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Decade of Molecular Targeted Therapy: Abdominal Manifestations of Drug Toxicities—What Radiologists Should Know

Stephanie Anne Holler Howard[1]
Katherine M. Krajewski
Eavan Thornton
Jyothi P. Jagannathan
Kevin O'Regan
James Cleary
Nikhil Ramaiya

OBJECTIVE. Novel drugs targeting molecular pathways involved in tumor development have revolutionized cancer treatment. Radiologists often focus on therapeutic response when evaluating cancer patients and may miss important signs of drug toxicity. This article familiarizes radiologists with the complications of molecular targeted agents in abdominal solid organs, enabling early identification and appropriate intervention and thus reducing patient morbidity and mortality.

CONCLUSION. Knowledge of the common abdominal toxicities—including hepatitis, cholecystitis, pancreatitis, fluid retention, and infection—is crucial for early diagnosis, which may spare patients devastating complications or the need for surgery.

Molecular targeted therapeutics attack proteins essential for a cancer cell's survival. Radiologists often focus on therapeutic response when analyzing cancer patients' scans, but they also need to be aware of the frequent use of molecular targeted agents and to actively look for clues of toxicity. Molecular therapies came of age when the U.S. Food and Drug Administration (FDA) approved imatinib mesylate in 2001 for the treatment of chronic myeloid leukemia, a cancer whose survival depends on the product of the Philadelphia translocation: the *BCR-ABL* transgene. Imatinib mesylate, a tyrosine kinase inhibitor, turns off *BCR-ABL*, thereby dramatically increasing survival of patients with chronic myeloid leukemia [1]. Since then, multiple agents have been developed targeting cell surface growth factor receptors and signal transduction proteins that transmit growth and survival signals to the cell nucleus. Table 1 summarizes frequently used molecular targeted agents and their common side effects.

Several FDA-approved therapies inhibit cell surface growth factor receptors and intracellular signal transduction proteins. Epidermal growth factor receptor is targeted in lung, head and neck, and colorectal cancers by multiple FDA-approved therapies including erlotinib, which has revolutionized the treatment of lung cancer [1]. Angiogenesis inhibitors, such as bevacizumab and sunitinib malate, inhibit the growth of new blood cells to cancers by preventing activation of the vascular endothelial growth factor pathway [1]. Inhibitors of the mammalian target of rapamycin (mTOR), including everolimus, block mTOR and have been approved by the FDA for the treatment of renal cell cancer [1]. Immune modulators, such as ipilimumab, provoke an immune response attacking cancer cells; ipilimumab was approved for use in melanoma in 2011 [2].

This article discusses abdominal toxicities of specific groups of molecular targeted therapies by organ and the systemic toxicities of fluid retention and infection.

Liver

Molecular targeted therapies may cause hepatic toxicity—notably, hepatitis and steatosis [3, 4]. Both tyrosine kinase inhibitors and immune modulators have been implicated in the development of hepatitis [2, 3]. Asymptomatic elevations of serum alanine aminotransferases have been reported in 4% of patients treated with erlotinib [5]. Fulminant hepatic failure is a very rare but fatal complication [6]. Ipilimumab, an immune modulator, causes hepatitis as an immune-related adverse event in fewer than 5% of patients. This complication often presents as asymptomatic elevation of liver function test results that typically resolves on discontinuation of therapy [2]. Imaging findings of hepatitis (Figs. 1 and 2) include alteration in hepatic echogenicity and attenuation, gallbladder wall thickening, ascites, and periportal low attenuation.

Keywords: abdominal toxicities, bevacizumab, drug, molecular targeted therapy, targeted therapy, toxicity

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[1]All authors: Department of Imaging, Dana Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02115. Address correspondence to S. A. H. Howard (sahoward@partners.org).

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TABLE 1: Potential Side Effects of Frequently Used Molecular Targeted Agents

Mechanism of Action, Generic Name	Brand Name, Manufacturer	Potential Side Effect(s) Noted in Some Drugs With This Mechanism of Action
Multitargeted tyrosine kinase inhibitor		Pancreatitis, fluid retention
Imatinib mesylate	Gleevec, Novartis	
Nilotinib	Tasigna, Novartis	
VEGF inhibitor		Steatosis, pancreatitis, cholecystitis, infection
Bevacizumab	Avastin, Genentech	
Multitargeted tyrosine kinase inhibitor with VEGF inhibition		Steatosis, pancreatitis, cholecystitis, infection
Pazopanib	Votrient, GlaxoSmithKline	
Sorafenib	Nexavar, Bayer HealthCare	
Sunitinib malate	Sutent, Pfizer	
Epidermal growth factor receptor inhibitor		Hepatitis
Erlotinib	Tarceva, Genentech	
Gefitinib	Iressa, AstraZeneca	
mTOR inhibitor		Cholecystitis
Everolimus	Afinitor, Novartis	
Immune modulator		Hepatitis
Ipilimumab	Yervoy, Bristol-Myers Squibb	

Note—VEGF = vascular endothelial growth factor, mTOR = mammalian target of rapamycin.

Development of hepatic steatosis in patients on combination chemotherapy with bevacizumab and with conventional regimens, such as "FOLFIRI" (5-fluorouracil [5-FU], leucovorin, irinotecan) or "FOLFOX" (5-FU, leucovorin, oxaliplatin), has been reported [4]; however, the hepatoxicity of irinotecan and oxaliplatin is well known, and hepatic steatosis cases may be attributed to these drugs. Case reports have documented steatosis and hepatitis in patients receiving molecular targeted therapies alone, including pazopanib and bevacizumab, and in combination with chemotherapeutic agents not typically associated with hepatic toxicity, such as paclitaxel [3, 4]. Given that steatosis may progress to steatohepatitis with inflammation, cell injury, or fibrosis accompanying fatty liver, correlation with hepatic enzyme levels on recognition of fatty liver is essential [7].

Steatosis may be suggested sonographically if the hepatic echogenicity exceeds that of the renal cortex, if there is poor delineation of the intrahepatic architecture, if the ultrasound wave is significantly attenuated, or if there is loss of definition of the hemidiaphragm [7]. Steatosis may be suggested on unenhanced CT when the attenuation (in Hounsfield units) of the affected liver drops to 10 HU less than the attenuation value of the spleen [7] (Fig. 3). Fatty liver is suggested on MRI if there is a loss of signal intensity on opposed-phase images in comparison with in-phase imaging or if there is signal loss after application of fat-saturation sequences [7].

Pancreas

Tyrosine kinase inhibitors can elevate serum amylase and lipase levels in up to 50% of patients [8, 9]. Acute pancreatitis, however, occurs rarely in patients taking these drugs [10]. Painless acute pancreatitis has been reported in a patient on sorafenib who presented only with fever; pancreatitis was diagnosed on the basis of CT findings of an edematous pancreas with peripancreatic inflammation and extremely elevated amylase and lipase levels [8]. Investigators have hypothesized that pancreatic ischemia from the antiangiogenic effect of the targeted agent is partly responsible for the pancreatic inflammation [10]. Pancreatitis typically resolves when the tyrosine kinase inhibitor is discontinued. CT findings include edematous pancreas with focal or diffuse peripancreatic inflammation (Figs. 4 and 5).

Gallbladder

Acute cholecystitis is a rare complication reported with the use of tyrosine kinase and mTOR inhibitors, specifically everolimus [11, 12]. These drugs may foster the development of cholecystitis by producing local endothelial injury and gallbladder ischemia [11]. Imaging findings include gallbladder wall thickening, wall edema or hyperemia, and pericholecystic fluid (Fig. 6). Conservative treatment, including discontinuation of the offending agent along with broad-spectrum antibiotics, has often led to complete symptomatic resolution [11, 12]; however, on occasion, surgical or interventional therapy may be required [13].

Fluid Retention

Tyrosine kinase inhibitors have been associated with fluid retention, with 80% of patients on imatinib mesylate developing edema of varying degrees [14]. Advanced age, low serum albumin level at baseline, and female sex increase the risk of developing edema, and the severity appears to be dose dependent [14]. Fluid retention on imaging manifests as pleural effusions, ascites, subcutaneous edema, and skin thickening (Fig. 7). Diuretics and dietary salt restriction may improve symptoms; however, in refractory cases, dose reduction or drug discontinuation may be necessary. Recognition of these findings as toxicity is essential so that fluid retention is not mistaken for peritoneal disease.

Infection

Abscesses have been reported in patients receiving treatment with antiangiogenic agents and sometimes occur within a metastasis [15]. Investigators have speculated that the necrotic focus at the site of the treated metastasis may create an anaerobic environment predisposed

to developing an abscess [15]. Detection of new gas within a metastasis with or without new rim enhancement should raise suspicion for abscess development in a patient with unexplained fever or pain or with increased WBC count (Figs. 8 and 9).

Conclusion

Molecular targeted therapies are revolutionizing cancer treatment. Knowledge of the common abdominal toxicities—including hepatitis, cholecystitis, pancreatitis, fluid retention, and infection—is crucial for early diagnosis, which may spare patients devastating complications or the need for surgery.

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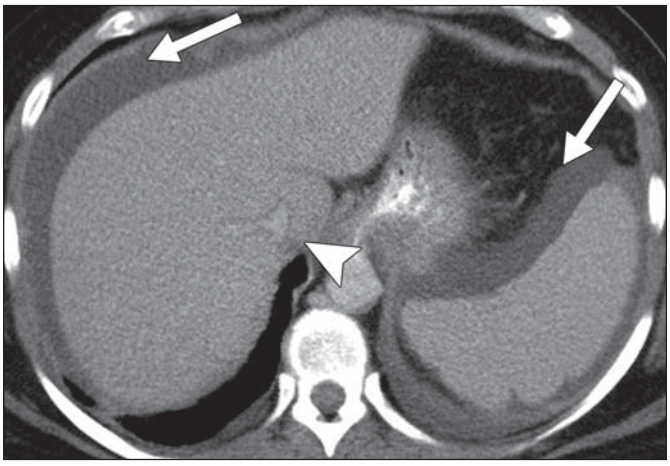
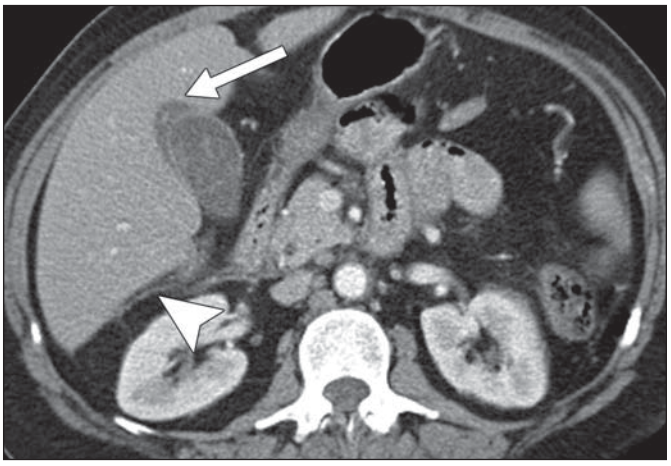


A



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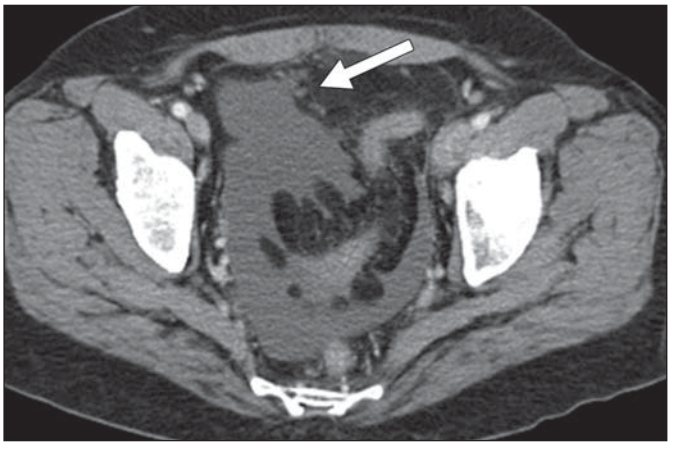


C

Fig. 1—71-year-old woman who presented with painless jaundice 2 months after initiation of erlotinib therapy. Although liver function test results were normal before treatment, values were elevated at presentation.
A, Axial contrast-enhanced CT image obtained at level of liver shows perihepatic and perisplenic ascites (*arrows*) and mild perivascular edema (*arrowhead*).
B, Axial CT image obtained more inferiorly than **A** reveals pericholecystic fluid (*arrow*). Arrowhead = indicates small volume peritoneal fluid.
C, Axial CT image of deep pelvis shows small- to moderate-volume ascites (*arrow*). All findings were new compared with pretreatment CT (not shown). Hepatic parenchymal biopsy revealed marked active hepatitis bridging to submassive hepatocyte necrosis without viral cytologic changes or evidence for malignancy; these findings are consistent with severe drug toxicity.

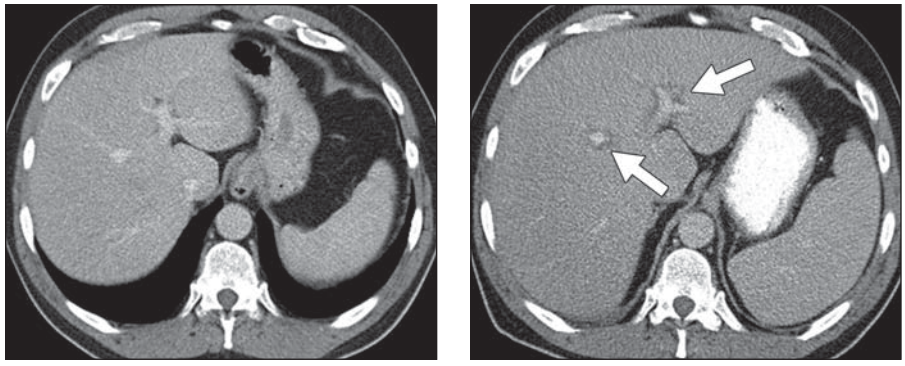


Fig. 2—58-year-old man with metastatic melanoma treated with ipilimumab.
A, Initial pretreatment CT image obtained with oral and IV contrast media at level of liver is unremarkable; pretreatment liver function test results were normal.
B, Two months after initiation of treatment, patient developed flulike symptoms. Axial CT image obtained with oral and IV contrast media at level of liver reveals interval development of periportal edema and hepatosplenomegaly (*arrows*). Liver function test results were elevated. Hepatic biopsy revealed severe active hepatitis with foci of confluent necrosis; these findings are consistent with drug-induced hepatitis.

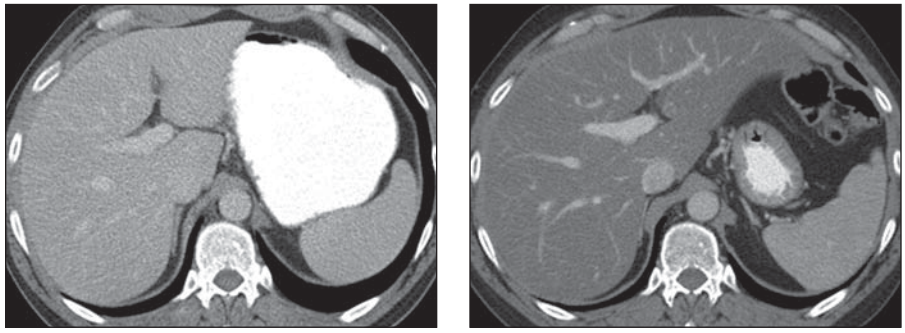


Fig. 3—43-year-old man with history of gastrointestinal stromal tumor who was started on single-agent sorafenib.
A, Axial contrast-enhanced CT image obtained before initiation of therapy reveals normal-appearing liver (attenuation: liver, 81 HU; spleen, 86 HU).
B, Axial contrast-enhanced CT image obtained after more than 1 year of treatment with sorafenib reveals severe steatosis (attenuation: liver, 26 HU; spleen, 86 HU).

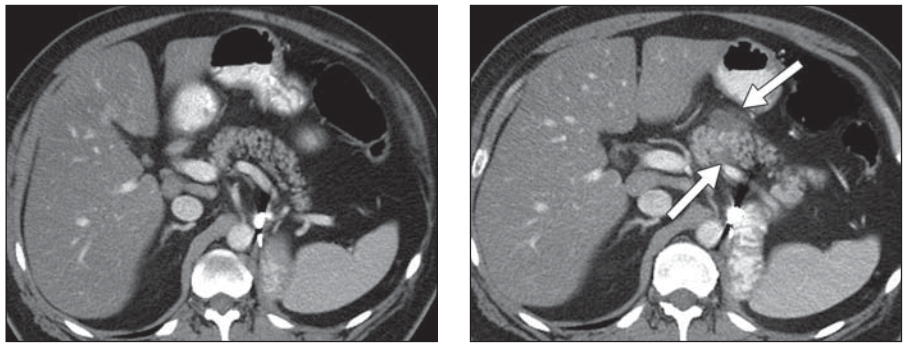


Fig. 4—54-year-old man with metastatic renal cell carcinoma.
A, Pretreatment axial CT image obtained with oral and IV contrast media at level of pancreas shows normal findings. Patient then received pazopanib.
B, After 3 months of treatment, patient developed nausea and vomiting. Symptoms lasted for approximately 3 weeks at which point drug was stopped. Axial CT image obtained with oral and IV contrast media reveals focal fluid and fluid stranding (*arrows*) at proximal pancreatic body; these findings are consistent with focal pancreatitis. Symptoms resolved with drug cessation.

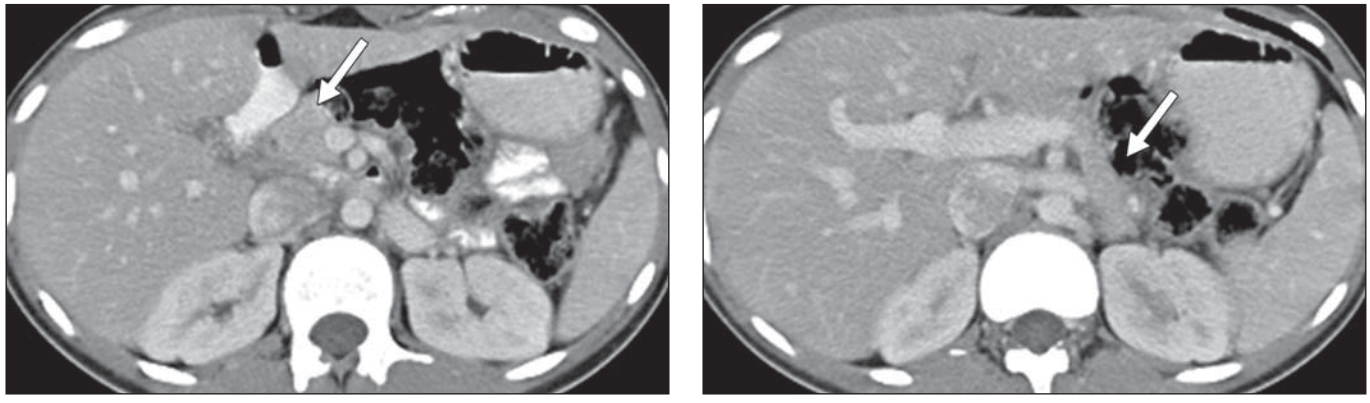
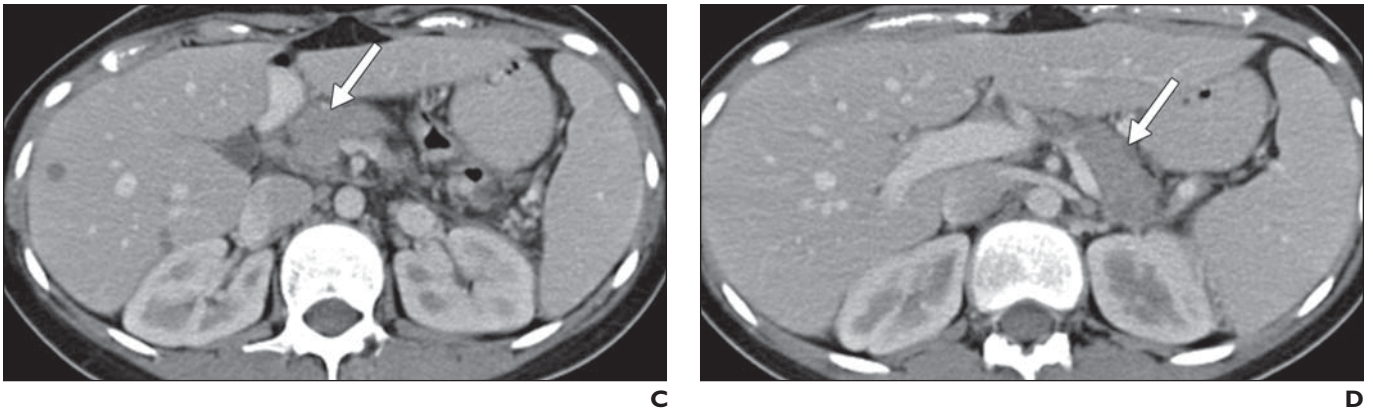


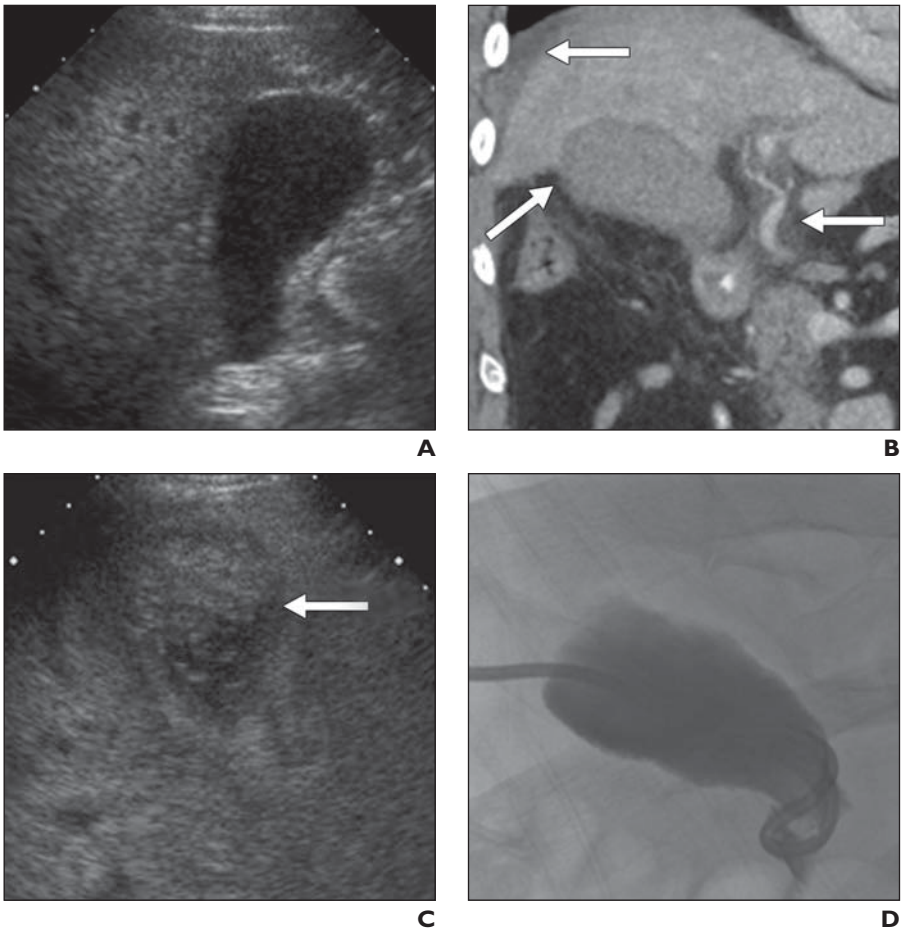
Fig. 5—19-year-old woman with history of metastatic gastrointestinal stromal tumor who was being treated with nilotinib.
A and **B,** Pretreatment axial CT images obtained with oral and IV contrast media at level of pancreatic head (**A**) and pancreatic body and tail (**B**) reveal unremarkable pancreatic parenchyma (*arrows*). Pancreatic body measures 6 mm in greatest width.

(Fig. 5 continues on next page)



C D

Fig. 5 (continued)—19-year-old woman with history of metastatic gastrointestinal stromal tumor who was being treated with nilotinib.
C and **D,** While on nilotinib, patient presented with nausea and abdominal pain and underwent CT; images were obtained using same timing as **A** and **B.** Axial CT images obtained with oral and IV contrast media at level of pancreatic head (**C**) and pancreatic body and tail (**D**) reveal edematous sausage-shaped pancreas (*arrows*) with decreased enhancement. Pancreas measures up to 17 mm in width at body and tail.



A B C D

Fig. 6—63-year-old man with metastatic renal cell carcinoma who began treatment with sunitinib malate.
A, Sonographic image of gallbladder obtained 1 month after initiation of therapy reveals no stones. Liver function test results 2 months after therapy initiation were normal.
B, Three months after initiation of therapy, patient presented with right upper quadrant pain. Coronal contrast-enhanced CT image obtained on day of presentation reveals perihepatic and pericholecystic fluid (*arrows*).
C, Ultrasound image obtained later on same day as **B** reveals that gallbladder is full of sludge and stones (*arrow*) and there is mild thickening of gallbladder wall. Liver function test results revealed elevation of total and direct bilirubin levels at 2.2 and 0.4 mg/dL, respectively. Despite withdrawal of therapy, placement of cholecystostomy tube and subsequent cholecystectomy were required.
D, Coronal fluoroscopic image obtained during cholecystostomy tube placement.

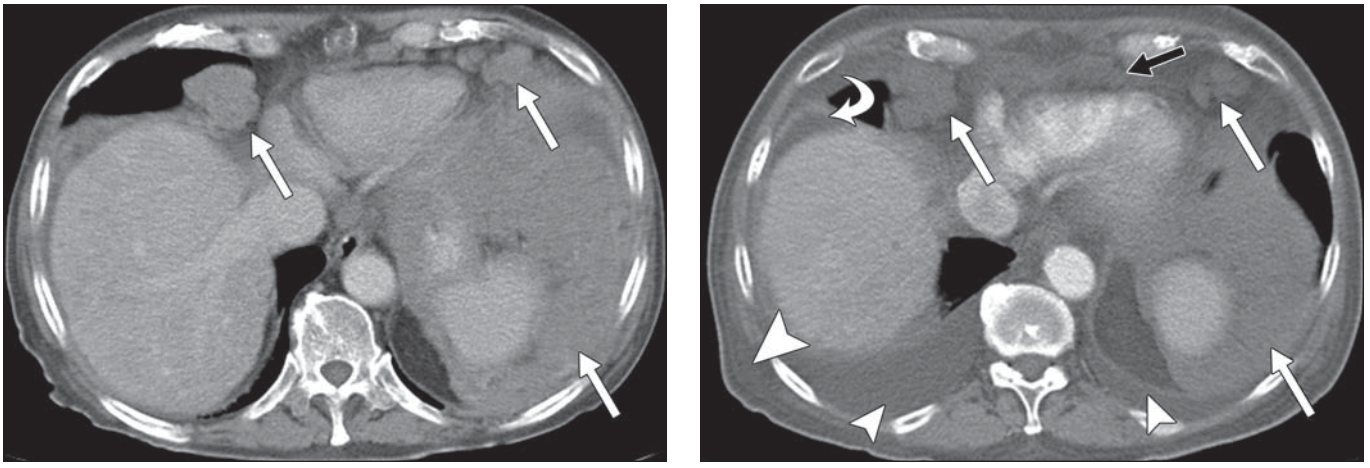


Fig. 7—80-year-old man with metastatic gastrointestinal stromal tumor who received treatment with imatinib mesylate.
A, Axial contrast-enhanced CT image obtained before treatment reveals no third spacing but shows multiple enhancing metastases (*arrows*) and diffuse enhancing peritoneal disease. Average attenuation of metastasis in right epicardial fat is 52 ± 11 HU (SD).
B, Axial contrast-enhanced CT image obtained 8 months after initiation of therapy reveals new stranding through subcutaneous fat (*large arrowhead*), new bilateral pleural effusions (*small arrowheads*), new peritoneal fluid (*curved white arrow*), and new pericardial effusion (*black arrow*). Of note, overall density of metastases (*straight white arrows*) has significantly decreased: Average attenuation of metastasis in right epicardial fat is 28 ± 11). These findings are consistent with interval treatment response.

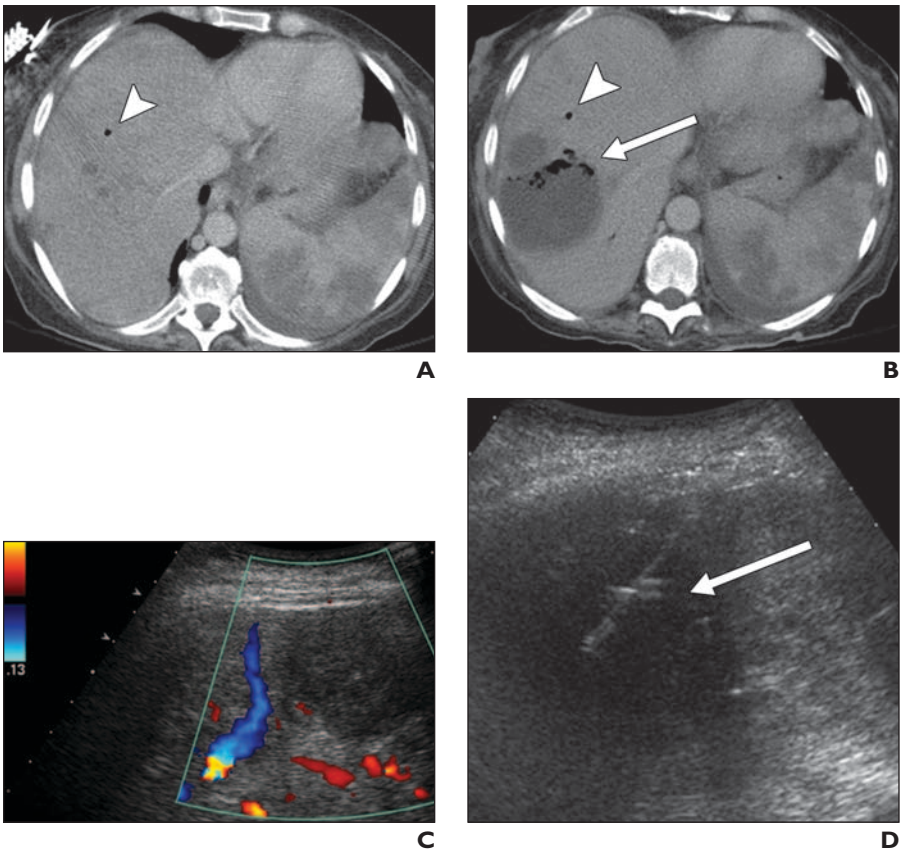
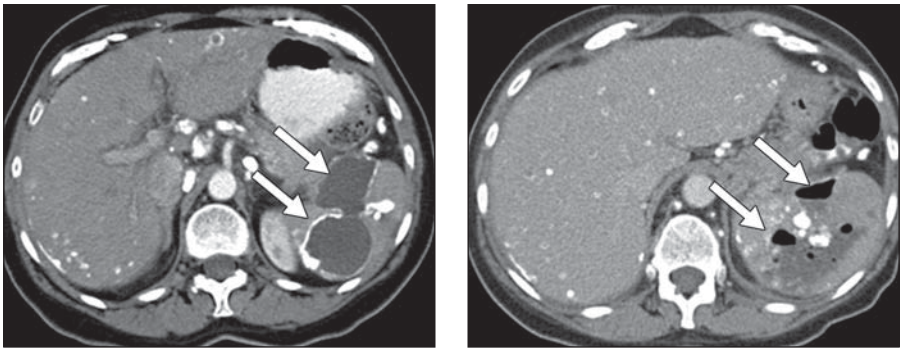


Fig. 8—44-year-old woman with history of metastatic carcinoid tumor on bevacizumab monotherapy.
A, Staging axial contrast-enhanced CT image obtained 3 months after initiation of therapy reveals small hypodense hepatic metastases. Arrowhead points to focus of pneumobilia, which was expected because biliary stent was in place.
B, Two weeks after **A**, patient developed acute right upper quadrant pain. Axial contrast-enhanced CT image obtained at same level as **A** shortly after pain developed reveals interval development of fluid collection containing air (*arrow*), highly concerning for abscess. Arrowhead again points to pneumobilia.
C, Color Doppler ultrasound image confirms hypoechoic, avascular collection.
D, Sonographic image obtained during percutaneous drainage shows needle within abscess (*arrow*). Microbiologic culture of drained fluid yielded gastrointestinal flora, including enterococci and lactobacilli.



A B

Fig. 9—67-year-old woman with metastatic ovarian carcinoma receiving bevacizumab and paclitaxel (Taxol, Bristol-Myers Squibb).
A, Axial contrast-enhanced CT image of abdomen obtained before initiation of therapy shows low-density metastases (*arrows*) in spleen with peripheral dense calcification. Multiple small calcified metastases in liver and calcified retroperitoneal nodes are also noted.
B, Patient developed new-onset severe nausea, upper abdominal pain, and fever 8 months after initiation of therapy. Axial contrast-enhanced CT image of abdomen shows locules of air in splenic metastases (*arrows*); this finding is consistent with superinfection. Chemotherapy was withheld and patient was treated with broad-spectrum antibiotics for 3 weeks; her symptoms resolved.

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