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CASE REPORT

Capecitabine-related liver lesions: sinusoidal dilatation mimicking liver metastasis

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Key Clinical Message

A 30-year-old lady treated with capecitabine for primary colon adenocarcinoma developed liver lesions suspicious for metastasis. Liver biopsies showed sinusoidal dilatation thought to be secondary to capecitabine. This case highlights the importance of differentiating between benign and malignant liver lesions during cancer surveillance preventing unnecessary liver resections for benign disease.

Keywords

Capecitabine, colonic adenocarcinoma, liver lesions, sinusoidal dilatation.

Introduction

Capecitabine (trade name Xeloda) is an orally administered chemotherapeutic drug used in cancer treatment. It is most commonly administered in the treatment of colorectal and breast cancer as both a neo-adjuvant and adjuvant agent, as well as in metastatic disease, either as a single agent or in combination with other agents. It is also used in gastric and esophageal cancers. Capecitabine is a prodrug that is converted to 5-fluorouracil (5-FU) in the body, which then irreversibly inhibits thymidylate synthesis, interrupting its role in DNA synthesis. The conversion into 5-FU preferentially occurs in tumor cells but also takes place in the liver by a three-step enzymatic cascade. Capecitabine has been associated with mild liver damage most notably causing hepatic steatosis and has more recently been reported to have a possible association with sinusoidal obstruction syndrome (SOS) [1]. Other drugs containing 5-FU and oxaliplatin are known to cause veno-occlusive hepatic injury as well as fatty change in the liver. The recognition and awareness of such adverse effects is important when managing patients taking these chemotherapeutic agents, and more documentation in the literature is required.

Case Presentation

A 30-year-old lady presented with a 7-month history of intermittent rectal bleeding. This was initially associated with constipation and perianal pain. She noticed bright red blood both separate to and coating the stool. She denied any weight loss or abdominal pain. She was otherwise fit and well with no other significant past medical history. With regard to her family history, her mother suffered from irritable bowel syndrome and had a benign polyp removed in her 40s. Her maternal and paternal grandparents both had lung cancer while her maternal grandmother had gallbladder cancer. She did not take any regular medications and had no known drug allergies. She was a nonsmoker and drank 10–14 units of alcohol per week.

On examination, her abdomen was soft and nontender with no palpable masses or organomegaly. Digital rectal

examination and rigid sigmoidoscopy were unremarkable. Unexpectedly, a flexible sigmoidoscopy showed a malignant looking sessile polyp in the lower rectum. Pelvic MRI scan showed thickening in the midrectum arising 7 cm from the anal verge with no extramural venous invasion and a threatened, but not invaded, circumferential resection margin anteriorly. Radiological staging on MRI and CT was T3 N0 M0 and histological biopsies confirmed a moderately differentiated adenocarcinoma.

The patient commenced a long course of neoadjuvant chemoradiotherapy using capecitabine as the radiosensitizing chemotherapeutic agent. While taking capecitabine, the patient reported episodes of angina-type chest pain, which resolved on completion of the chemotherapy course and did not require any cardiac treatment. A MRI scan following the neoadjuvant therapy showed a good response with the tumor being downstaged to T2. She proceeded to a laparoscopic ultra low anterior resection with defunctioning loop ileostomy. Histological analysis of the resected specimen showed complete pathological response, pT0 pN0 (0/20), EMV negative, R0.

A surveillance CT scan was performed at 3 months which identified four new subcapsular wedge-shaped liver lesions suspicious for metastatic liver disease (Fig. 1).

These lesions were confirmed on Primovist MRI scanning as four new foci of low T1 signal within the liver, none of which were of high T2 signal and no hepatic steatosis. Post Primovist contrast, there was minimal arterial enhancement and no rim enhancement; the lesions were low signal on the delayed hepatobiliary phase (Fig. 3A).

A subsequent PET–CT scan showed no FDG avid liver lesions and no extrahepatic disease. There was doubt on the etiology of these new liver lesions as they did not demonstrate the typical characteristics of metastasis. They were not visible on ultrasound but it was agreed via MDT that a CT-guided core biopsy of the most accessible lesion should be performed. Histological examination revealed sinusoidal dilatation only with no other specific findings and no metastatic tumor (Fig. 2).

Liver function tests remained normal throughout the course of treatment and surveillance. The multidisciplinary team meeting opinion was that there was insufficient evidence for metastatic disease and therefore a close surveillance policy was adopted.

A repeat Primovist MRI scan 2 months later showed the same peripheral wedge-shaped areas of reduced T1 signal. They appeared more peripheral and more clearly defined than previously with no new areas of abnormality demonstrated and no enhancing lesions. Five months following the first postoperative scan, a third MRI scan was repeated and showed partial resolution of the four lesions in keeping with a benign etiology (Fig. 3B). Carcinoembryonic antigen levels were normal throughout.

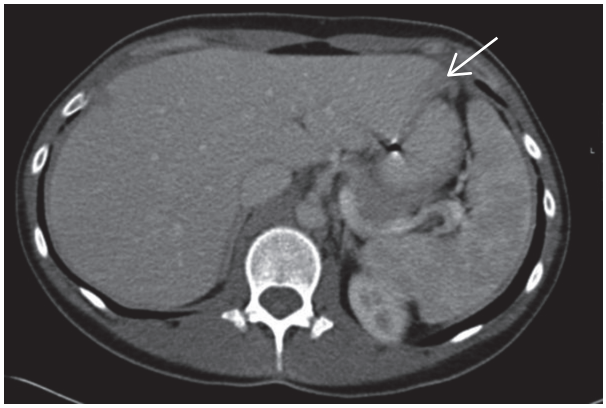

Figure 1. Axial multidetector computer tomography demonstrating low attenuation lesion within the subcapsular aspect of the left lobe (arrow).

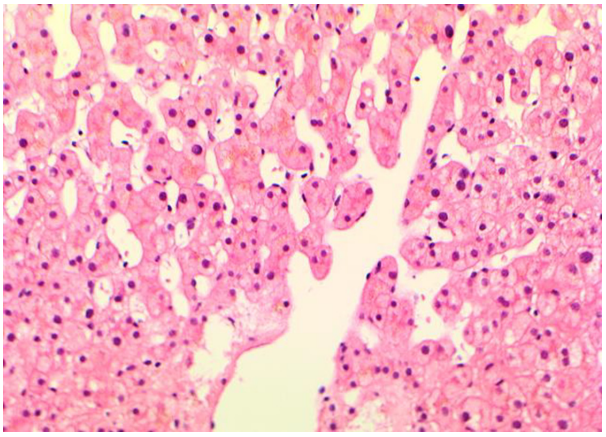

Figure 2. Liver biopsy specimen showing sinusoidal dilatation with no evidence of malignancy.

Discussion

Chemotherapy-associated hepatotoxicity in cancer patients is a key area of ongoing research. It is especially important given the essential need to differentiate benign lesions from malignant liver metastases. Studies so far have reported associations between 5-fluorouracil and hepatic steatosis, and irinotecan-associated steatohepatitis [2]. Morris-Stiff et al. [3] found that 50% of liver resections following irinotecan- and oxaliplatin-based regimes had hepatic steatosis and 20% had SOS. Sinusoidal obstruction syndrome following oxaliplatin does not appear to increase the risk of perioperative death, whereas irinotecan-associated steatohepatitis can increase both morbidity and mortality posthepatectomy by reducing the hepatic reserve, thus leading to liver failure [2]. More recently, Chin et al. [4] published a case report on

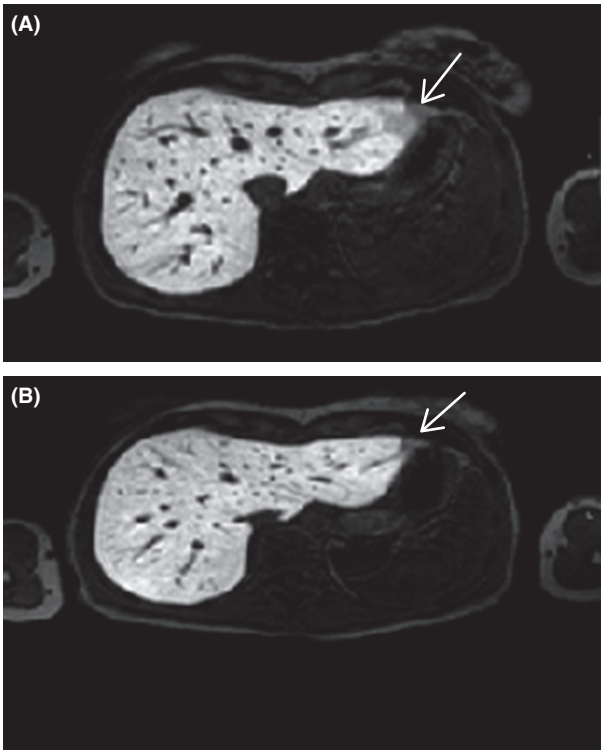

Figure 3. (A) Axial T1-weighted Primovist MRI in the delayed hepatobiliary phase with low signal lesion corresponding to lesion on CT. (B) Axial T1-weighted Primovist MRI in the delayed hepatobiliary phase with partial resolution of lesion at 5 months.

capecitabine-induced hepatic steatosis in a patient with stage III colon cancer treated with adjuvant chemotherapy.

Capecitabine, known commercially as Xeloda, is a relatively new agent approved by the FDA in 2001. It is an orally administered chemotherapeutic drug used most commonly in the treatment of colorectal and breast cancer in both localized and metastatic disease. Capecitabine is converted to 5-flurouracil preferentially in tumor cells but also in the liver by a three-step enzymatic cascade, where it irreversibly inhibits thymidylate synthesis, involved in DNA synthesis. Phase I and II clinical trials showed that a regimen consisting of oral capecitabine in combination with radiotherapy is an active and well-tolerated regimen with similar efficacy to the infusional 5-FU/radiotherapy regimen as demonstrated by the National Surgical Adjuvant Breast and Bowel Project R-04 trial and the German Margit trials. Although capecitabine has demonstrated substantial benefits as neoadjuvant treatment in locally advanced rectal disease [5], metastatic colorectal cancer, and metastatic breast cancer [6], it remains a fairly toxic drug with a number of side effects; some of which are still underreported, including the association with SOS.

Sinusoidal obstruction syndrome, also referred to as toxic sinusoidal injury, veno-occlusive disease, or "blue liver syndrome", is a commonly recognized vascular pattern of drug-induced liver injury, frequently associated with oxaliplatin-based chemotherapy. Kakar et al. [7] analyzed liver biopsies from 51 patients with sinusoidal dilatation. 66.7% of these cases had confirmed venous outflow impairment. For the 17 other cases; vascular causes included nodular regenerative hyperplasia, portal vein thrombosis, congenital absence of the portal vein, and sickle cell anemia. In three more patients, sinusoidal dilatation was identified postsurgery (gastric bypass, cholecystectomy, and splenectomy). In our patient, the most likely cause for sinusoidal dilatation was as a result of the long course of chemoradiotherapy using capecitabine. Capecitabine is a precursor to 5-fluorouracil, which has already been documented to cause sinusoidal dilatation; hence, the association is plausible. Further, a study by Klinger et al. [1] also reported a likely association between capecitabine and SOS. However, the patient in Klinger's case report also received oxaliplatin and bevacizumab as well as capecitabine, and had to confirm liver metastasis prior to receiving chemotherapy. The differential diagnosis in our case is that of sinusoidal dilatation induced by surgery. However, there are no documented cases or evidence in the literature of vascular processes in the liver following colorectal cancer resections, nor have we identified such a problem in all our previous colorectal surveillance patients.

Primovist MR imaging is used preferentially in most hospitals for detecting colorectal liver metastases. Gadoxetic acid, Primovist, a liver-specific contrast agent directed at hepatocytes [8], was approved by the FDA in 2004. It is understood to be superior to diffusion-weighted MRI and multidetector CT scanning in detecting liver metastases. Bluemke et al. showed that there was a 2–15% more accurate classification of benign and malignant lesions compared with CT images of the same patients. They also showed a lower rate of false positives with Primovist MRI imaging [9]. Hammerstingl et al. [8] showed a higher rate of detection of smaller hepatic lesions and distinctly lower false-positive results. In our patient, Primovist MRI imaging was used to assess the hepatic lesions identified on the 3-month surveillance CT scan, and for the follow-up interval imaging.

It is important to keep an open mind when assessing new liver lesions during the surveillance period postcolorectal cancer treatment. Potential side effects of chemotherapeutic agents should always be considered especially when they can induce liver lesions that can mimic metastatic liver disease. Our case also highlights the important role of regular multidisciplinary team discussions with joint hepatobiliary involvement, interval

imaging, and histological opinion of any suspicious lesions. This multidisciplinary approach helped to make a confident diagnosis and avoid unnecessary surgery. While it is important not to delay potentially curative treatment for resectable liver metastases, we need to be aware of other causes of liver lesions including veno-occlusive injury by chemotherapeutic agents that are likely to reveal their benign nature with close surveillance and close interval scanning.

Furthermore, ongoing research to evaluate the short- and long-term side effects of capecitabine are needed. As Primovist is a relatively new contrast agent, it is important to be aware of rare complications that could mimic disease.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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