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Case Report

Drug Induced Atypical Multifocal Variant of Fatty Liver Disease Mimicking Metastatic Liver Disease

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ABSTRACT
Fatty infiltration of the liver commonly occurs in a diffuse pattern. However, in very rare presentation in the form of multiple focal lesions of the liver, mimicking metastases do occur. Accurate diagnosis is important to differentiate this condition from metastatic liver disease and hepatobiliary infections. We report a patient who consumed long term herbal remedies, presenting with multifical liver lesions that mimicked metastatic disease and in whom, specialized imaging and a needle biopsy proved the cause to be due to multifocal fatty infiltration of the liver.
Key words: Fatty liver disease, Metastatic liver disease, Multifocal liver lesions, Complementary and Alternative medication, Herbal medicine, Steatosis, Imaging of liver.

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INTRODUCTION

Fatty liver is a very common abnormality that is seen on imaging of abdomen in both inpatient and outpatient scenario. Typically, the accumulation of fat in the liver can be diffuse, diffuse with focal sparing and focal in nature. Rarely, unusual patterns of deposition can be seen, mimicking a variety of other diseases, especially metastatic diseases of the liver. Astute differentiation between these conditions is of utmost importance in patient management.[1] In the era of magnetic resonance imaging, and the rise of specialized techniques of imaging within these modalities, a diagnostic dilemma can be sorted out sooner, unlike in the past. Inflammatory, malignant and vascular conditions are commonly mimicked by heterogenous and non- uniform distribution of fat. Apart from imaging characteristics, a wealth of knowledge regarding risk factors for these diseases and strong history evaluation also adds to ease of diagnosis and avoidance of unnecessary interventions. Alcoholism and non-alcoholic fatty liver disease are the commonest causes of fatty liver disease.[2] Commonly, many drugs are implicated in development of fatty liver disease. Hepatic steatosis is defined as fat deposition in hepatocytes, which is microscopically distributed as microvesicular (multiple small fat vesicles spread throughout the cell) or macrovesicular (large single fat droplet in cytoplasm displacing the nucleus) patterns. Drug induced liver injury is when there is specific biochemical and histologic pattern of hepatocyte injury with timing between initiation of suspected drug intake and onset of liver disease and improvement in liver function after offending drug stoppage. Scoring systems such as Maria and Victorino method, Naranjo scale and Roussel-Uclaf Causality Assessment Method (RUCAM) have been utilized to diagnose drug induced liver injury of any kind.[3] Drug induced injury occurs usually within 90 days of initiation and improves in 2 weeks to 1 month of drug discontinuation (in hepatocellular and chlestatic injury respectively). Drug induced steatohepatitis can occur even months after drug initiation. Many drugs are implicated in steatohepatitis and fatty liver disease. These include, though not exhaustive, aspirin, valproate, zidovudine, didanosine, tetracycline, ibuprofen, glucocorticoids, amiodarone, 5-FU, irinotecan, methotrexate, tamoxifen and vinyl chlorides. Complementary and alternative medications have been considered to cause a spectrum of liver injury from hepatocellular to cholestatic and steatotic type liver dysfunction.[4] Here we present a case of herbal remedy induced fatty liver disease in a middle aged man, in whom, imaging features mimicked multiple cholangiolar abscesses versus metastatic disease. The use of specific specialized imaging sequences helped in delineating the cause to be a rare form of hepatic steatosis, the multi focal variety, which is seldom reported in literature.

CASE REPORT

A 40 year old non obese man without any known comorbidities, with a 10 year history of irritable bowel syndrome presented to our outpatient department with features of loss of appetite, right upper abdominal pain and lethargy since a period of one month. Prior to onset of his symptoms, he was regularly consuming complementary and alternative medication in the form of herbal remedy three months before, for his constipation and bloating. He denied abdominal distension and bleeding diathesis. The patient has not been on any other medications other than

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the herbal remedy regularly and has been on intermittent proton pump inhibitors for his bloating and dyspepsia. There was no history suggestive of active alcoholism or other recreational substance abuse. He is not known to suffer from prior liver diseases and has neither received blood transfusions nor underwent any surgical procedures in the recent past. On examination, the patient was moderately built with a BMI of 21.8, conscious and alert, afebrile and hemodynamically stable. There was no evidence of pallor or icterus, cyanosis, clubbing, significant lymphadenopathy or edema. The abdomen was distended, which was soft to palpation with mild tenderness in the right upper quadrant in the absence of organomegaly or free fluid. The respiratory, cardiac and neurological evaluation was well within normal limits. On further investigations, he was found to have hemoglobin of 12.3 g/dL with normal leucocyte and platelet counts. The erythrocyte sedimentation rate (ESR) was 60 mm. Liver function tests revealed the presence of hyperbilirubinemia (total bilirubin of 2.5 mg/dL with a direct fraction of 1.8 mg/dL) and alanine and aspartate transaminase elevated to more than 2.5 times the upper limit of normal. The serum gamma glutamyl peptidase and serum alkaline phosphatase were also raised more than 3 times the upper limit of normal. Kidney function tests were within normal limits and work up for hepatotropic viruses suchas hepatitis A, B, C and E were negative. HIV, Hepatitis C and E RNA were also negative and atypical viral serology including parvovirus B and cytomegalovirus (CMV) were also negative. His autoimmune markers, viz. antinuclear antibody, anti smooth muscle antibody, anti liver-kidney microsomal antibody and anti liver soluble antigen were negative. An ultrasonography imaging of the abdomen, revealed the presence of multiple hyperechoic areas, dispersed throughout both lobes of the liver (right > left) with maintained hepatic architecture in the absence of free fluid or splenomegaly [Figure 1 A and B]. Furthermore, a contrast enhanced magnetic resonance imaging (MRI) was performed which showed hypointense lesions on T1- weighted images and same lesions that were slightly hyperintense on T2-weighted images. Magnetic resonance imaging. Axial Fiesta sequences showed the corresponding images seen on ultrasound as patchy hyperintense areas followed by MRI in-phase with their corresponding out-phase acquisitions showing signal loss in patchy areas that was suggestive of multifocal patchy fatty infiltration [Figure 1 C and D]. From the combination of in-phase and opposed phase MRI, these scattered lesions were shown to be fatty infiltrations. A subsequent sonography guided needle biopsy of the liver (FNAC) lesion confirmed the histologic diagnosis of hepatic steatosis [Figure 2]. The patient was treated with N acetyl cysteine infusions, high protein supplements and was advised a low fat diet, life style modifications and not to take complementary and alternative medications. He remained well 2 months after the initial diagnosis.

DISCUSSION

Fatty liver disease is very common in certain population groups such as alcohol consumers (45%), dyslipidemic patients (50%), those who are obese (75%) and more than 95% in those who are obese alcohol consumers.[5] The standard of diagnosis in fatty liver disease is liver biopsy and histopathology. Currently specialized cross sectional imaging has become helpful in diagnosis of fatty liver albeit the need for liver biopsy. The latter is reserved only for confirmation of cases in dilemma. Fatty liver is diagnosed when liver echogenicity exceeds that of renal cortex or spleen with loss of diaphragmatic definition and poor visualization of intrahepatic components, especially the venous vasculature early on. On contrast enhanced imaging with computed tomography, fatty liver produces greater attenuation than the spleen intrahepatic vessels appear attenuated. Fatty liver occurs in the presence of absolute liver attenuation of 40 HU.[6] With the emergence of MRI and its technical evolution, fatty liver disease diagnosis on cross sectional studies has become more prevalent. Chemical shift gradient echo imaging with in and out/opposed phase acquisitions are most widely used for assessment of fatty liver. The basic fundamental is that signal intensity of the normal liver parenchyma is similar on in phase and opposed phase imaging. In the presence of loss of signal intensity on opposed phase imaging, in comparison to in phase, fatty liver can be safely diagnosed. This can also help in quantifying the amount of fat, by assessment of degree of signal intensity loss. In the in phase gradient echo imaging, either T1 or T2, higher than normal liver intensity is suggestive of fat deposition.[7] Cur-

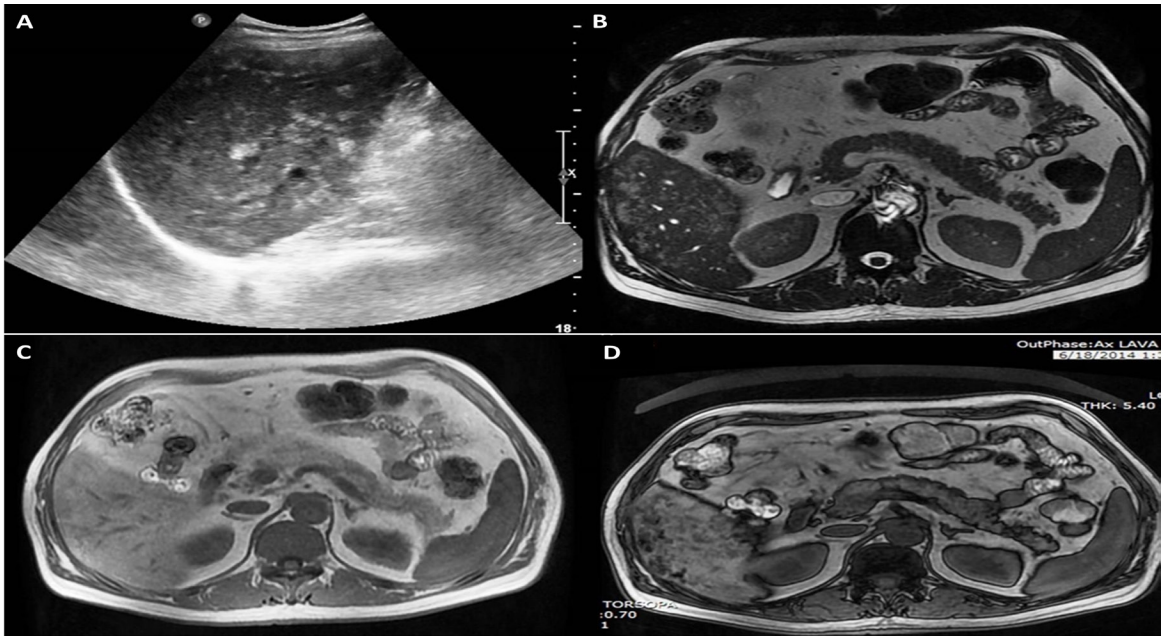

Figure 1: Ultrasound image (A) and corresponding MRI Axial Fiesta imaging (B) showing multiple small ill-defined hyperechoic areas and corresponding patchy hyperintense areas respectively; magnetic resonance imaging in-phase (C) with the corresponding opposed-phase (D) acquisitions showing signal loss in patchy areas corresponding with multifocal patchy fatty infiltration.

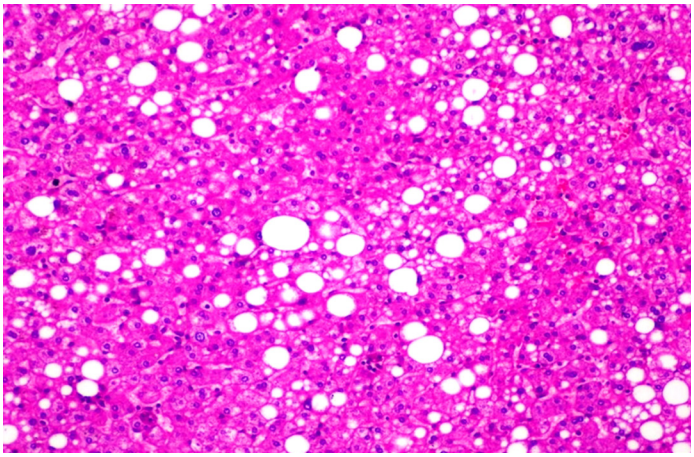

Figure 2: Hepatic steatosis, diagnosed on FNAC from scattered liver lesions. H and E stain (20x).

rently, proton magnetic resonance spectroscopy is the most reliable and accurate in diagnosis of fatty liver disease.[8] In our case, hepatic steatosis was mainly secondary to drug (herbal remedy) induced liver injury. The patient's initial presentation and the finding of scattered lesions in the liver initially struck as that of scattered abscesses or metastatic liver disease, even though other red flag symptoms and signs of pyogenic abscess and malignancy were absent. Drug induced steatosis has been well described. Drugs that mainly cause steatosis include methotrexate, nucleoside reverse transcriptase inhibitors, tetracycline and valproic acid and those that cause steatohepatitis include mainly amiodarone, tamoxifen and valproic acid. Even though our patient did not consume any of these commonly implicated drugs, the only offending agent that resulted in his current liver injury could be well attributed to recent long standing intake of herbal remedy and improvement of his condition with drug withdrawal. Herbal and dietary supplements are an upcoming cause of drug induced liver injury world-wide. Fatty liver can have different patterns of deposition such as diffuse (most commonly encountered), focal and focal sparing (that characteristically occur in specific areas such as adjacent to falciform ligament, in the porta-hepatis and in gall bladder fossa, mostly due to variant venous circulation), perivascular deposition (characterized by halos of fat surrounding hepatic and portal veins), subcapsular deposition (seen mostly in renal patients of insulin dependent diabetes mellitus, in whom addition of insulin to the dialysate exposes subcapsular hepatocytes to a higher concentration of insulin leading to fatty deposition, manifested as discrete nodules or confluent peripheral lesions) and multifocal fat deposition, which is the most uncommon type in which the lesions are scattered in atypical locations throughout the liver.[9] Rochon *et al* in 1990 had reported on the association of multifocal hepatic fatty lesions simulating metastases in a patient who had acquired immunodeficiency syndrome and pathologically proved CMV hepatitis. Furthermore, mutifocal heaptic steatosis in association with acquired immunodeficiency has been reported by Sterling *et al*, Redvanly *et al* and Glasgow *et al* in patients with similar presentations.[10-13] Tamai *et al* in 2006 reviewed a case of multi focal hepatic steatosis in a follow up patient of adenocarcinoma of breast who had undergone extensive chemo radiation. In their report, they utilized Levovist enhanced sonography in which the hepatic lesions retained contrast microbubbles to the same degree as liver parenchyma, ruling out the presence of malignancy. Levovist is a galactose-based contrast media which accumulates in liver parenchyma in the late phase of sonography. Levovist accumulates inside in sinusoids or Kupffer cells. Acoustic emission from these by ultrasonic pressure improves visualization of isoechoic or liver metastases. Levovist contrast scanning may not be available at all centers. In such cases, magnetic resonance imaging with in phase and opposed phase sequences are best utilized to differentiate fatty lesions from malignancy.[14] Kroncke *et al* reported the use of this modality in hepatic steatosis and concluded that the combination of in phase and opposed phase gradient echo imaging can sensitively differentiate between metastases and multi focal fatty infiltration.[15] Even when the imaging is highly suggestive of fatty liver disease, a strong suspicion of malignancy can only be ruled by a selectively guided FNAC from the liver lesions. In our report, the hepatic lesions on magnetic resonance imaging were strongly suggestive of hepatic steatosis. Even then, for conclusive evidence, an FNAC was performed and fatty liver disease was confirmed. Focal fatty changes on FNAC can still be erroneously made even in the presence of malignancy and astute clinical acumen is required in such situations. To avoid un-necessary biopsy, MRI imaging or Levovist imaging are good options to tackle the dilemma. Our patient did not have any underlying comorbidities as described previously as the cause of multifocal fatty liver and occult infectious causes were all ruled out. The use of herbal remedy was a strong factor leading to multifocal fatty liver disease in our patient, a scenario that has never been reported before. In patients who present with multifocal liver lesions, a carefully taken history, including drug history and a simple change in modality of imaging with specific sequences can aid the treating physician to confirm diagnosis and avoid un wanted alarming provisional diagnoses.

CONCLUSION

The utility of a single diagnostic modality is usually insufficient in diffuse liver lesions. Clinical presentation, medical and family history are important contributing factors. Use of contrast-enhanced imaging are methods of choice, but, imaging-guided biopsy is extremely useful and mandatory in specific situations. Multifocal fatty infiltration of the liver is an important differential diagnosis in patients presenting with multiple liver lesions requiring precision diagnosis to differentiate from metastatic malignancy and hepato-biliary infections.

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CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATION USED

RUCAM: Roussel-Uclaf Causality Assessment Method; 5-FU: 5 Flurouracil; BMI: Body mass index; ESR: Erythrocyte sedimentation rate; MRI: Magnetic resonance imaging; FNAC: Fine needle aspiration cytology; CMV: cytomegalovirus.

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