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Case Report

Focal nodular hyperplasia after oxaliplatin-based chemotherapy: A diagnostic challenge☆☆

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ABSTRACT

Chemotherapy could induce benign liver alterations presenting as diffuse or focal lesions mimicking metastases. Oxaliplatin-induced vascular liver injury is described in literature, but the association with FNH-like lesions has been reported in a limited number of cases. We herewith describe the case of a 67-year-old male, who had laparoscopic right-sided hemicolectomy, 8 years ago, because of colonic adenocarcinoma (pT3N0M0) and subsequent adjuvant chemotherapy (capecitabine + oxaliplatin), who referred to the ultrasound service of our Radiology Unit because of abdominal pain. Five-years follow-up was negative for metastases. Ultrasound examination showed 2 small hypoechoic hepatic nodules, in segment VIII and VII, confirmed at CT, suspected for metastases. FDG-PET was negative, and blood tumor markers were within normal ranges. For further evaluation we performed gadoxetic acid (Gd-EOB-DTPA)-enhanced MRI that showed hyperintensity of the nodules in the hepatobiliary phase with central small hypointensity due to a central scar. Considering the previous oxaliplatin-based chemotherapy the findings were compatible with FNH-like lesions and the diagnostic suspicion was confirmed at ultrasound-guided core needle biopsy. Knowledge of the possible occurrence of FNH-like lesions in oncologic setting, along with the detection of typical MRI appearance, is important for appropriate management and may avoid unnecessary biopsy or surgery and reduce patients' anxiety.

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Introduction

The onset of new hepatic lesion in a patient with a history of cancer is highly concerning for metastasis, however benign liver alterations may occur after chemotherapy treatment [1]. These chemotherapy-induced hepatopathies comprise a wide variety of parenchymal and vascular entities, presenting as diffuse or focal lesions (ie steatosis, steatohepatitis, fibrosis, pseudocirrhosis or sinusoidal obstruction syndrome) [1,2].

In the last 2 decades the use of gadoxetic acid (Gd-EOB-DTPA) in magnetic resonance imaging (MRI) has helped to overcome false-negatives in the assessment of tumor response to chemotherapy due to liver parenchymal changes [3–6]. On the other hand, focal chemotherapy-induced alterations, which were previously considered to be mainly a pathologic diagnosis, is becoming a relatively new challenge for radiologists because new chemotherapies have increased its occurrence on imaging, and the focal features may mimic hepatic metastases [7,8].

Knowledge of the possible occurrence of chemotherapy-induced hepatotoxicity, along with the recognition of the typical MRI appearance, are essential to avoid mistakes in liver metastasis detection, and to define the most appropriate clinical management strategy [1].

In particular, recently the extensive use of oxaliplatin to treat patients with colorectal cancer has been reported to be associated with the development of different vascular liver injuries such as sinusoidal obstruction syndrome, and focal nodular hyperplasia (FNH) [9,10]. In a few cases, these vascular changes can be so severe as to induce liver failure, and increase morbidity after hepatectomy [7]. However, in literature the association between oxaliplatin and FNH-like lesions has been reported in only a limited number of cases (less than forty) including case reports and 2 case series of 14 and 15 cases [1,9,11–15].

We reported the case of a 67-year-old man who had laparoscopic right-sided hemicolectomy, 8 years ago, and then systemic chemotherapy with XELOX regimen (capecitabine and oxaliplatin) who developed 2 focal liver nodules which turned out to be FNH-like lesions.

Case report

A 67-year-old male patient with a history of pT3N0M0 colon carcinoma with neuroendocrine differentiation, who had laparoscopic right-sided hemicolectomy 8 years ago, and was subsequently treated with 8 courses of systemic chemotherapy with XELOX regimen (oxaliplatin 130 mg day 1 and Xeloda 1000 mg/m²/12h for 14 days, every 21 days) for 6 months, was referred to the Ultrasound Service of our Radiology Unit because of abdominal pain. Computed tomography (CT) scan performed at the end of chemotherapy, 7 years ago, showed normal aspect of the liver with no evidence of focal lesions (Fig. 1); 5-years follow-up was regular.

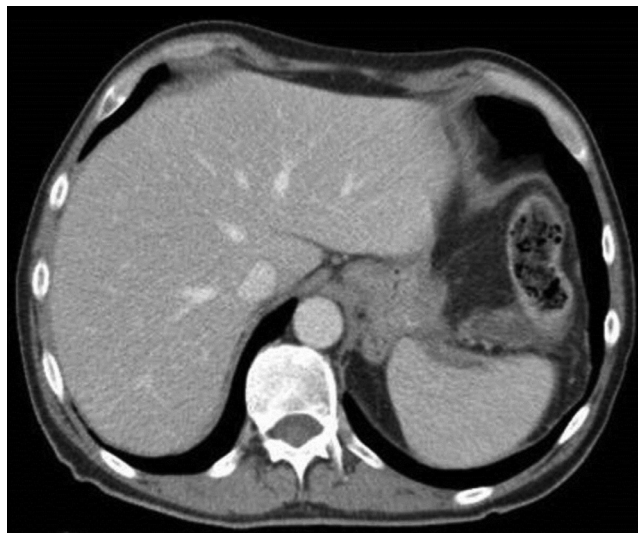


Fig. 1 – CT scan performed after completion of chemotherapy, 8 years ago, revealed normal aspect of the liver with no evidence of focal lesions.

Ultrasound examination showed 2 small hypoechoic hepatic nodules in a background of steatosis (Fig. 2). CT confirmed the onset of 2 lesions in segment VIII and VII (maximum diameter respectively 17 mm and 13 mm) characterized by intense and homogeneous contrast enhancement in the arterial phase with persistent enhancement on venous and delayed phase (Fig. 3), suspected for metastases. Then patient underwent a fluorodeoxyglucose - positron emission tomography (FDG-PET) scan that did not reveal any uptake or signs of metastases (Fig. 4). The hepatocellular liver enzymes were at upper normal limit and blood tumor markers (carcinoembryonic antigen, alpha-fetoprotein, and CA19-9) were within normal ranges.

For further evaluation, we performed Gd-EOB-DTPA-enhanced MRI of the liver: the nodules were slightly hyperintense to liver parenchyma on T2- and nearly isointense on T1- and diffusion weighted images (Fig. 5). MRI Contrast-enhanced dynamic study was similar to the CT and in the hepatobiliary phase, at 20 minutes, lesions were hyperintense with central small hypointensity due to a central scar (Fig. 6). On the basis of previous oxaliplatin-based chemotherapy the imaging findings were compatible, with FNH-like lesions.

To confirm the diagnostic suspicion, multidisciplinary team decided to perform an ultrasound-guided core needle biopsy from the largest nodule in segment VIII of the liver. At histology the lesion showed features resembling focal nodular hyperplasia such as vague nodularity, a few incomplete fibrous bands and ductular reaction, inflammation with no or minimal sinusoidal dilatation, steatosis or hemorrhage. On the basis of Masson stain and glutamine synthetase pseudo map-like the findings were in keeping with the diagnostic suspicion of FNH-like lesion [16–18] (Fig. 7). During a 24-months follow up the patient is alive, free of tumoral recurrence, and the nodules were stable in size.

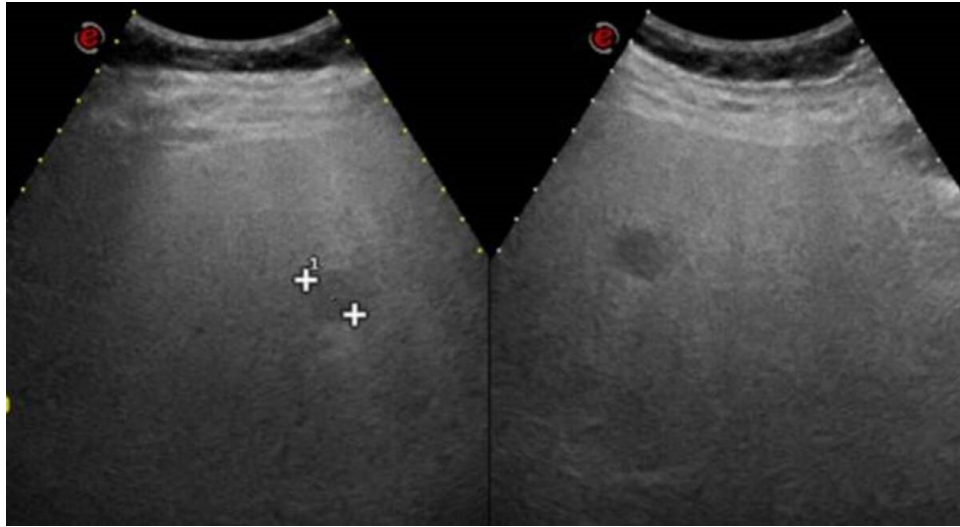


Fig. 2 – The ultrasound examination performed 6 year after completion of chemotherapy showed the onset of 2 small hypochoic hepatic nodules in a background of hepatic steatosis.

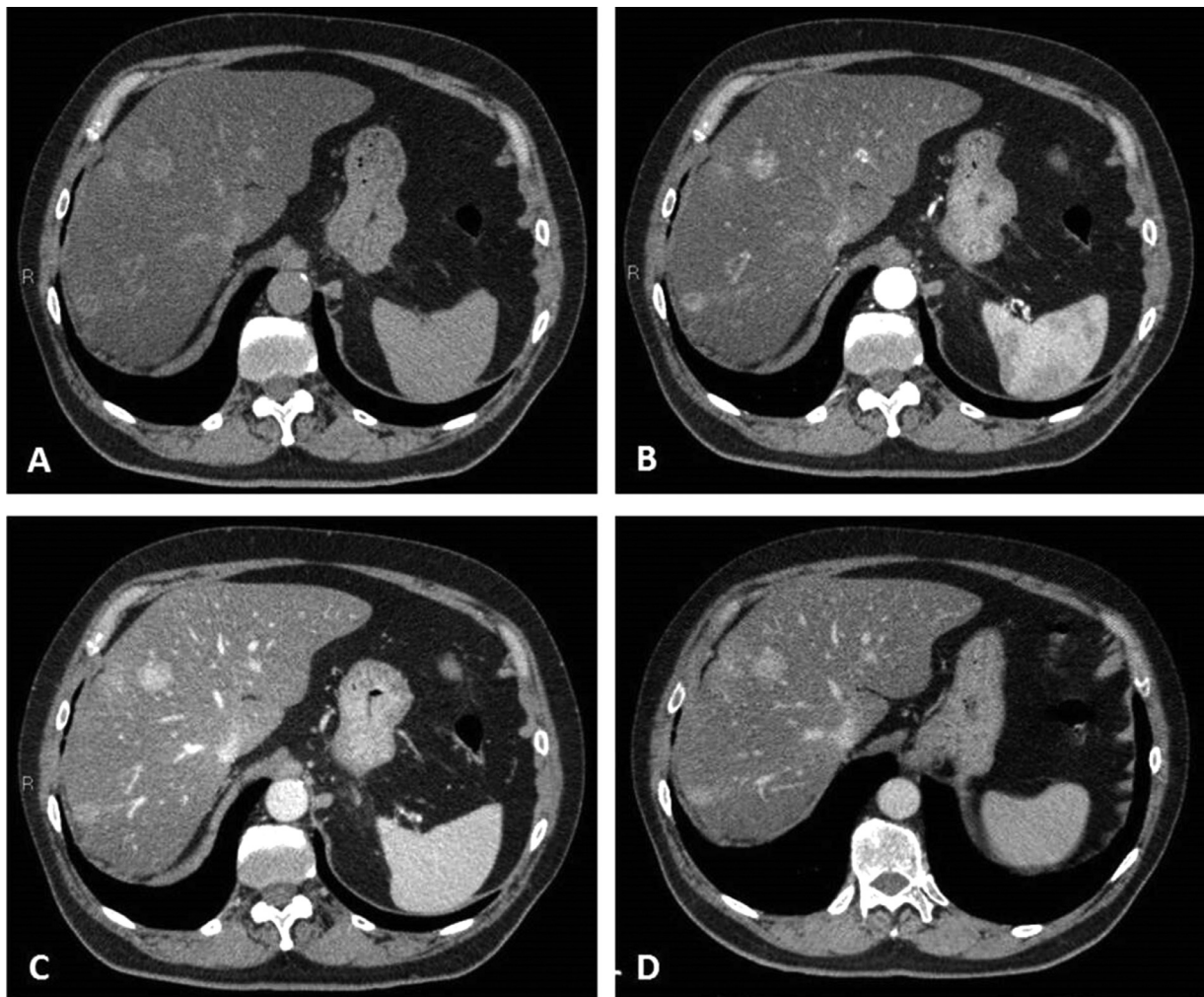


Fig. 3 – Computed tomography confirmed the presence of 2 new hepatic nodules in segment VIII and VII slightly hyperdense on unenhanced CT (A), characterized by intense and homogeneous contrast enhancement in the arterial phase (B) with persistent enhancement on venous (C) and delayed phase (D), suspected for metastases.

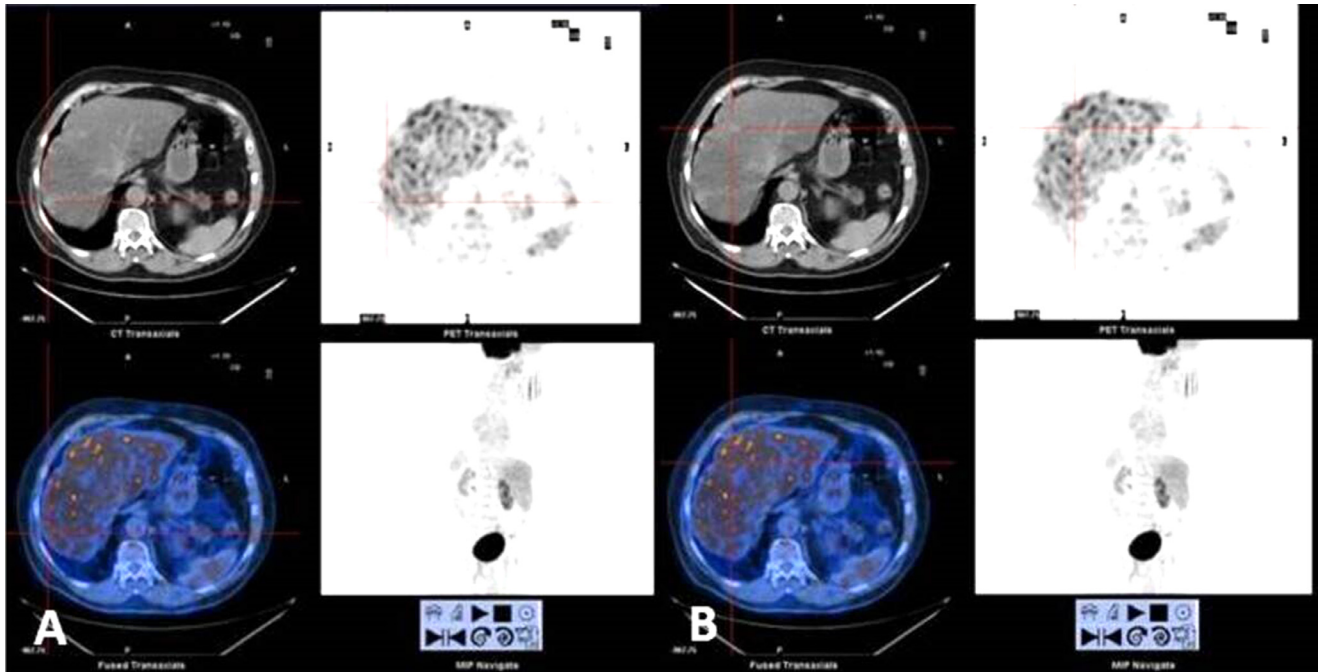


Fig. 4 – Fluorodeoxyglucose - positron emission tomography (PET) scan that did not reveal any uptake or signs of metastases in the site of lesions detected with US and CT (A lesion in segment VII), (B lesion in segment VIII).

Discussion

We presented the case of a patient affected by colorectal cancer who developed 2 FNH-like lesions after oxaliplatin-based chemotherapy.

FNH represent a benign condition that affects normal liver, with a prevalence in ultrasound studies ranging between 0.8% and 3.2% [19]. Histologically, FNH contains all the cell types found in normal hepatic parenchyma, but their structural organization is anomalous. The lesion includes a rearrangement of structurally normal hepatocytes and Kupffer cells with foci of bile-duct proliferation. The bile ducts within the nodule's present signs of active, exuberant proliferation, and they are not connected to the biliary tree. The ducts themselves (especially those in the peripheral regions of the fibrous septa) are surrounded by an intense inflammatory infiltrate [20].

Occasionally, the periseptal zones display evidence of fatty degeneration, bile formation, and Mallory bodies. Specific assays for copper may reveal deposits of the metal within the nodules [20].

Its clinical course is mostly asymptomatic and, therefore, FNH is often diagnosed incidentally during routine abdominal imaging. Because of typical imaging appearance, liver biopsy is not required in most cases and, if performed, has excellent diagnostic performance [20].

FNH-like lesions can occur de novo after systemic chemotherapy and they were initially described in children or young adults treated with high-dose chemotherapy or undergoing chemotherapy before hematopoietic stem cell transplantation [21–26].

Although the exact etiology of FNH is unknown, it is thought to be initiated by local changes in liver perfusion causing a hyperplastic regenerative response of the liver parenchyma. In patients receiving oxaliplatin-based chemotherapy, such changes may be due to portal vein injuries at the level of the sinusoids, and the resulting portal hypertension plays an important role. The natural history of these lesions remains unknown, too. Few spontaneous regressions after the suspension of the chemotherapy have been reported as well as some protective effects of bevacizumab on the development of this toxicity [1,7].

The exact prevalence of the alteration is still unknown [1,10]: in literature the association between oxaliplatin and FNH-like lesions has been reported in only a limited number of patients including occasional case reports and 2 case series with respectively 14 and 15 patients [1,9,11–15].

Post oxaliplatin-based chemotherapy FNH-like lesions are usually multiple and the mean interval between the completion of treatment and the identification of new lesions was 48 months. These alterations are generally smaller than classic FNH and up to 42% of them may increase in size at imaging after a mean follow-up of 29 months; importantly the interval for occurrence of hepatic metastases from colorectal cancer is much shorter. Therefore, the long interval for the lesion occurrence along with typical imaging appearance at MRI are important features to exclude metastases [1,27].

In our case, we identified 2 FNH-like lesions, with a maximum diameter respectively of 17 mm and 13 mm, 72 months after the end of chemotherapy and the nodules remained stable in size during a 24-months follow-up.

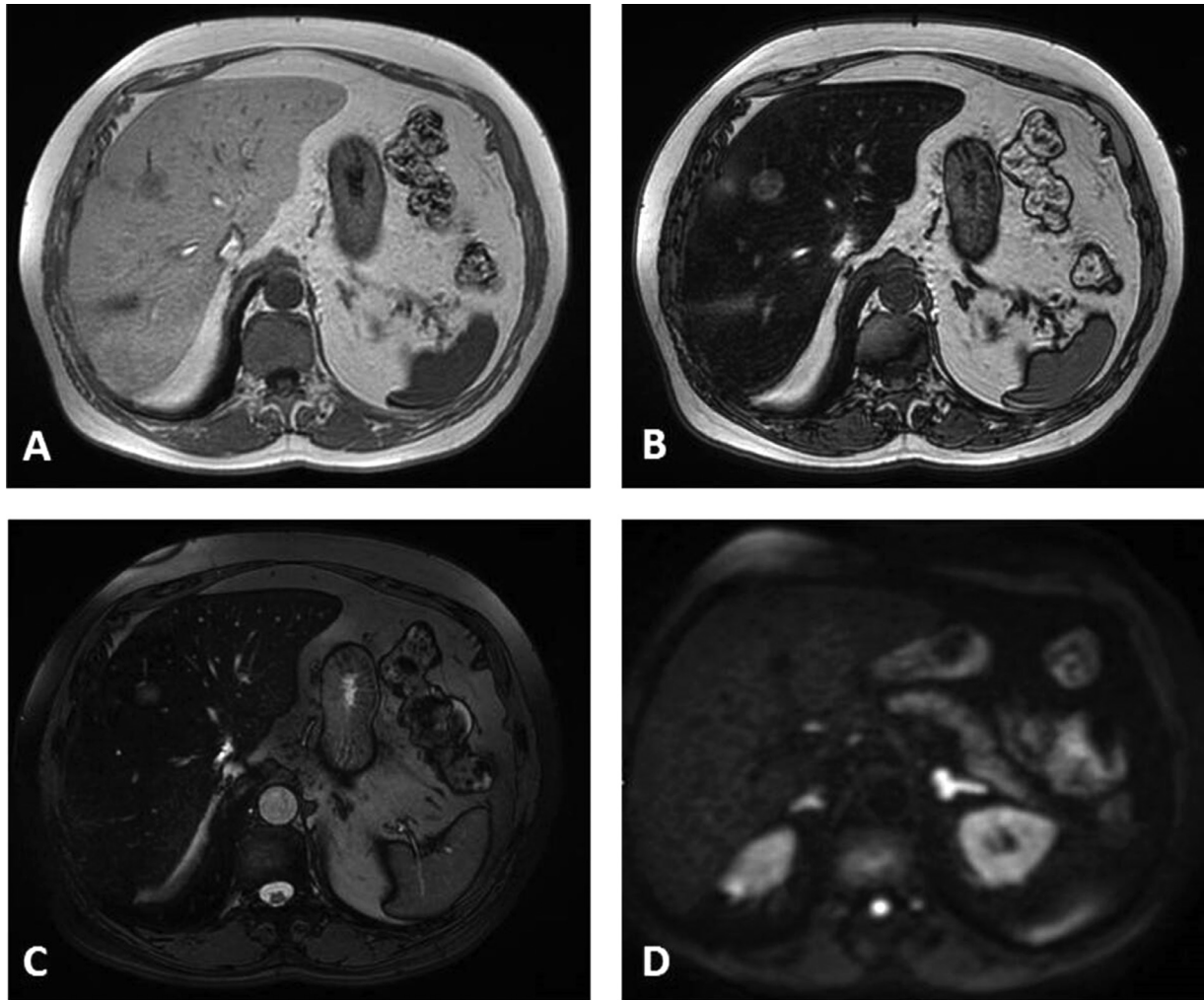


Fig. 5 – At unenhanced MRI the nodule in segment VIII was isointense to liver parenchyma on T1- “in phase” (A) and “out of phase” (B) sequences, slightly hyperintense on T2- (C) and nearly isointense on diffusion weighted images (D). The nodule in segment VII showed some morphologic characteristics.

In many of the cases reported in literature, despite the typical imaging findings patients underwent biopsy or surgical resection because the lack of significant knowledge of this association, and the concern for delaying a diagnosis of metastasis [9,26].

FNH-like nodules do not have any risk of malignant transformation and, therefore, do not require any follow-up or treatment. However, 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 [7].

In particular, MRI with hepatobiliary contrast agents represent the imaging modality of choice for the diagnosis of FNH-like lesions. At MRI, FNH-like lesions are nearly isointense to liver parenchyma on T2-, T1- and diffusion-weighted images; after contrast medium administration they demonstrated homogeneous and strong enhancement in the arterial phase and persistent enhancement on portal venous or delayed phase in most cases; however, washout may be occasionally detected

and, in these cases, the differential diagnosis with HCC is difficult. In the hepatobiliary phase, FNH-like nodules are usually hyper- or isointense to the surrounding liver parenchyma, due to equal or higher OATP1B3 expression compared with the background liver tissue, and a ring (or doughnut-like) pattern is observed in approximately 50% cases. Usually the signal intensity is homogeneously iso- to hyperintense on hepatobiliary when lesions are small, while it may demonstrate a hyperintense rim, and a central hypointense area if the lesions are larger [1,7,28–30].

In healthy and oncologic patients, FNH and FNH-like lesions are likely the most common lesions showing hyperintensity on hepatobiliary phase; while in cirrhotic patients imaging evaluation should be aimed at excluding the presence of the small proportion of HCC that may show hyperintensity in hepatobiliary phase [7,31].

In our case, the neuroendocrine differentiation of the colonic adenocarcinoma could increase the challenges in differential diagnosis because also metastases from a neuroendocrine tumor typically show strong enhancement on arterial

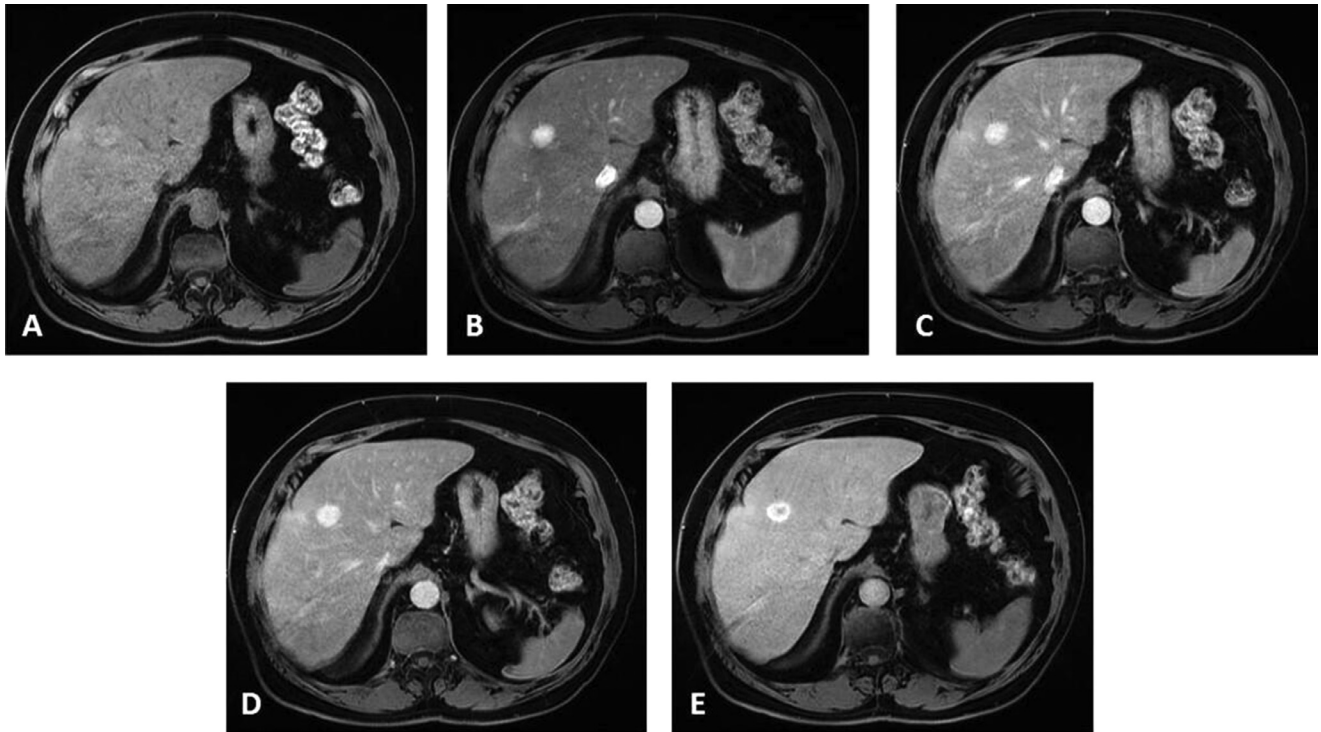


Fig. 6 – Gd-EOB-DTPA-enhanced MRI confirmed the contrastographic behavior of CT scan and revealed hyperintensity of the lesion on hepatobiliary phase image with central small hypointensity due to a central scar. The nodule in segment VII showed the same contrastographic behavior.



Fig. 7 – Histology (A) H&E-stained. Bland hepatocytes surrounded by fibrous septa that contain artery branches and variable degree of bile ductular reaction (most important distinguishing features) and variable amount of mixed inflammatory infiltrate. (B) Immunoreactivity for glutamine synthetase with a map-like pattern of staining. (C) Masson stained. Fibrous septa were highlighted by this special stain.

phase however the hyperintensity in the hepatobiliary phase was highly predictive of FNH-like lesions.

In this specific clinical setting, negative FDG-PET, although important to exclude liver metastases, has some limitations considering the tendency of lower accuracy of FDG-PET after chemotherapy [32].

In conclusion, an increasing proportion of patients with colorectal cancer nowadays receive oxaliplatin-based chemotherapy with the risk in for development a wide variety of parenchymal and vascular injuries, such as FNH-like

lesions. Knowledge of the possible occurrence of these liver alterations lesions in oncologic setting, along with the detection of typical MRI appearance, may reduce the risk of misdiagnosing these lesions as metastases while directing the patient toward a conservative management avoiding unnecessary biopsy or surgery. Moreover, this case confirms the value of hepatobiliary contrast agents in the evaluation of the liver in patients with cancer, not only for the detection of small metastases but also for the differentiation of metastases from benign lesions.

Patient consent

Written informed consent was obtained from the patient. The data that support the findings of this study are available from the corresponding author, (LV), upon reasonable request.

We confirm that this work is original and has not been published elsewhere nor it is currently under consideration for publication elsewhere.

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