REVIEW

CT and MR imaging of chemotherapy-induced hepatopathy

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Abstract

Chemotherapy-induced hepatopathy includes a wide variety of parenchymal and vascular hepatic changes on imaging, including diffuse or focal hepatopathies (i.e. hepatitis, steatosis, fibrosis, pseudocirrhosis, or sinusoidal obstruction). These changes can profoundly alter the hepatic parenchyma on imaging and result in both false negative and false-positive diagnoses of hepatic metastases and lead to errors in patient management strategies. It is therefore important for radiologists to have a comprehensive knowledge of the imaging patterns that may develop following chemotherapy. The purpose of this review is to explore the broad spectrum of hepatic parenchymal and vascular chemotherapy-induced changes on CT and MR imaging.

Keywords Chemotherapy · Hepatopathy · Computed tomography · Magnetic resonance imaging · Sinusoidal obstruction syndrome

Introduction

Drug-induced hepatotoxicity includes a diverse set of responses that can occur after exposure to any chemical compound, including cytotoxic chemotherapeutic agents. Most cases of chemotherapy-induced hepatotoxicity are idiosyncratic and the clinical presentation ranges from asymptomatic patients with increased liver laboratory tests, to overt hepatic injury and fulminant hepatic failure [1, 2].

The mechanisms of action of chemotherapeutic agents can vary from blockage at the different phases of the cell cycle—e.g. S-phase for antimetabolites, M-phase for alkaloids—to blockage of different enzymes, including topoisomerase I or II, or tyrosine kinases (Supplementary Table 1). The final effect is programmed cell death or arrested cellular replication. The different mechanisms of action of chemotherapeutic agents may result in a broad spectrum of clinical, pathological and radiological hepatic injuries, including diffuse hepatopathy (i.e. hepatitis, steatosis, fibrosis, pseudocirrhosis, or sinusoidal obstruction) or focal hepatopathy. In addition, as most drugs tend to be lipophilic compounds, they are readily taken up by the liver and interfere with the

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tight regulation and balance of hepatic processes [3]. Chemotherapy can be locally or systemically delivered. In patients treated with hepatic intraarterial chemotherapy infusion—i.e. chemoinfusional therapy and chemoembolization with or without drug-eluting beads—hepatotoxicity mainly occurs as chemical hepatitis and biliary sclerosis, while the systemic toxicity profile is reduced [4, 5].

Clinicians have the task of detecting the early signs of chemotherapy-induced hepatopathy and determining whether the drug should be stopped due to hepatotoxicity or continued (e.g. whether hepatic adaptation and tolerance are likely to occur). Liver function is usually carefully assessed before and during chemotherapy, but there are no perfect laboratory tests to predict the likelihood of serious chemotherapy-induced hepatic injury. Although the frequency of liver laboratory tests is still controversial, assessment of liver function before each cycle of chemotherapy is considered mandatory in clinical practice. However, liver function test abnormalities may not always be found in chemotherapy-related hepatotoxicity (e.g. nonalcoholic steatohepatitis is not always accompanied by transaminase increase) [6]. Therefore, it is important that morphologic features or density/signal changes are reported by radiologists to help the clinicians rule out some degree of hepatotoxicity.

Diffuse chemotherapy-induced hepatopathy has been extensively studied in the radiological literature, and in the last two decades the use of gadoxetic acid has helped overcome false-negatives in the imaging of the tumor response following chemotherapy due to liver parenchymal changes [7]. On the other hand, focal chemotherapy-induced hepatopathy—which was previously considered to be mainly a pathological diagnosis—is a relatively new challenge for radiologists because effective new chemotherapies have increased its occurrence on imaging and the focal features may mimic hepatic metastases [8–10]. A false-positive diagnosis of new hepatic metastases can result in incorrect patient management with changes in the therapeutic strategy and unnecessary biopsies or surgery. MR imaging, especially with the use of hepatobiliary contrast agents and diffusion-weighted imaging, helps characterize these lesions and prevents misdiagnoses [9, 10]. It is certainly important to be aware of chemotherapy-induced hepatotoxicity to avoid mistakes in liver metastasis detection and to define the most appropriate clinical management strategy, but the real prognostic role of this damage is still uncertain. Indeed, Vigano et al. [11] demonstrated that chemotherapy-induced hepatotoxicity does not negatively impact long-term prognosis.

The purpose of this review is to explore the broad spectrum of hepatic parenchymal and vascular changes induced by systemic chemotherapy that may occur on CT and MR imaging.

Chemotherapy-induced diffuse hepatopathy

Acute and chronic hepatocellular injury

Acute hepatocellular injury after chemotherapy may lead to hepatocellular necrosis or apoptosis, steatosis, and/or cellular degeneration. Unlike viral hepatitis-induced injury, chemotherapy may also lead to zonal necrosis or localized confluent necrosis [12]. Acute hepatocellular injury may progress to portal inflammation with varying degrees of lobular inflammation and portal fibrosis. The findings of acute injury on CT or MR imaging are usually aspecific and may include hepatosplenomegaly, gallbladder wall thickening, reduced and heterogeneous liver enhancement, abdominal ascites, reduced portal flow, and the presence of periportal edema [2]. Although there are no imaging data in the literature yet, we hypothesize that the severe acute hepatic dysfunction after chemotherapy may be recognized during the hepatobiliary phase as impaired hepatocellular uptake of gadoxetic acid. For the moment, the diagnosis is still based on clinical and laboratory findings.

Chronic hepatocellular injury may lead to focal or diffuse morphological changes. Focal morphological changes include perilesional capsular retraction (Fig. 1)—which is common and associated with tumor response—and confluent fibrosis (Fig. 2). Diffuse morphological changes result in a condition known as "hepar lobatum" or *pseudocirrhosis*. This term indicates CT and MR imaging features similar to cirrhosis (Fig. 3), in particular, fine diffuse liver surface nodularity, multifocal capsular retraction, decreased liver size, enlargement of the caudate lobe and signs of portal hypertension, that lack the classic pathological attributes of cirrhosis [13]. Although pseudocirrhosis was initially described in patients with liver metastases in the absence of chemotherapy, it is clearly favored by chemotherapy [13, 14]. The pathogenesis of pseudocirrhosis is not yet fully understood, but two theories have been investigated: it may be due to shrinkage of liver metastases and subsequent severe desmoplastic fibrosis or to nodular regenerative hyperplasia caused by chemotherapy-induced hepatic injury [14]. Pseudocirrhosis has been mostly reported in patients with liver metastases from breast cancer treated with chemotherapy [15], with up to 75% of these patients showing varying degrees of abnormal liver surface and almost 9% having signs of portal hypertension [16]. Pseudocirrhosis has also been described in patients with esophageal cancer, pancreatic cancer, thyroid cancer, and colorectal cancer [17]. The development of pseudocirrhosis is often associated with a poor patient outcome, probably due to the complications of portal hypertension [17]. The recognition of pseudocirrhosis is crucial in patients with severe portal hypertension because

Fig. 1 48-year-old woman with hepatic metastases from colorectal adenocarcinoma treated with oxaliplatin and capecitabine (XELOX). Portal venous phase post-chemotherapy axial CT scan shows progressive perilesional capsular retraction at 2-month follow-up (arrow) (**a**) and 4-month follow-up (arrowhead) (**b**), compared to pre-chemotherapy axial CT scan (**c**)
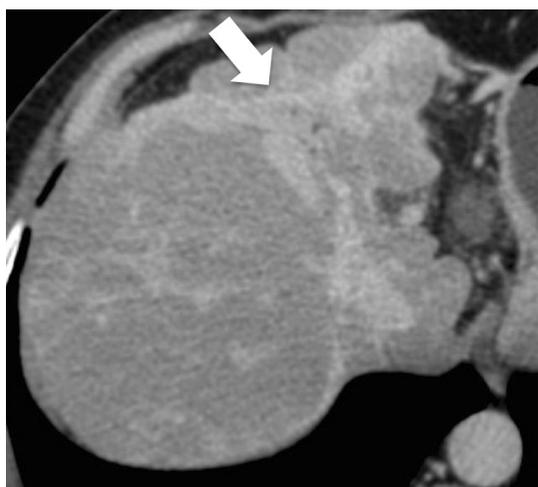

Fig. 2 51-year-old woman with hepatic metastases from breast cancer treated with chemotherapy. Post-chemotherapy axial CT scan shows marked confluent fibrosis during the delayed phase (arrow)

chemotherapy may be interrupted or changed to avoid major complications.

Steatosis and steatohepatitis

Chemotherapeutic drugs may lead to nonalcoholic fatty liver disease ranging from simple hepatic steatosis to steatohepatitis in up to 47% and 28% of patients, respectively [18–20]. The pathogenesis is based on a disturbed lipid metabolism via altered lipoprotein synthesis in the hepatocytes resulting into increased hepatocellular lipid content, recruitment of inflammatory cell and mitochondrial accumulation of large amounts of reactive oxygen species in the hepatocytes after exposure to chemotherapeutic drugs [3]. Different degrees of hepatic steatosis may occur after irinotecan or oxaliplatin regimens [19–21], and fat deposition > 30% seems to be more common following irinotecan than oxaliplatin [21, 22].

On CT hepatic steatosis usually results in lower attenuation of the hepatic parenchyma (Figs. 4 and 5) and in

Fig. 3 41-year-old woman with hepatic metastases from breast cancer treated with docetaxel and epirubicin for 6 months, then vinorelbine and 5-fluorouracil for the following 6 months. Post-chemotherapy axial CT scan in the portal venous phase shows marked changes in the nodular hepatic margins with multifocal capsular retractions known as pseudocirrhosis or "hepar lobatum" (**a**), which was not found on pre-chemotherapy axial CT scan 13 months earlier (**b**)
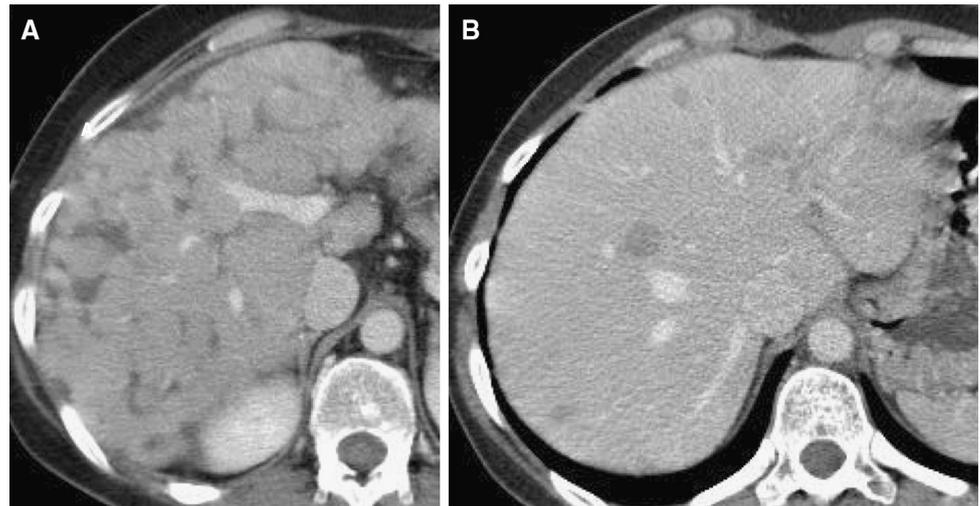

Fig. 4 53-year-old woman with pancreatic adenocarcinoma treated with FOLFIRINOX (i.e. fluorouracil with irinotecan hydrochloride, folinic acid and oxaliplatin). Post-chemotherapy non-contrast axial CT scan demonstrates marked hypoattenuation of the liver parenchyma and relative hyperattenuation of the intrahepatic vessels, consistent with severe hepatic steatosis (**a**), which was not found on axial CT scan performed 3 years earlier (**b**)
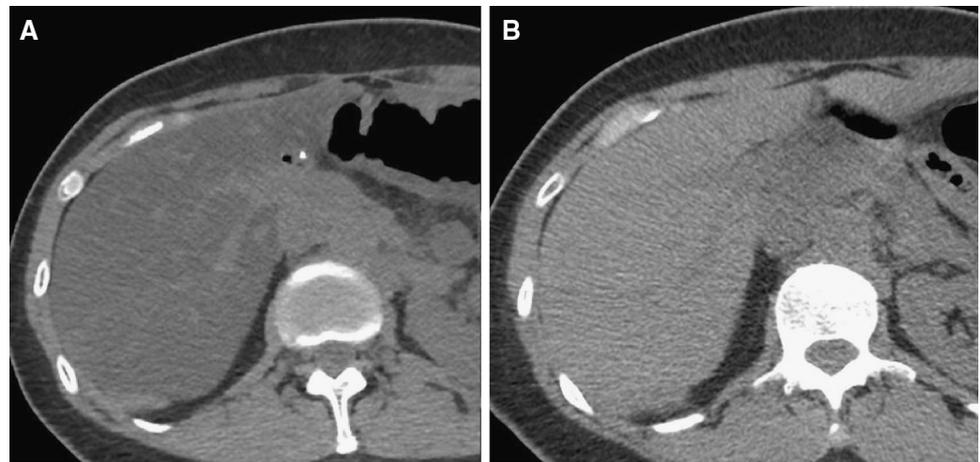
Fig. 5 67-year-old woman with hepatic metastases from pancreatic adenocarcinoma treated with three cycles of gemcitabine–oxaliplatin (GEMOX). Post-chemotherapy axial unenhanced CT scan shows a markedly hypoattenuating liver due to chemotherapy-induced diffuse liver steatosis. Due to this marked hypoattenuating liver parenchyma, the pancreatic metastasis (arrow) in segment VII is relatively hyperattenuating

decreased tumor-to-liver attenuation during the portal venous phase which may hinder the detection of metastases (Fig. 6) [23]. MR imaging is more robust for the detection of metastases in steatotic livers. Specifically, high peak hepatobiliary phase parenchymal enhancement increases tumor-to-liver contrast allowing detection of liver metastases that are not visible on CT (Fig. 7) [7, 24].

Although CT may be sufficient for the diagnosis of severe post-chemotherapy steatosis, it does not provide accurate quantification of intrahepatic fat. The relatively recent MR imaging approach using multi-echo sequences to calculate the proton density fat fraction (PDFF) is one of the most accurate techniques for non-invasive intrahepatic fat quantification [25, 26].

One of the main clinical problems associated with fat deposition is chemotherapy-induced steatohepatitis. The use of preoperative chemotherapy is associated with a trend toward an increased incidence of steatohepatitis (relative risk: 1.89). In particular, patients who receive irinotecan-based regimens have a 3.45-fold greater risk of developing
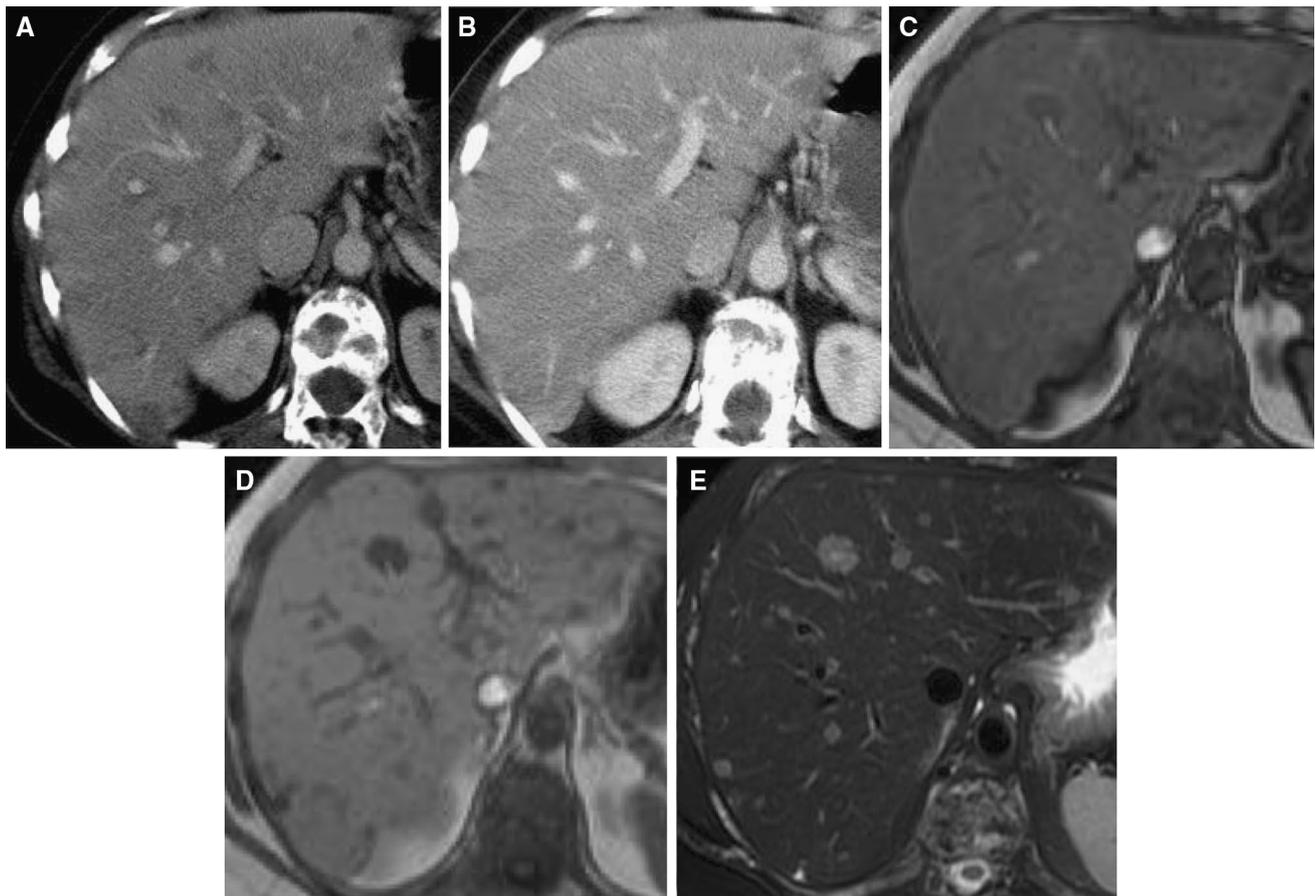
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Fig. 6 40-year-old woman with hepatic metastases from breast cancer treated with vinorelbine and 5-fluorouracil. Portal venous phase pre-chemotherapy axial CT scan shows multiple bilobar small hypoattenuating metastases (**a**). Post-chemotherapy axial CT scan in the portal venous phase shows no lesions (**b**). One month later, post-chemother-apy MR shows diffuse fatty infiltration on the opposed-phase image (**c**) compared to the in-phase image (**d**), and clearly demonstrates numerous metastases on fat-suppressed axial T2-weighted sequence (**e**)

steatohepatitis than chemotherapy-naive patients [23]. The postoperative outcome is negatively influenced by the presence of preoperative chemotherapy-associated steatohepatitis, with a risk of increased postoperative morbidity and mortality as well as liver surgery-specific complications [26–28]. Thus, irinotecan should be avoided in patients with severe steatosis identified on imaging [29], and indications for major liver resection in these patients should be discussed at multidisciplinary sessions. Because of the important clinical impact of this event, the diagnosis and quantification of fatty infiltration and inflammation is highly important after chemotherapy. While hepatic fat can be quantified by MR PDFF, hepatic inflammation cannot yet be precisely and non-invasively quantified on imaging. However, in the last few years, Liver*MultiScan* (LMS, Perspectum Diagnostics, Oxford, UK), a multiparametric MRI-based method providing parametric maps of PDFF and T1 relaxation times for measuring iron-corrected T1, has emerged as a promising diagnostic tool to diagnose, quantify, stratify and monitor

steatohepatitis [30]. Moreover, MR elastography is used in many tertiary centers as a non-invasive technique for the detection and staging of liver fibrosis and to differentiate isolated fatty liver disease from steatohepatitis with or without fibrosis [31]. However, extensive validation of these promising recent MR imaging techniques are needed.

Chemotherapy-induced diffuse/focal hepatopathy

Sinusoidal changes

Sinusoidal changes including sinusoidal obstruction syndrome (SOS), centrilobular sinusoidal dilatation or peliosis, have been described in 77.4%, 42.3%, and 10.6%, respectively, of patients receiving oxaliplatin-based chemotherapy for colon cancer [20]. Post-chemotherapy sinusoidal changes may spontaneously regress, and Han et al [32] have reported

Fig. 7 51-year-old woman with hepatic metastases from breast cancer treated with epirubicin and cyclophosphamide followed by docetaxel. Hepatobiliary phase post-chemotherapy MR scan (**a**) and diffusion-weighted imaging (**b**) at high b value ($b = 600$) shows a large metastasis (arrow) in segment V/VIII and a small metastasis (arrowhead) in segment II. At the 3-month follow-up portal venous phase CT (**c**) the hepatic parenchyma is diffusely hypoattenuating due to steatosis, the large metastasis in segment V/VIII seems to have decreased in size while the small lesion in segment II is not visible. However, 10 days after the CT the MR (**d**) diffusion-weighted image at high b value ($b = 600$) shows that the large metastasis in segment V/VIII is larger than before the CT and MR image, and the small metastasis in segment II is still present
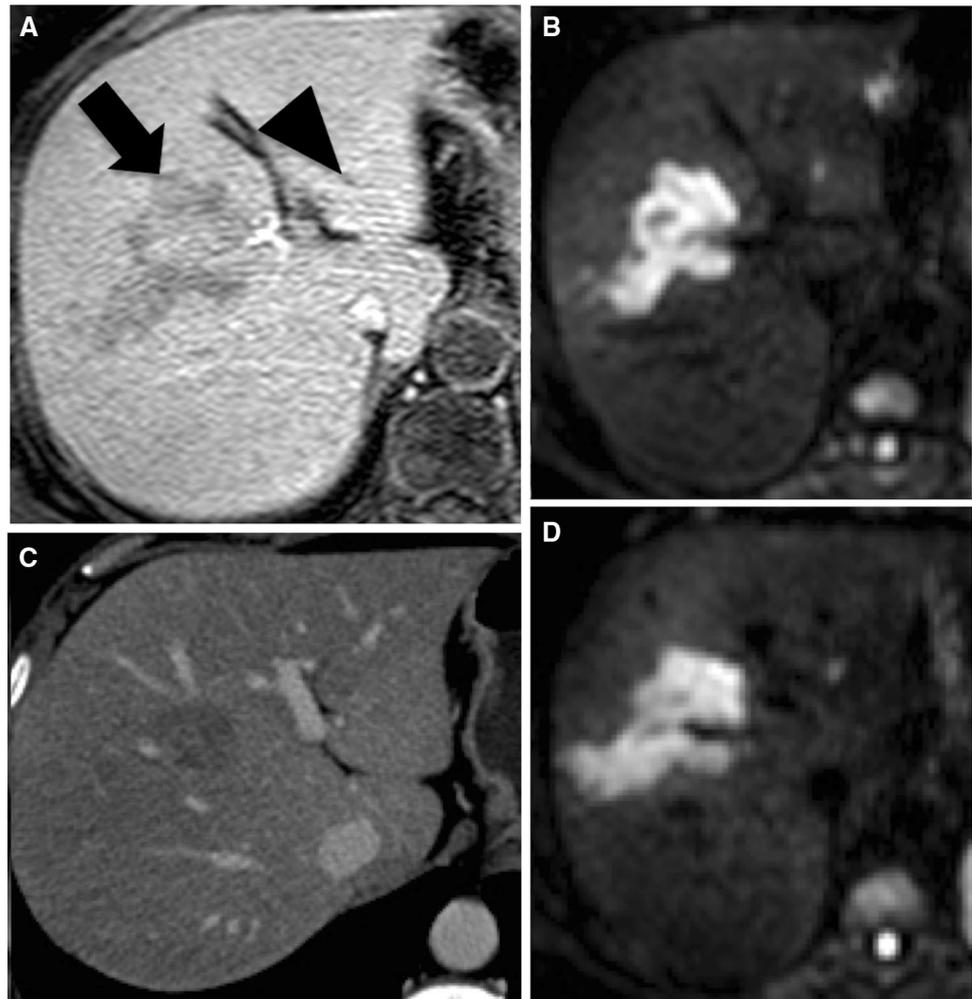
complete radiological remission a mean 82.5 days $\pm$ 68.8 after oxaliplatin discontinuation, though SOS may persist with signs of portal hypertension and splenomegaly.

Hepatic SOS, formerly called "veno-occlusive disease" or "blue liver syndrome", is the most common sinusoidal change after chemotherapeutic drugs and is considered to be a serious, potentially life-threatening complication [20]. Although SOS may be secondary to different chemotherapeutic drugs, it is more common with oxaliplatin [20, 31]. On pathology hepatic SOS may include acute, subacute or chronic features [30]. In the acute form, the chemotherapeutic drugs cause endothelial cells to detach from the sinusoidal wall, and extravasation of erythrocytes into the Disse's spaces favored by discontinuities in the endothelial lining [34]. This results in downstream embolization, thus blocking hepatic sinusoids. Therefore, when a liver tissue sample is obtained 1–3 weeks after drug exposure, the acute features of SOS at pathology include hemorrhage in markedly dilated sinusoids with centrilobular hepatocellular necrosis and denuded sinusoids [32]. The severity of sinusoidal congestion may be graded from 0 to 3 [35]: grade 1 (i.e. mild) when

centrilobular involvement is limited to one-third of the lobular surface, grade 2 (i.e. moderate) when two thirds of the lobular surface is affected, and grade 3 (i.e. severe) when the whole lobule is affected. In the subacute form proliferation and activation of hepatic stellate cells and subendothelial fibroblasts occur over days and weeks resulting in deposition of collagen matrix in the perisinusoidal spaces and centrilobular vein, with progressive obliteration of the venule [33, 34]. Finally, when SOS persists for weeks, months or even years, sinusoidal fibrosis, severe destruction of the lobular parenchyma and nodular regeneration may occur [33].

Hepatic SOS may result in major postoperative morbidity, reduced functional reserve of the liver and a higher complication rate after major hepatectomy [26, 27, 36, 37]. In addition, grade 2–3 SOS has been associated with lower pathological tumor response compared to grade 0–1 SOS (16.9% vs. 26.6%, respectively) [11]. Thus, it is important to prevent SOS and detect this event before surgery to identify the best timing for hepatic resection and for further chemotherapy. Preoperative laboratory tests, including a low platelet count and high aspartate aminotransferase-to-platelet

ratio index (APRI) score (cut off point of 0.36), is predictive of SOS [38, 39]. The combination of the APRI score and the albumin-bilirubin grade effectively identifies high-risk patients for liver resection [40]. Bevacizumab seems to have a protective effect against oxaliplatin-induced hepatopathy, with a lower incidence of oxaliplatin-related SOS and a

reduced rate of thrombocytopenia [38, 41, 42]. Although it has only been shown in animal models, a chow diet also seems to have a protective effect [43]. The diagnosis of SOS on imaging includes a wide range of findings. Cross-sectional imaging may demonstrate indirect signs of SOS related to reduced liver outflow and portal hypertension,
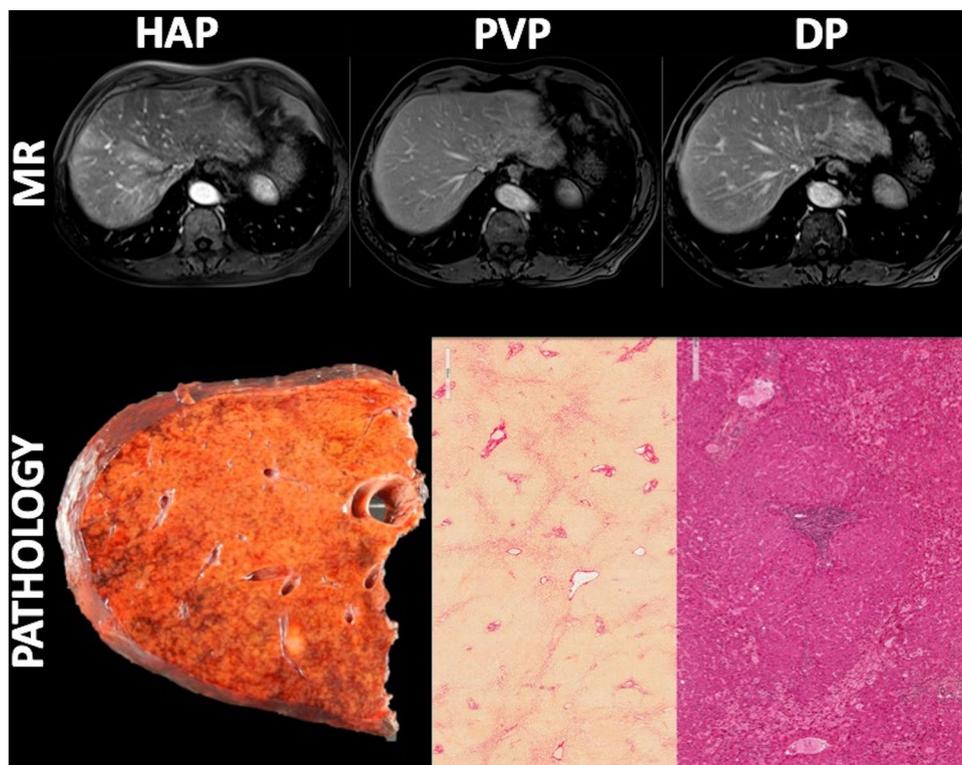
Fig. 8 70-year-old man with synchronous hepatic metastases from colon adenocarcinoma treated with FOLFOX (i.e. folinic acid, fluorouracil and oxaliplatin). Top row: post-contrast MR imaging demonstrates diffuse patchy parenchymal enhancement of segments VII and VIII during the hepatic arterial phase (left image), which are isointense during portal venous (middle image) and delayed (right image) phases. Bottom row: macroscopic and microscopic findings of sinusoidal obstruction syndrome from right hepatectomy. At macroscopy (left image), the non-neoplastic hepatic parenchyma is diffusely mottled mainly in the periphery, with geographic areas of congestion alternating with a relatively normal-looking liver. Microscopy (middle and right images) shows sinusoidal dilatation and congestion with atrophy and disruption of hepatocyte plates
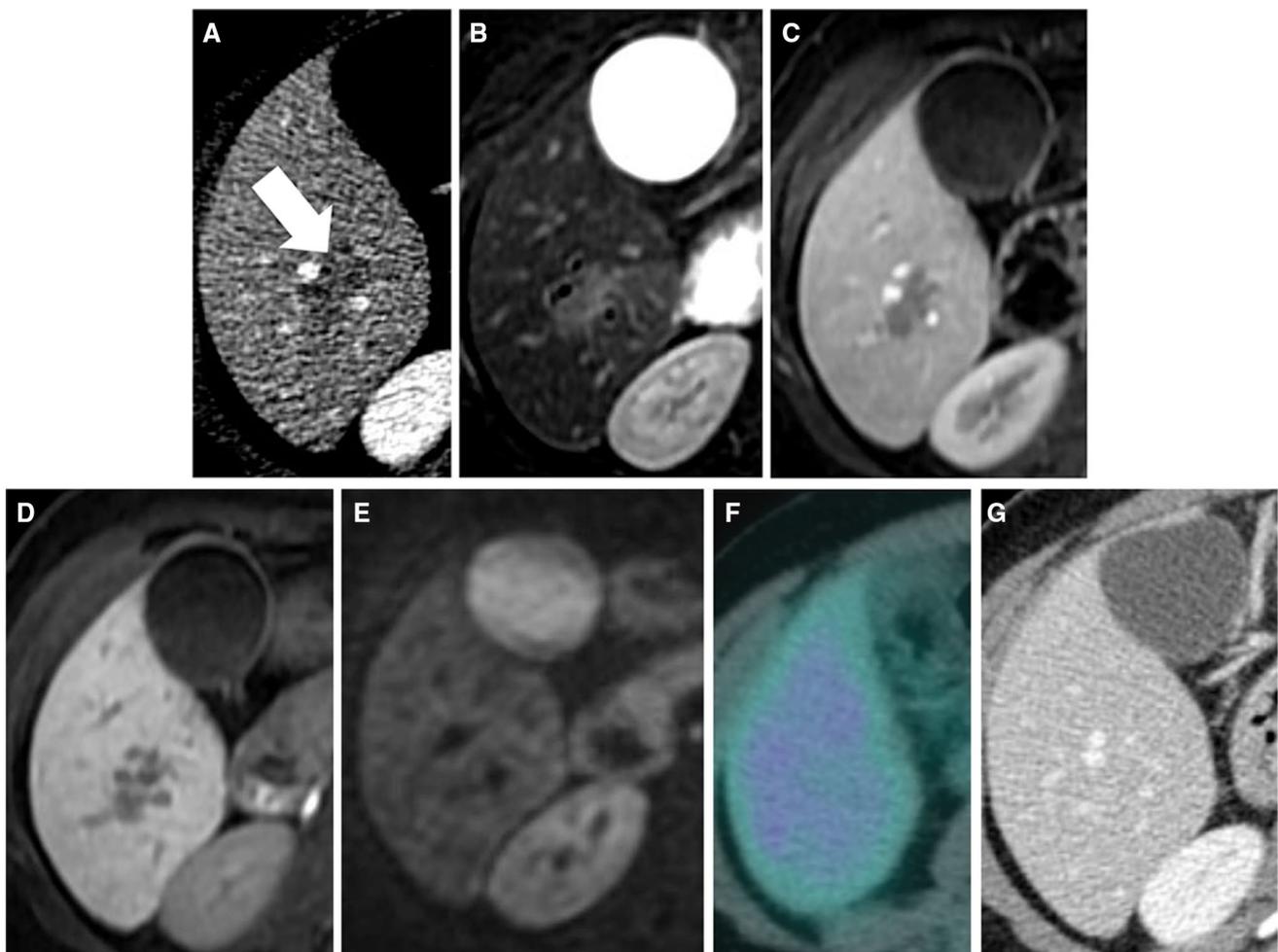

Fig. 9 44-year-old man with nodal metastases from colon adenocarcinoma treated with FOLFOX therapy (i.e. folinic acid, fluorouracil and oxaliplatin). Hepatobiliary phase post-chemotherapy axial MR demonstrates reticular hypointensity (arrow in the right lobe of the liver (**a**), which was not evident on pre-chemotherapy MR (**b**). The most likely diagnosis is sinusoidal obstruction syndrome due to chemotherapy with oxaliplatin
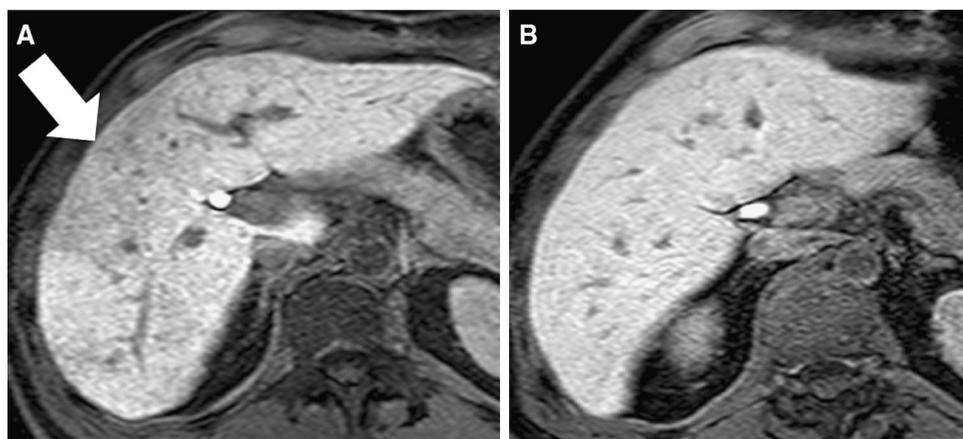
such as ascites, hepatosplenomegaly, gallbladder wall thickening, periesophageal varices and the patency of paraumbilical veins. It is important to note that splenic volume is considered to be a preoperative indicator of SOS [38]. On contrast-enhanced CT and MR imaging, SOS appears as patchy liver enhancement with a mosaic appearance, usually located in the peripheral parenchyma of the right lobe (Fig. 8) [44, 45]. Gadoxetic acid-enhanced MR imaging is a sensitive and highly specific tool for the diagnosis of SOS (sensitivity: 75%; specificity: 96–100%) [46]. In the hepatobiliary phase the typical features and independent predictors of SOS usually include a hypointense reticular hepatic parenchyma (Fig. 9), the clover-like sign (i.e. normal hepatic enhancement preserved around hepatic veins in a heterogeneous liver) and peripheral distribution [47]. Interestingly, anomalies during the hepatobiliary phase are well correlated with the pathological grades [46]. The reason for the hypointensity is the markedly reduced OATP1B3 expression due to damage in the centrilobular hepatocytes [48].

Less frequently, SOS may present as a new focal lesion, mimicking a metastasis and described as focal hepatopathy [10] (Fig. 10). Unlike hepatic metastases, focal hepatopathy secondary to SOS shows no rim-enhancement during the arterial and portal venous phases, intermingled hypointensity and ill-defined margins during the hepatobiliary phase as well as lack of diffusion restriction on diffusion-weighted images [10].

Hepatic peliosis

Although it is less common, this condition, which may occur after chemotherapy, is characterized at pathology by

Fig. 10 45-year-old woman with hepatic metastasis from colon cancer treated with FOLFOX therapy (i.e. folinic acid, fluorouracil and oxaliplatin). Portal venous phase post-chemotherapy CT scan shows a new focal hypoattenuating lesion (arrow) in segment VI (**a**). The lesion was then confirmed on gadoxetic acid-enhanced MR imaging as a focal mild hyperintensity on T2-weighted sequence (**b**), hypointensity on portal venous phase (**c**) and hepatobiliary phase (**d**) image and inapparent on diffusion-weighted image (**e**). PET scan performed 2 months later did not reveal any area of uptake (**f**) and the lesion disappeared at 5-month follow-up portal venous phase axial CT scan (**g**), confirming a diagnosis of focal hepatopathy secondary to sinusoidal obstruction syndrome
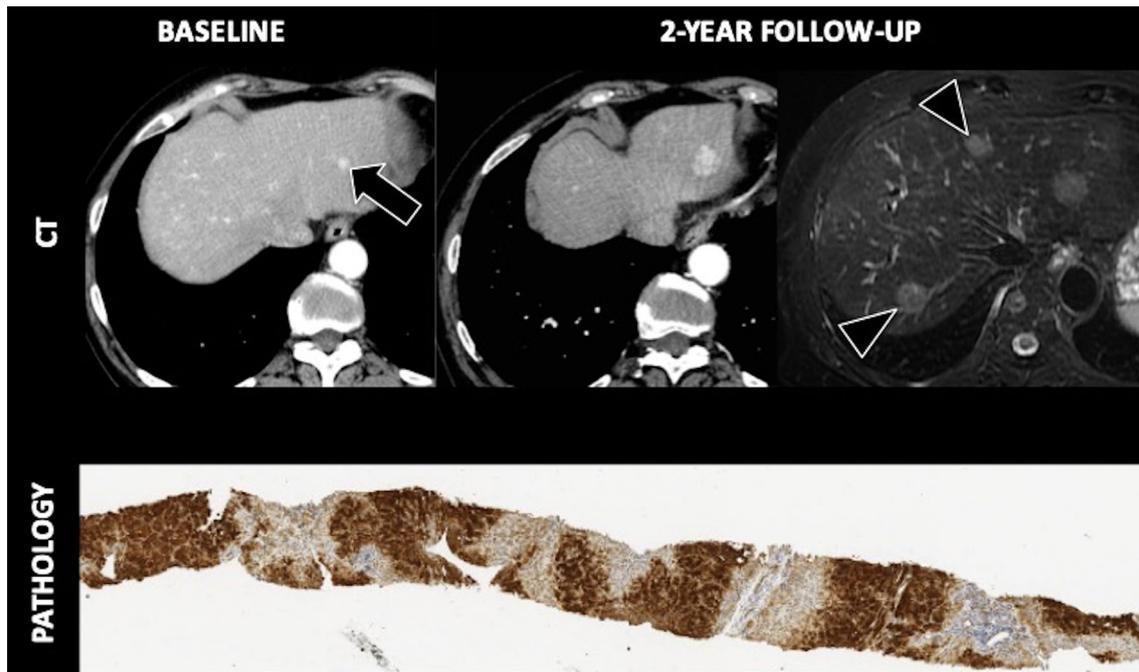
Fig. 12 55-year-old woman with a history of left colectomy for colon cancer treated with FOLFOX therapy (i.e. folinic acid, fluorouracil and oxaliplatin). Top row: Baseline post-chemotherapy CT scan shows a single lesion (arrow) in segment II that is hypervascular during the arterial phase (left image), and increases in size at 2-year CT follow-up (middle image). MR imaging (right image) reveals two other liver lesions (arrowheads) in segments IV and VII on the T2-weighted sequence that were not present in previous CT scans. Bottom row: Biopsy confirms the diagnosis of a focal nodular hyperplasia—like lesion with immunostaining showing map like appearance on glutamine synthase

FNH-like lesions are usually multiple, and diagnosed on follow-up imaging at a mean time of 48 months after the end of chemotherapy [9, 58]. These FNH-like lesions are usually smaller than classic FNH [50] and up to 42% of them may increase in size at imaging after a mean follow-up of 29 months (Fig. 12) [9]. Because of the development of multiple de novo lesions after chemotherapy and the potential increase in size, the radiologist should know the typical imaging features of FNH-like lesions to avoid a misdiagnosis of hepatic metastases [58]. On contrast-enhanced CT and MR imaging, FNH-like lesions usually show bright and homogenous arterial contrast enhancement and
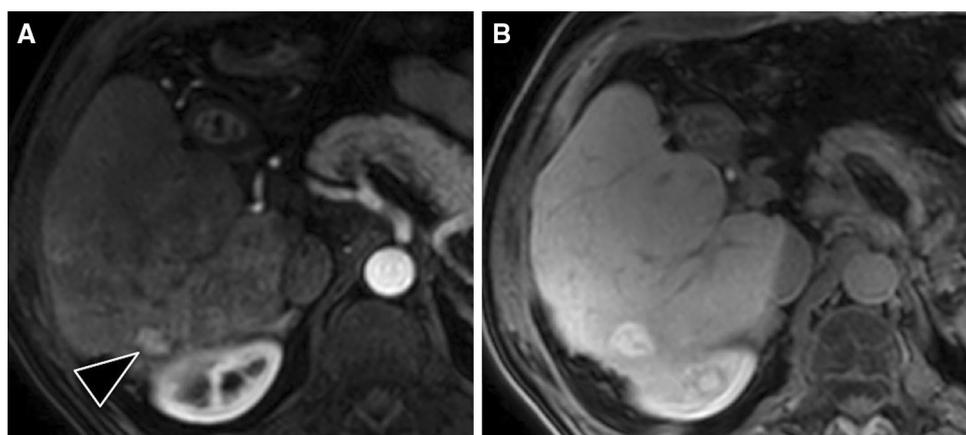
Fig. 13 59-year-old man with hepatic metastases from colorectal adenocarcinoma treated with FOLFIRINOX (i.e. fluorouracil with irinotecan hydrochloride, folinic acid and oxaliplatin) and cetuximab. Post-chemotherapy gadoxetic acid MR imaging confirms the presence of a lesion (arrowhead) in segment VI with bright enhancement during the arterial phase (**a**) and hyperintensity during the hepatobiliary phase (**b**), consistent with the diagnosis of a focal nodular hyperplasia—like lesion

isoattenuation to the surrounding liver parenchyma during the portal venous and delayed phases. A central scar is present in fewer than 50% of cases [9, 50]. The specificity for the diagnosis of this entity with non-invasive imaging has improved with the use of hepatobiliary MR contrast agents. Post-chemotherapy FNH-like lesions are usually iso- to hyperintense during the hepatobiliary phase because of a similar or stronger OATP1B3 expression in the lesion than in the background liver (Fig. 13) [59, 60]. In addition, a ring or doughnut-like enhancement may be present in up to 50% of cases and is characterized by a hyperintense periphery and a hypointense center [9].

Systemic chemotherapy-induced hepatic parenchymal and vascular changes may complicate characterization on imaging and patient management. Laboratory tests and imaging can help define the most appropriate clinical management strategy. As stated by Vauthey et al. [29], knowledge of the full spectrum of possible chemotherapy-induced hepatopathies is highly important to obtain a clear clinical picture. First, preoperative chemotherapy may increase the risk of hepatic insufficiency. In addition, knowledge of pre-existing hepatic injury can help determine the choice of chemotherapy; if possible, irinotecan should be avoided in patients with severe steatosis and oxaliplatin in those with splenomegaly. Finally, because of the possible benefits of preventing SOS, bevacizumab is the best choice when targeted therapy is being considered in addition to cytotoxic chemotherapy and if tumor downsizing is not a major consideration. In our opinion, liver biopsy is indicated in specific clinical situations, in particular for the characterization of atypical lesions (i.e. atypical FNH-like lesions or peliosis) and to grade suspected SOS when major hepatectomy is planned.

Conclusion

Chemotherapy-induced hepatotoxicity includes a broad spectrum of parenchymal and vascular hepatic changes at imaging. These changes may alter liver morphology, structure and vascularization potentially resulting in diffuse hepatopathy which may hinder the detection of hepatic metastases or in focal hepatopathy which may mimic hepatic metastases. A comprehensive knowledge of the profiles of chemotherapy-induced hepatotoxicity at imaging can help identify and overcome these potential imaging difficulties after chemotherapy and avoid patient mismanagement.

Compliance with ethical standards

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