended for patients' taking antiangiogenic drugs to evaluate for the development of multiorgan infarction and peripheral arterial/venous thromboemboli [8].

Hepatobiliary/pancreatic

Oncology patients often present to the ED with right upper quadrant pain. Hepatic steatosis occurs in nearly 50 % of patients undergoing treatment with certain chemotherapeutic agents [17]. The entity has been reported in patients on the chemotherapeutic agents oxaliplatin and irinotecan as well as combination chemotherapy regimens such as FOLFIRI (5-fluorouracil [5-FU], leucovorin, irinotecan) or FOLFOX (5-FU, leucovorin, oxaliplatin) with or without bevacizumab (monoclonal antibody) [18, 19]. Hepatic steatosis may cause hepatomegaly, and given how fast the hepatomegaly develops, there will be abdominal discomfort/pain secondary to liver capsule distention. Imaging characteristics include diffuse or focal increase in hepatic echotexture on ultrasound or hypodense liver parenchyma when compared to the spleen on CT (Fig. 9). Decreased liver attenuation secondary to hepatic steatosis may make lower attenuation liver metastases difficult to delineate [19].

Another etiology of right upper quadrant pain includes acalculous cholecystitis, most often seen in critically ill patients following trauma or major surgery. Although a rare complication, cholecystitis has been associated with tyrosine kinase inhibitors and mTOR inhibitors such as everolimus [20, 21]. Sorafenib, a molecular targeted agent used

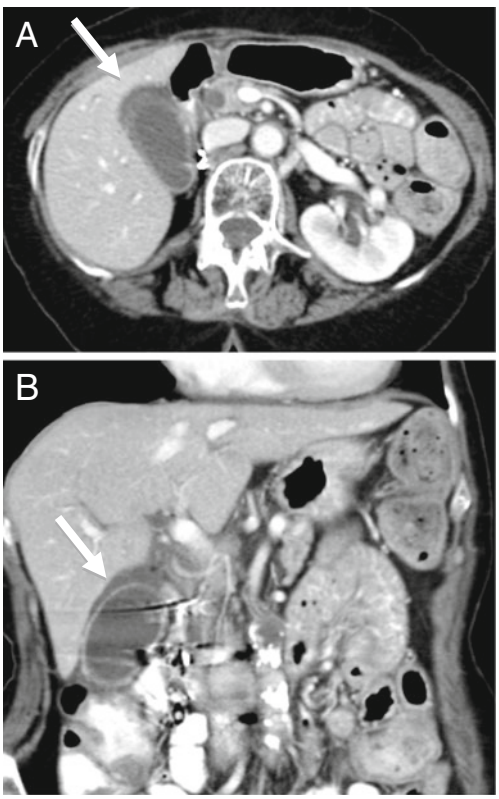

Fig. 10 A 58-year-old female with history of metastatic renal cell carcinoma presented with epigastric pain. Patient was being treated with sorafenib. Axial (**a**) and coronal (**b**) images from a contrast-enhanced CT performed the day of presentation revealed pericholecystic fluid (*arrows*). No gallstones were seen on CT or ultrasound (not shown). Given the patient's mild symptoms, conservative therapy was utilized to good effect

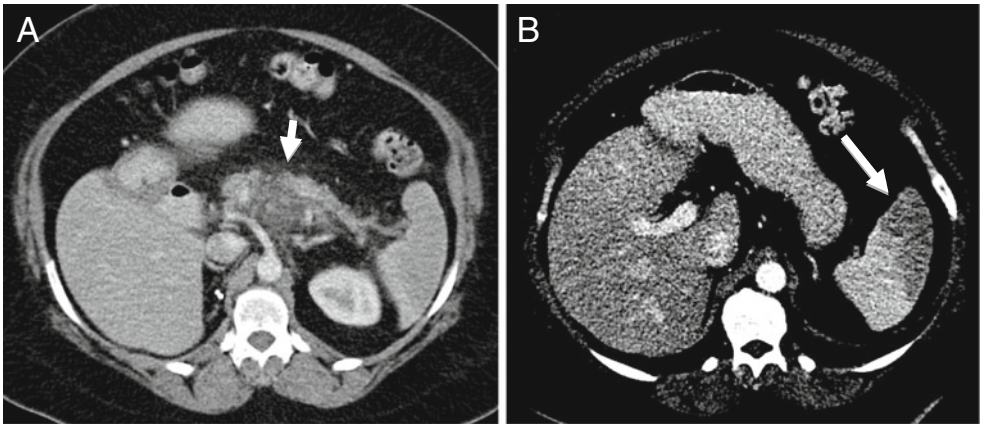

Fig. 11 A 57-year-old female with metastatic renal cell carcinoma presented with abdominal pain. **a** Axial CT image in soft tissue windows demonstrate ill-defined peripancreatic fat stranding and mild enlargement of the pancreas (*short arrow*), consistent with sunitinib-induced pancreatitis. **b** Axial image in liver window demonstrates low attenuation within the anteroinferior aspect of the spleen (*long arrow*), likely associated splenic infarction

in renal cell carcinoma, has been shown to cause acalculous cholecystitis in patients without any other predisposing factor (Fig. 10) [22]; the mechanism is thought to be secondary to vascular endothelial damage and reduction in gallbladder blood flow. Treatment depends on the severity of symptoms; conservative treatment with discontinuation of the offending agent and broad-spectrum antibiotics has been effective, although surgical treatment and/or cholecystostomy tube placement may be indicated.

Acute pancreatitis is a common side effect of chemotherapeutic agents [23]. It is less common in patients on MTT regimens (reportedly <4 %), despite the fact that tyrosine kinase inhibitors have been reported to elevate amylase and lipase levels in up to 50 % of patients [22, 24, 25]. Imaging CT features include diffuse pancreatic enlargement with peripancreatic inflammatory fat stranding (Fig. 11) and have been reported to manifest 3–4 weeks after initiating therapy. Differentiating acute pancreatitis secondary to therapeutic agents from other causes is generally not possible with imaging alone. Symptoms and corresponding imaging findings usually resolve after termination of the instigating agent.

Gastrointestinal

Numerous chemotherapy-induced and MTT-related GI complications may occur at any time during cancer treatment.

Bowel perforation can be a surgical emergency, requiring immediate operative intervention. Patients with bowel perforation present with nausea, vomiting, and an acute abdomen (peritoneal symptoms). Imaging findings on CT include frank pneumoperitoneum or localized extraluminal locules of air. The etiology of bowel perforation may be secondary to spontaneous tumor rupture (infiltrating tumors), neoplastic ulceration, tumor necrosis

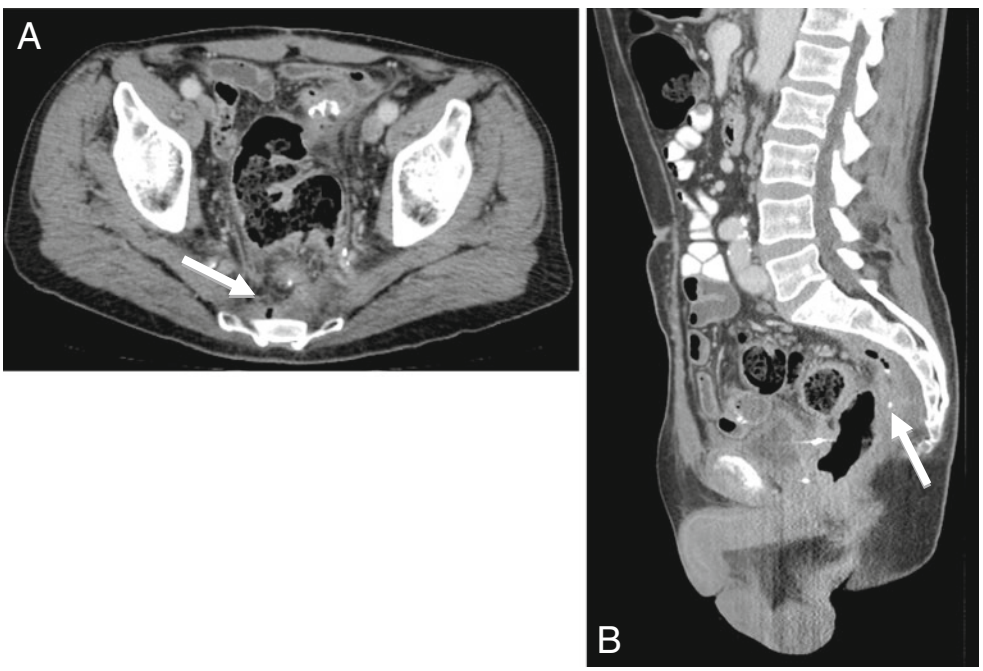

Fig. 12 A 68-year-old male with rectal cancer, status post lower anterior resection, and recently completed three cycles of FOLFIRI and bevacizumab presented with lower back pain. Contrast-enhanced axial (**a**) and sagittal (**b**) CT demonstrates locules of air in presacral soft tissue (air-containing abscess) compatible with anastomotic breakdown (*arrows*)

occurring secondary to therapy, or drug-induced perforations [26]. The exact mechanism of drug-induced MTT-associated bowel perforation is unknown. Several mechanisms have been proposed, including anti-VEGF effects compromising bowel wall integrity, intestinal wall disruption due to necrosis of the serosal tumor deposits, impaired healing of pathologic or surgical bowel injury, and ischemia related to mesenteric thrombosis (in case of bevacizumab) [8].

Treatment agents with an increased incidence of bowel perforation include taxol, cytosine arabinoside, and monoclonal antibodies such as bevacizumab (recombinant humanized monoclonal antibody targeted against VEGF) used for colorectal, lung, and renal cancers [26–29]. Perforations secondary to bevacizumab may occur at the surgical anastomosis, sites of residual malignancy, or uninvolved GI lumen affected by ulcerations (Fig. 12). Other antiangiogenic agents implicated in bowel perforations include sunitinib and sorafenib [28]. Treatment includes permanent discontinuation of the offending agent and, depending on clinical status, either surgical intervention or conservative treatment with antibiotics and bowel rest.

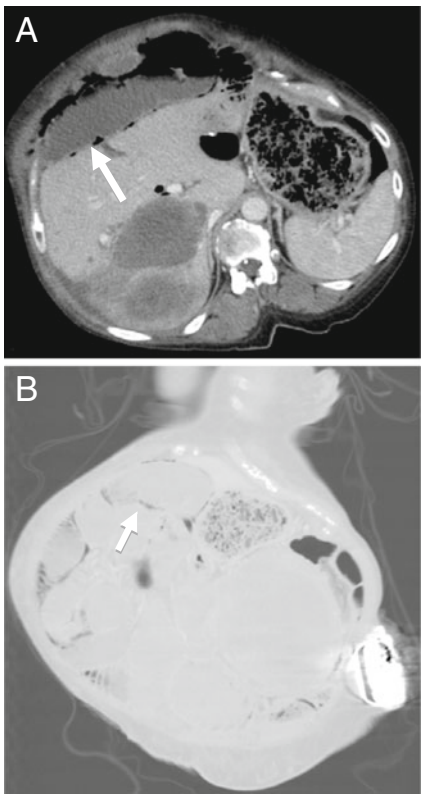

Fig. 13 A 52-year-old female with GIST on sorafenib developed abdominal discomfort. **a** Axial and **b** coronal reformatted contrast-enhanced CT of the abdomen shows pneumatosis (*arrows*) and pneumoperitoneum (not shown). Sorafenib was discontinued immediately, and the patient was placed on bowel rest. The patient's symptoms resolved following conservative management alone

Pneumatosis intestinalis occurs secondary to cytotoxic damage to GI mucosa as well as increased mucosal permeability. The patient may be asymptomatic with pneumatosis found incidentally during routine imaging; it has been reported in patients receiving bevacizumab, sunitinib, and sorafenib [30–32]. Chemotherapeutic agents associated with pneumatosis intestinalis include cyclophosphamide and vincristine [17]. Imaging CT findings include subserosal and submucosal gas-filled cysts in the GI tract with or without pneumoperitoneum (Fig. 13). It is important to differentiate benign pneumatosis intestinalis from ischemic colitis, which presents with associated CT findings of altered mucosal enhancement, bowel dilation and wall thickening, and portal venous gas. Treatment for uncomplicated cases includes cessation of the offending agent and close monitoring.

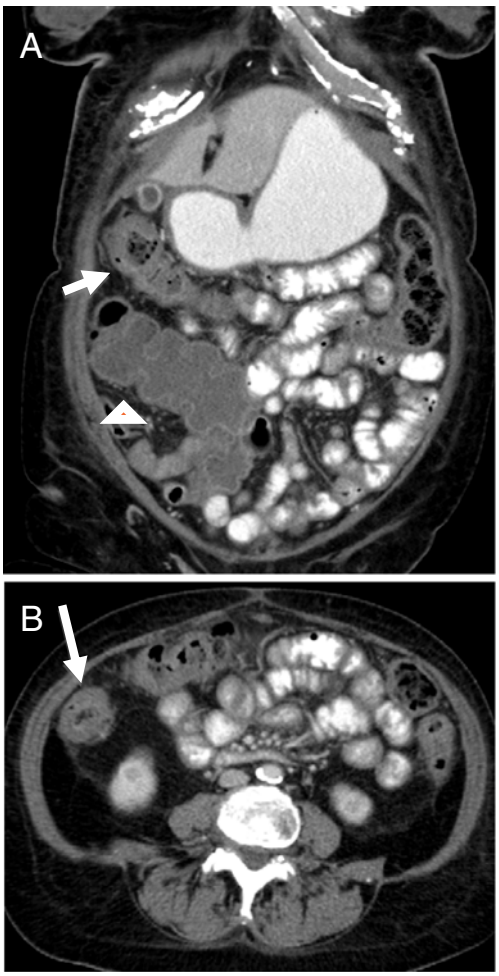

Fig. 14 An 81-year-old female with metastatic GI tumor presented with diarrhea and abdominal pain; the patient had been treated with sorafenib. Contrast-enhanced coronal (**a**) and axial (**b**) CT demonstrates bowel wall thickening (*long arrow*), adjacent fat stranding (*short arrow*), and fluid-filled distended bowel lumen (*arrowhead*), consistent with colitis. Sorafenib was temporarily discontinued and colitis resolved

Patients presenting with enteritis and colitis often complain of diffuse or focal abdominal pain, nausea, and diarrhea. CT imaging of colitis will demonstrate bowel wall thickening, adjacent fat stranding, and fluid-filled distended bowel lumen (Fig. 14). Implicated agents include common chemotherapeutic drugs such as 5-FU, floxuridine, irinotecan, as well as less frequently, newer MTT regimens including cetuximab, epidermal growth factor receptor (EGFR) agents, and VEGF targeted agents [8]. For more common chemotherapeutic agents, the mechanism is secondary to nontargeted toxic effects on rapidly proliferating GI cells; the mechanism of MTT regimens is less well-known.

Intratumoral hemorrhage

Intratumoral hemorrhage secondary to treatment can occur at any site and patients may present with acute onset of severe pain at the site of tumoral hemorrhage. Large, bulky tumors have a higher propensity of hemorrhage and may require surgical intervention [33]. Hemoglobin drops of more than 2 g/dl may prompt treatment cessation [33]. The tyrosine kinase inhibitor imatinib has been associated with intratumoral hemorrhage in patients' with gastrointestinal stromal tumors (GIST) [33–35]. Imaging findings on non-contrast CT may demonstrate fluid–fluid levels within previously homogenous lesions with interval enlargement in lesion size (Fig. 15). Caution should be taken as enlargement of lesions secondary to intratumoral hemorrhage may be misconstrued as progression of disease [33, 35] (Fig. 12).

Musculoskeletal and soft tissue

Bisphosphonate therapy is used as an adjunct to chemotherapy to prevent bone loss, particularly in those patients with prostate, multiple myeloma, and breast cancer. Increasingly described in the literature are subtrochanteric bisphosphonate-associated insufficiency fractures [36, 37]. On plain radiograph imaging, these fractures initially present as cortical thickening (termed "bump" or "beak") along the lateral or tension side of the proximal subtrochanteric femur, eventually

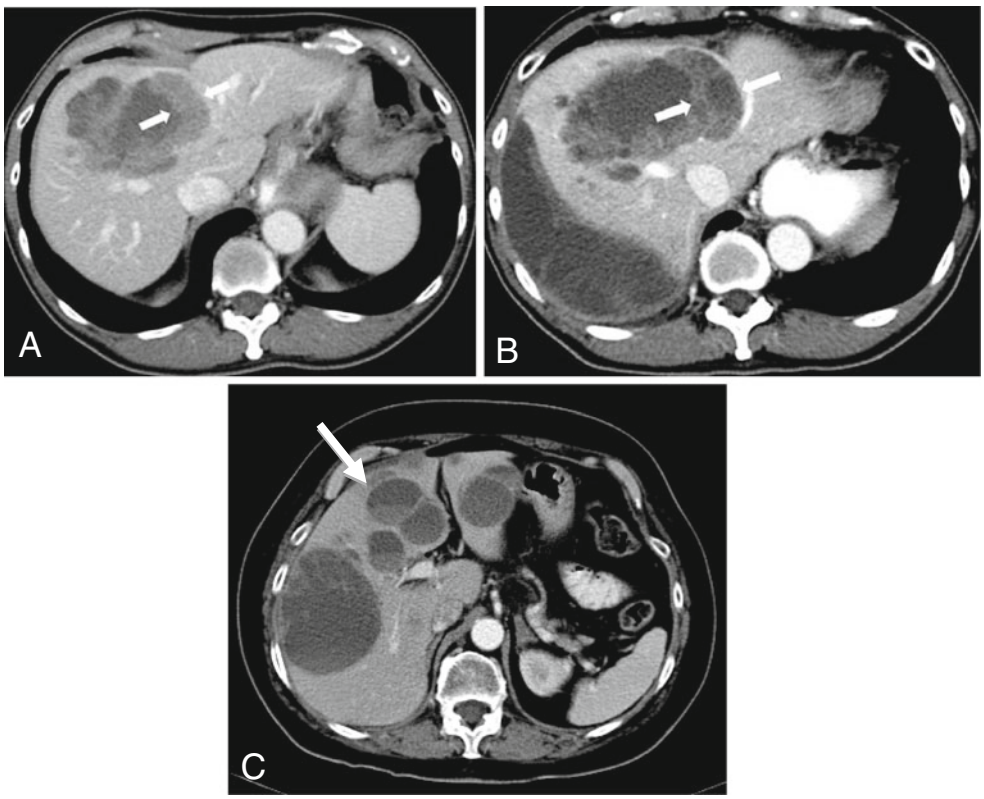

Fig. 15 A 63-year-old man with metastatic GIST on sunitinib. **a** Pretreatment axial contrast-enhanced CT of the abdomen shows a large low attenuation metastasis in segment 8 of the liver. *Arrows* point to the enhancing soft tissue component of the liver metastasis. During the course of the therapy, the patient developed severe acute right upper quadrant pain, and **b** axial contrast-enhanced CT of the abdomen shows increase in size of the liver metastasis due to internal hemorrhage. Note that the solid component medially in the mass has decreased in keeping with response to treatment (*arrows*). There is no active extravasation of contrast to suggest active hemorrhage at the time of the CT. The patient was admitted to the hospital for close observation and pain management. A complete blood count was checked every 6 h and the patient remained hemodynamically stable with stable hematocrit. Sunitinib was discontinued while the patient remained an inpatient. **c** Axial contrast-enhanced CT of a different patient shows fluid–fluid levels in liver metastases (*arrow*) after treatment, another manifestation of intratumoral hemorrhage

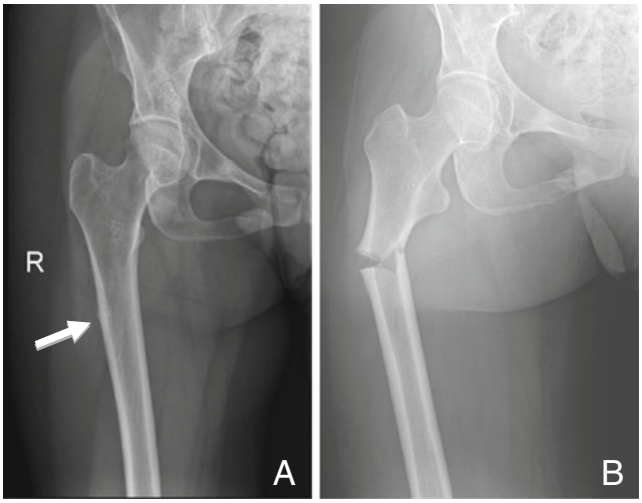

Fig. 16 A 71-year-old female with history of breast cancer presents with vague right hip pain and no history of trauma. Plain radiograph demonstrates subtle cortical thickening (termed "bump" or "beak") along the lateral or tension side of the proximal femur (**a**, *long arrow*), consistent with subtrochanteric bisphosphonate-induced insufficiency fracture. This eventually progressed to a complete transverse fracture (**b**). Patient was treated with open reduction and internal fixation with intramedullary rod (not shown)

progressing to a complete fracture (Fig. 16). Patients with fractures associated with long-term bisphosphonate use often report minimal or no significant trauma history and symptoms of vague discomfort and thigh pain [36]. The etiology of these fractures is thought to be secondary to abnormal bone remodeling from prolonged osteoclast suppression in the subtrochanteric femoral shaft [36]. The fractures are often bilateral, and therefore, it is advisable to obtain radiographs of the contralateral femur to assess clinically silent fractures. Management options include bisphosphonate discontinuation, a trial of nonweight bearing, and/or prophylactic placement of intramedullary fixation rod [38].

Dramatic fluid retention has been documented in nearly 80 % of patients receiving imatinib (a small molecule tyrosine kinase inhibitor), manifesting in patients with pleural effusions, diffuse anasarca, skin thickening, and ascites (Fig. 5) [10]. These findings may be mistaken for peritoneal disease. Fluid retention is thought to be secondary to capillary leak syndrome [8]. The symptoms are dose-dependent and increase with advanced patient age [10]. Treatment includes supportive care of diuretics and salt restriction; however, discontinuation of offending agent may be indicated if symptoms do not resolve in a timely manner.

Conclusion

Recent advances in chemotherapeutic and newer MTT regimens continue to revolutionize care of cancer patients. Given the increased use of new MTTs as well as common chemotherapeutic agents, treatment-related complications may present as both common and uncommon imaging entities. It is important for radiologists to be familiar with these drug toxicities to ensure appropriate and timely patient management in the emergency setting.

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