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Case Report

Multinodular fatty liver after herpes-zoster vaccine: Case report and review of the literature

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Abstract

Multinodular fatty liver (MNFL) is a pattern of fatty infiltration of the liver characterized by multiple well-circumscribed nodules on hepatic imaging, often raising the concern of metastatic malignancy. Here we describe a case of MNFL and review the published literature. There is likely some association between traditional risk factors for hepatic steatosis (e.g. alcohol, rapid weight change, metabolic syndrome, medications, TPN) and MNFL. Further study and reporting of cases of MNFL are needed to better characterize its pathogenesis and natural history.

Key words: Steatosis, steatohepatitis, nonalcoholic fatty liver disease, focal fatty liver

Multinodular fatty liver (MNFL) is a pattern of fatty infiltration of the liver characterized by multiple well-circumscribed nodules which are hyperechoic on ultrasound and of relatively low attenuation on computerized tomography scan, often raising the concern of metastatic malignancy. This entity has been described mostly in the radiological literature, usually as isolated case reports or small case series. Its pathogenesis and natural history are not well-known. Here we describe a case of MNFL and review the published literature.

Case

A 72 year-old female received the varicella-zoster (VZ) vaccine at the time of a routine check up with her primary care physician. She was asymptomatic and her laboratory tests were non-contributory, including liver tests. She subsequently developed anorexia, malaise, diarrhea, and a rash on her chest three weeks later. Biopsy of the rash showed acantholytic dermatosis, which subsided after a couple of weeks. Initial laboratory studies were significant for alkaline phosphatase 715 U/L (range 31-103 U/L), aspartate aminotransferase 82 U/L (range 7-36 U/L), alanine aminotransferase 114 U/L (range 4-45 U/L), total bilirubin 1.1 mg/dL (range 0.2-1.1 mg/dL), and albumin 4.8 g/dL (range 3.7-5.1 g/dL). Serologic tests for hepatitis B, hepatitis C, Epstein Barr virus, VZ and cytomegalovirus were all negative. Cytomegalovirus, Epstein Barr virus and VZ were not detected by polymerase chain reaction. Nuclear and smooth muscle antibodies were negative. An ultrasound done at that time showed a heterogeneous liver. A computerized tomography scan showed numerous enhancing liver lesions suggestive of metastatic liver disease. This was confirmed on subsequent magnetic resonance imaging *(Figure 1)*.

Her past medical history was significant for hyperlipidemia, gastroesophageal reflux disease, cardiac arrhythmia, hypothyroidism, and depression. She was on a stable medical regimen of levothyroxine, esomeprazole, fluoxetine, glucosamine, atenolol, trazodone, risedronate, calcium, and estrogen. She was afebrile, body mass index was 23.6, and physical examination was non-contributory.

An ultrasound-guided biopsy of one of the liver lesions was performed. Pathology showed mild portal and lobular inflammation with a small area of diffuse mild microvesicular steatosis and a focus of macrovesicular steatosis. No dysplasia or malignancy was identified.

Because of the concern for metastasis, a repeat guided biopsy was ordered. However, computed tomography at the time of this biopsy showed complete resolution of the hepatic lesions. Repeat laboratory studies at that time showed complete normalization of her hepatic profile.

Approximately two months later, the patient again developed malaise. Hepatic profile was again abnormal: alkaline phosphatase of 382 U/L, aspartate aminotransferase 55 U/L (range 7-36 U/L), alanine aminotransferase 90 U/L (range 4-45 U/L), total bilirubin 0.9 mg/dL (range 0.2-1.1 mg/dL), and albumin 3.9 g/dL (range 3.7-5.1 g/

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Abbreviations:
MNFL: multinodular fatty liver
VZ: varicella-zoster
PCT: porphyria cutanea tarda

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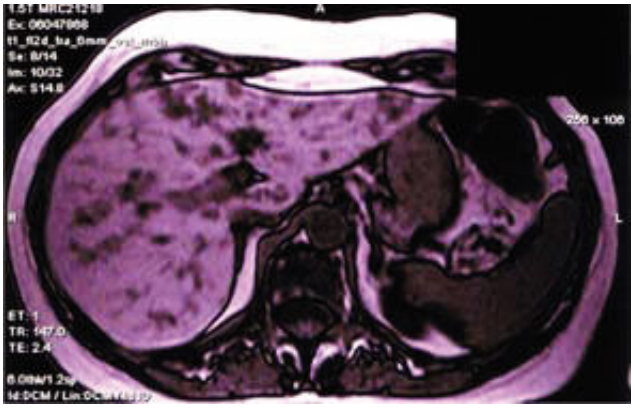

Figure 1. Magnetic resonance imaging showing multiple enhancing liver lesions suggestive of metastatic liver disease.

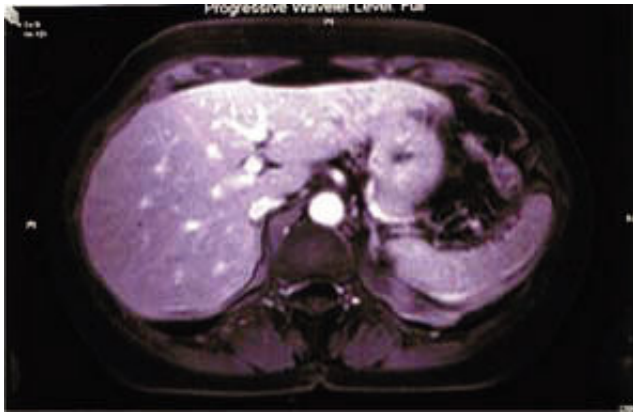

Figure 2. Magnetic resonance imaging of the liver done 9 months after initial presentation was essentially normal.

dL). Magnetic resonance imaging done at that time showed only new diffuse perivascular T1 low intensity and T2 hyperintensity, producing a mottled appearance of the liver. A percutaneous liver biopsy obtained at that time showed only mild hepatitis and cholangitis. An endoscopic retrograde cholangiopancreatography was unremarkable.

Since the time of the second biopsy, the patient had one more episode of malaise with subsequent elevation of liver profile numbers that again resolved on its own. Latest magnetic resonance imaging of the liver done 9 months after her initial presentation was essentially normal *(Figure 2).*

Published sases

At least 103 cases of MNFL have been reported in the literature to date. 49 of these cases had histopathology with 88% confirming steatosis,[1-15,17-20,22,24,25] 10% not reporting the results of biopsy,[2] and 2% showing histology consistent with hepatitis C only.[21] In 42 cases, there was resolution of the liver lesions with various therapeutic interventions or with time.[2,3,8,11-13,19,20,24-26] Broadly, the cases can be categorized into patients with underlying chronic liver disease, malignancy, metabolic syndrome, patients on total parenteral nutrition or medications known to cause hepatic steatosis, and patients with porphyria.

Chronic liver disease

36 cases, or 35% of the total number of cases, had underlying chronic liver disease. The vast majority (91%) of these patients had alcoholic liver disease,[2,3,11,12,25,26] which is known to more commonly cause diffuse hepatic steatosis and steatohepatitis. Smaller percentages had underlying hepatitis C (8%)[11,17,21] or were compound heterozygotes for the hereditary hemochromatosis H63D/C282Y mutations (6%).[15,16]

Malignancy

32 cases, or 31% of the total number of cases, underlying malignancy,[14] had primary or metastatic liver tumor,[10] 5 had breast cancer,[1,9,13,25] 2 had cervical cancer,[1,18] 2 had primary central nervous system malignancy,[1] 2 had gastric cancer[13,14] 1 had ovarian cancer,[13] 1 had lung cancer,[24] 1 had colorectal cancer,[14] and 4 had an unreported type of malignancy.[2] It is not immediately obvious why there may be an association between malignancy and MNFL, but one may speculate on several possible explanations: 1) Patients with malignancy undergo more abdominal imaging than patients without malignancy, and MNFL would therefore simply be detected more often in these patients; 2) Patients with malignancy may have rapid and/or large changes in weight which may predispose to hepatic steatosis, though it is not clear why they may develop MNFL rather than diffuse steatosis; 3) This may be a variant of chemotherapy associated steatosis or steatohepatitis, which has been most commonly reported in patients undergoing neoadjuvant chemotherapy for colorectal cancer prior to hepatic metastectomy.[27,28]

Metabolic syndrome

19 cases, or 18% of the total number of cases, were patients who had elements of the metabolic syndrome.[1-3,5,6,9,12,16,19,24] Support for at least an association between MNFL and the metabolic syndrome was demonstrated in two cases by reversal of MNFL that paralleled weight loss or improvement of insulin resistance. In one case report, an obese patient with gastric cancer who lost approximately 40 pounds after gastric resection had complete resolution of his MNFL.[13] In another case of a patient with coronary artery disease, hyperlipidemia, obesity, and newly diagnosed diabetes mellitus, MNFL resolved after initiation of rosiglitazone.[19]

Medications or total parenteral nutrition

11 cases, or 11% of the total number of cases, were patients on medications known to be associated with hepatic steatosis or patients on total parenteral nutrition, which is also known to be associated with hepatic steatosis. 7 patients were on steroids,[1] 2 were on hormone replacement therapy,[15] and 2 were on total parenteral nutrition.[1,2]

Porphyria

10 cases, or 10% of the total number of cases, were patients with some form of porphyria. 4 patients had porphyria cutanea tarda (PCT) and 6 were other variants of chronic hepatic porphyria.[12,16] Of the four patients with PCT, the suspected etiologies of the PCT in each were valproate,[8] an unclassified hepatotoxin,[13] hepatitis and alcohol,[11] and alcohol alone.[25] Interestingly, withdrawal of the offending agent, either alcohol[11,25] or valproate,[8] along with chloroquine therapy,[8,11,25] or phlebotomy[11] resulted in complete resolution of the PCT and MNFL. It is unclear whether resolution of MNFL in these cases was related to the PCT therapy itself or simply withdrawal of alcohol or valproate, which are both associated with hepatic steatosis.

Discussion

Our case does not fit neatly into the characteristics of any of the previously described cases of MNFL. Our patient did not have underlying chronic liver disease, malignancy, or metabolic syndrome. She was on hormone replacement therapy but had been on this chronically. Finally, she had no obvious symptoms of porphyria, though we did not check for any biochemical evidence of subclinical porphyria. Involvement of the small bile ducts, represented by a normal endoscopic retrograde cholangiopancreatography, elevation of the alkaline phosphatase, and cholangitis on liver biopsy, seems to be very uncommon in the reported cases of MNFL. In the literature, there is only one similar MNFL case presenting with significant elevation of the alkaline phosphatase. This was a report describing a patient with presumed disseminated malignancy who had expired. At autopsy, no malignancy was found, but the liver was enlarged with several areas of focal fatty infiltration. There was no comment on the bile ducts.[7]

Given the temporal relationship between the VZ vaccine and our patient's symptoms, it is tempting to relate the two, especially given that all her work up was noncontributory. However, review of published data did not reveal any reports of even elevated liver tests, let alone MNFL, in patients receiving the VZ vaccine.[29] Nevertheless, an idiosyncratic reaction to the vaccine is plausible. It could have evoked a transient immune response to similar endogenous proteins inciting an autoimmune reaction (molecular mimicry), similar to the proposed mechanism of autoimmunity in patients with primary biliary cirrhosis.[30]

Though it is currently not possible to determine the exact pathogenesis of MNFL, the available literature indicates that there is likely some association between traditional risk factors for hepatic steatosis (e.g. alcohol, rapid weight change, metabolic syndrome, medications, total parenteral nutrition) and MNFL. Further study and reporting of cases of MNFL are needed to better characterize its pathogenesis and natural history.

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