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Multifocal Nodular Fatty Infiltration of the Liver: A Case Report of a Challenging Diagnostic Problem

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Female, 59
Final Diagnosis: Multifocal nodular fatty infiltration of the liver
Symptoms: None
Medication: —
Clinical Procedure: Laparoscopy
Specialty: Surgery

Objective: Rare disease
Background: Fatty infiltration of the liver usually has a diffuse pattern, but in very rare cases it presents as multiple focal lesions of the liver, mimicking metastases. A correct diagnosis is crucial to address prognosis and eventual treatment.

Case Report: We present the case of a completely fit and asymptomatic patient referred for multiple bilateral liver metastases of unknown origin. She had no previous history of malignancy. She was extensively investigated with all locally available methods, including ultrasound scan, computed tomography, magnetic resonance imaging, upper and lower gastrointestinal endoscopy, and diagnostic laparoscopy. Imaging-guided biopsy and laparoscopic biopsy confirmed the diagnosis of multifocal fatty infiltration of the liver.

Conclusions: The diagnosis of this condition can be challenging and an accurate initial clinical history must be part of a thorough clinical examination. Multimodal imaging is mandatory, but diagnostic laparoscopy with direct macrobiopsy may be necessary to clear all doubts.

MeSH Keywords: Fatty Liver • Liver Neoplasms • Neoplasms, Unknown Primary

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/897283>



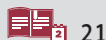
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Background

Fatty infiltration of the liver usually follows a diffuse pattern, with diffuse increased echogenicity on ultrasound scan (USS), reduced density on computed tomography (CT), and T1-hyperintense texture on magnetic resonance imaging (MRI). In very rare cases, it has a nodular pattern of infiltration, with bilateral discrete lesions mimicking metastatic disease. Clearly, this poses difficult problems in diagnosis and treatment, especially in patients with a history of cancer [1]. We present the case of a patient referred for liver metastases of unknown origin.

Case Report

Our patient was a 59-year-old woman with no remarkable past medical history apart from stress incontinence due to pelvic floor disorder. During gynecological workup, an ultrasound scan (USS) of the abdomen and pelvis was requested, which showed multiple bilateral hyperechoic liver lesions, with no halo and no mass-effect. The liver was diffusely “bright” with respect to the right kidney. There was no free fluid and no splenomegaly or any other abnormality (Figure 1). She did not complain of any symptoms. In particular, there were no gastrointestinal or hepatobiliary symptoms, no weight loss, and no signs of active infection. She had no history of cancer or recent trips abroad and no significant family history.

She was physically fit and very active. Physical examination was completely unremarkable. In particular, no enlarged lymph nodes or masses were palpable, no suspect moles were visible, and no breast lesions were palpable. Her weight was 68 kg and her BMI was 23.5.

Blood tests and tumor markers (CEA, AFP, Ca19.9, and Ca125) were all normal.

In particular, lipid profile showed cholesterol and triglycerides levels within the normal range: total cholesterol was 4.3 mmol/L, LDL cholesterol was 2.3 mmol/L, and triglycerides were 2.1 mmol/L.

Computed tomography (CT) scans of chest, abdomen, and pelvis were requested and results confirmed the presence of multiple bilateral hypodense liver lesions, not enhanced after intravenous contrast, and without mass-effect (Figure 2). Liver volume was not deranged. There was no free fluid or enlarged lymph nodes. The appendix was distended. No breast lesions were detected and there were no other findings.

The initial impression was of a tumor of the appendix, with liver metastases.

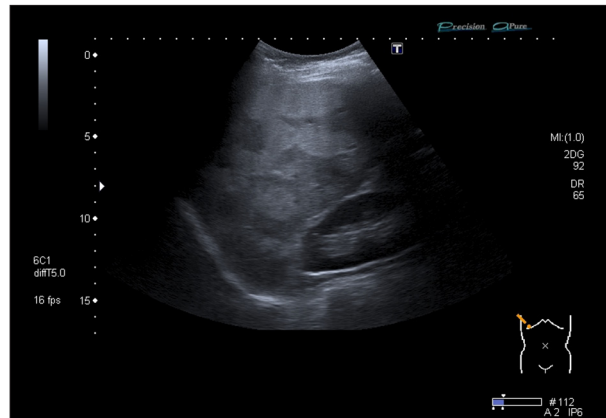


Figure 1. Ultrasound scan of the liver showing multiple homogeneous hyperechoic lesions.

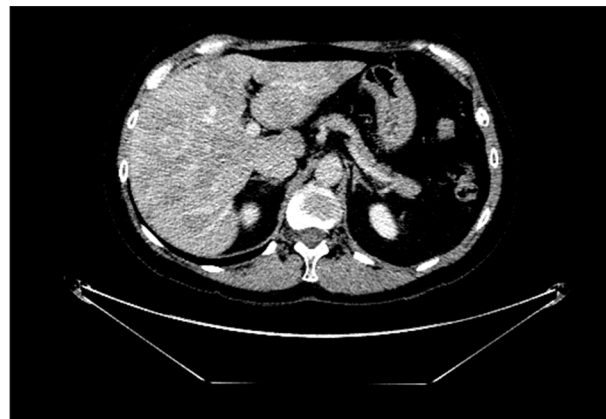


Figure 2. Portal-phase CT of the abdomen showing multiple bilateral hypodense lesions of the liver. A dilated appendix on CT scan raised the possibility of a mucinous tumor of the appendix with liver metastases.

A CT-guided biopsy showed fatty infiltration of the liver, but sampling error could not be excluded.

At this point the case was discussed at our Colorectal Cancer Multidisciplinary Team (CCMDT) meeting, at which the general agreement was that there was not sufficient evidence to make a definitive diagnosis and that further investigations were needed.

Esophago-gastro-duodenoscopy and pancolonoscopy were performed to discover the eventual primary tumor, and both were negative.

MRI of the liver showed multiple bilateral moderately-intense lesions on T1-weighted opposed-phase sequences (Figure 3). No lesions could be seen in fat-suppression images.

A diagnostic laparoscopy was carried out. No free fluid or peritoneal lesions were found. The liver had multiple bilateral

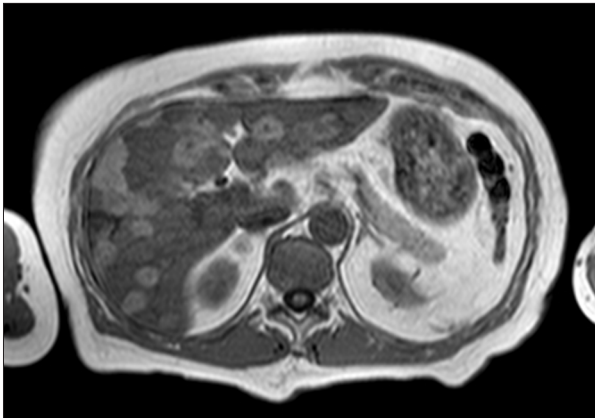


Figure 3. T1-weighted gradient-echo opposite-phase MRI image of the liver showing multiple bilateral moderately intense lesions.



Figure 4. Laparoscopic view showing multiple, whitish, depressed, soft lesions of the liver, not showing any true capsule.

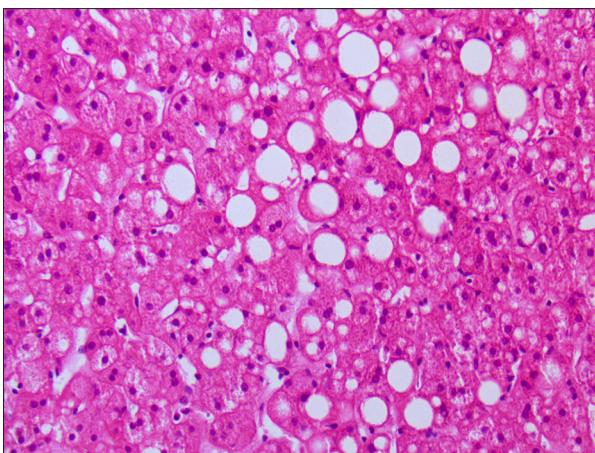


Figure 5. Liver macrobiopsy taken at laparoscopy. Hematoxylin-eosin stained $\times 200$ section shows preserved liver architecture and intracytoplasmic fat vacuoles. Mild-to-moderate fatty change of the liver.

depressed lesions that were soft in consistency (Figure 4). A macrobiopsy was taken from segment 3 and the appendix was removed, although it was apparently normal. Histology confirmed fatty infiltration of the liver (Figure 5) and a totally normal appendix.

The patient was informed of the diagnosis of multifocal nodular fatty infiltration of the liver (MNFIL) and was enrolled in a surveillance program. We arranged for her to have liver US and blood tests with lipid profile on a yearly basis. The first surveillance US done 6 months after the initial diagnosis showed an unchanged situation. She has remained completely asymptomatic. Because her lipid profile was within the normal range, anti-hyperlipidemic medications were not considered at the time. We suggested she continue her regimen of healthy diet and regular physical exercise.

Discussion

The diagnosis of liver lesions may be a challenge for clinicians and radiologists. The widespread use of USS allows the early diagnosis of focal liver lesions, especially in the follow-up of patients with history of cancer. Liver USS is part of our scheme of postoperative follow-up after curative colorectal resection for cancer. It is not uncommon to identify multiple metastases of the liver even before identification of the primary tumor if a USS is performed only on the basis of vague upper abdominal symptoms. In fact, USS is the first-line investigation in patients presenting with dyspepsia and upper abdominal pain/discomfort and it is also part of the baseline workup for other abdominal and pelvic conditions. Our patient was referred for a USS of the abdomen and pelvis as part of the diagnostic evaluation for her pelvic floor disorders.

Unfortunately, despite its high sensitivity for liver lesions [1], USS still has a high rate of false-positive results. Multiple bilateral liver lesions are often reported as metastases, but this appearance may be mimicked by other benign lesions, such as hemangiomas, abscesses, nodular multifocal fatty infiltration, or malignant conditions such as multifocal hepatocellular carcinoma and lymphoma.

In a seriously ill patient who is in poor general condition and has a history of cancer and/or abnormal blood test results, the diagnosis of malignant disease (usually metastatic) is obviously most likely; on the contrary, in young, fit, and asymptomatic patients who have normal blood test results and no relevant past medical history, other possible diagnoses must be considered. In the evaluation of patients with multiple liver lesions, the practitioner must take into account clinical presentation, past medical history, long-term medications, and family history [2].

Liver metastases can be hypoechoic, isoechoic, or hyperechoic. Colorectal cancer liver metastases are usually hypoechoic or can show a bullseye or target-like appearance.

The most common diagnosis of multiple hyperechoic liver lesions in an asymptomatic patient is hemangiomas, but before considering this diagnosis, malignancy must be excluded.

Our patient was completely asymptomatic and had no significant past history; most importantly, she had no history of cancer and her blood test results were normal. Clinically speaking, the diagnosis of multiple liver metastasis of unknown primary origin was quite unlikely, but a more precise diagnosis was required.

Unfortunately, unenhanced USS has a low specificity and more than one-fourth of reports are inconclusive [3]. Contrast USS could be helpful in differentiating benign from malignant lesions [1,4], but it was not yet available at our hospital.

A CT scan showed an even worse situation, with multiple bilateral hypodense lesions (which is the most frequent presentation of liver metastases) and dilatation of the appendix, so the radiologist inferred the liver lesions were metastases from appendicular cancer.

The differential diagnosis of CT-hypodense lesions should also consider other benign and malignant conditions, such as simple cysts, adenomas, abscesses, lymphoma, and fatty infiltration. Although the CT images were quite suggestive, the diagnosis of malignant disease was not completely consistent with the total absence of any clinical sign or symptom.

CT-guided biopsy raised for the first time the possibility of MNFIL, but sampling error could not be excluded. Even if in expert hands CT-guided biopsy yields accurate results in the vast majority of cases, our CCMDT felt that confirmation of this diagnosis was required, so further investigations were performed.

Upper and lower gastrointestinal endoscopies were negative, so we could confidently rule-out the presence of an oesophageal, gastric, duodenal, or colorectal tumor, but other malignancies could not be excluded, such as the proposed appendicular cancer.

MRI of the liver showed multiple moderately intense focal lesions in T1-weighted opposed-phase sequences. MRI can provide information on the histologic characteristics of liver lesions, with a very high specificity, especially for fat-containing lesions [5]. The appearance of MNFIL on MRI obviously depends on the sequence used; it is usually moderately hyperintense in T1-weighted sequences due to the presence of fat tissue. Special sequences such as opposed-phase T1-weighted

or turbo-spin echo T2-weighted sequence with or without fat suppression may be useful, but usually the combination of contrast-enhanced CT and multiple-sequence MRI yields the best results (Table 1) [6–18]. Although MRI has been proposed as a valid alternative to biopsy [6,7], we felt that the risk of misdiagnosis was so high that we could not rely only on indirect investigations (albeit with high specificity, such as with MRI) for such an important differential diagnosis.

Diagnostic laparoscopy helped to clarify the case. The appendix was macroscopically and microscopically normal. The liver had normal volume and margins, but had multiple, bilateral, soft, depressed, whitish lesions. Macrobiopsy on one of these lesions confirmed fatty infiltration. To the best of our knowledge this is the first reported case of MNFIL in which definitive diagnosis was obtained by laparoscopy (Table 1). In another case, laparoscopy was performed but did not provide any useful information because no liver lesion was detected [14].

Laparoscopy is a powerful approach to rule-out malignancy and to confirm diagnosis in case of liver lesions of unknown origin. In expert hands, it allows a thorough exploration of the abdomen, but to get the most value out of this technique, all abdominal spaces and accessible organs must be visualized with a systematic approach, including access to the lesser sac to explore the pancreas and the posterior gastric wall. It should always be accompanied by esophago-gastro-duodenoscopy and pancolonoscopy to maximize its predictive value in ruling-out malignancies.

Undoubtedly, laparoscopic ultrasound could have been of great value in our case in order to perform a complete anatomical evaluation of liver lesions and to rule-out small pancreatic or biliary neoplasms, but at the time this technique was not yet widely available.

It is not clear what evolution one can expect in a case of MNFIL such as the present one. Theoretically, spontaneous resolution is a possibility, as well as progressive reduction of liver function, especially if MNFIL is associated with other important comorbidities.

In this case, MNFIL was not associated with any coexisting disease or medical treatment [7,8,11,19,20]. The patient was completely asymptomatic and her lipid profile was within normal limits, so she was offered only long-term surveillance with yearly blood tests and US scanning.

The majority of scientific articles dealing with this topic reported in the literature focussed on diagnosis of MNFIL, which is definitely the most challenging phase. There is no consensus on the best treatment for this condition or even if MNFIL warrants any treatment. In 1 case, resolution of MNFIL was attributed

Table 1. Some of the cases of MNFIL reported in the literature.

Author, year	No. cases	US	CT	MRI	Laparoscopy	Biopsy
Hashimoto et al., 1990 [6]	6	Multiple hyperechoic nodules (3) Diffuse hyperechogenicity (3)	Hypodense lesions			Imaging-guided biopsy (1)
Ishida et al., 1999 [7]	5	Multiple echogenic nodules	Hypodense lesions (4) Negative CT-scan (1)			US-guided biopsy
Cai et al., 2000 [8]	1		Hypodense lesions			US-guided biopsy
Kroncke et al., 2000 [9]	5		Multiple hypodense lesions	T1-weighted in-phase: isointense (2) or slightly hyperintense (3) T1-weighted opposed phase: hypointense lesions T2-weighted: isointense (1), slightly hyperintense (2)		CT-guided biopsy (3) Liver resection (1)
Kemper et al., 2002 [10]	2	Multiple lesions	Multiple target-like lesions, with hypodense margin and isodense centre	T2-weighted: hyperintense No lesions seen in fat-suppression images		Imaging-guided biopsy (?)
Daberkow et al., 2004 [11]	1	Hyperechoic lesions	Hypodense lesions			
Marin et al., 2006 [12]	1	Multiple hyperechoic lesions	Hypodense lesions	T1-weighted in-phase: no lesions T1-weighted opposed-phase: hypointense T2-weighted: hyperintense		US-guided biopsy
Tamai et al., 2006 [13]	1	Hyperechoic homogeneous lesions with harmonic imaging Contrast-enhanced US: no tumor	Multiple low density areas, no enhancement	T1-weighted in-phase: isointense lesions T1-weighted opposed phase: hypointense lesions T2-weighted: slightly hyperintense		US-guided biopsy
Berkelhammer et al., 2007 [14]	1		Hypodense lesions	Liver lesions No lesions in fat-suppression images	No lesions detected	Imaging-guided biopsy

Table 1 continues. Some of the cases of MNFIL reported in the literature.

Author, year	No. cases	US	CT	MRI	Laparoscopy	Biopsy
Ichikawa et al., 2007 [15]	1		Multiple target-like lesions, with hypodense margin and isodense centre			US-guided biopsy
Plasencia-Martinez et al., 2009 [16]	1	Multiple hyperechoic lesions	Hypodense lesions	T1-weighted in-phase: hyperintense T1-weighted opposed-phase: hypointense T2-weighted: isointense		
Emamaullee et al., 2010 [17]	1	Multiple nodules	Hypodense lesions	T1-weighted opposed-phase: hypointense		US-guided biopsy
Decarie et al., 2011 [18]	1	Multiple hyperechoic nodules	Hypodense lesions	T1-weighted in-phase isointense T1-weighted opposed-phase: hypointense		
Tebala et al., present case	1	Multiple hyperechoic	Hypodense lesions	T1-weighted opposed-phase: moderately intense lesions No lesions in fat-suppression images	Multiple whitish depressed soft lesions, no gross capsule	CT-guided biopsy Laparoscopic biopsy

to the administration of rosiglitazone, an insulin sensitizer, in combination with healthy diet, exercise, weight loss, and vitamin E. In that case the patient was an obese woman with hyperlipidemia, deranged LFT, and reduced glucose tolerance that improved after rosiglitazone administration. Although the authors claimed that the resolution of MNFIL was mainly due to the insulin sensitizer, as demonstrated elsewhere [21], they admitted that lifestyle changes and vitamin E had at least a synergic role [14]. Treatment of steatosis in dyslipidemic patients is linked with the treatment of their obesity and, probably, glucose intolerance; therefore, all agents able to increase insulin sensitivity can be effective in treating fatty infiltration of the liver [21]. However, there is no evidence of their efficacy in MNFIL or in non-obese patients with normal lipid profile.

Conclusions

The diagnosis of focal liver lesions can be challenging. A single diagnostic modality is usually insufficient to fully characterize focal lesions of the liver. Clinical presentation must be taken into account, as well as past medical history and family history. USS is extremely sensitive but has a low specificity. Contrast-enhanced CT and MRI are the methods of choice, but in our opinion, imaging-guided or laparoscopic biopsy is mandatory in doubtful cases. Laparoscopy can play a crucial role in confirming the diagnosis, in particular to rule-out a malignancy. Multifocal nodular fatty infiltration of the liver should be considered in the differential diagnosis of multiple liver lesions, especially if the patient's clinical presentation is not consistent with advanced malignant disease.

Conflict of interest

The Authors have no conflict of interest to disclose.

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