Minimally invasive percutaneous endovascular therapies in the management of complications of non-alcoholic fatty liver disease (NAFLD): A case report

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Radiology Case. 2015 Sep; 9(9):36-43 :: DOI: 10.3941/jrcr.v9i9.2557

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of disorders from simple steatosis to inflammation leading to fibrosis, cirrhosis, and even hepatocellular carcinoma. With the progressive epidemics of obesity and diabetes, major risk factors in the development and pathogenesis of NAFLD, the prevalence of NAFLD and its associated complications including liver failure and hepatocellular carcinoma is expected to increase by 2030 with an enormous health and economic impact. We present a patient who developed Hepatocellular carcinoma (HCC) from nonalcoholic steatohepatitis (NASH) cirrhosis. Due to morbid obesity, she was not an optimal transplant candidate and was not initially listed. After attempts for lifestyle modifications failed to lead to weight reduction, a transarterial embolization of the left gastric artery was performed. This is the sixth such procedure in humans in literature. Subsequently she had a meaningful drop in BMI from 42 to 36 over the following 6 months ultimately leading to her being listed for transplant. During this time, the left hepatic HCC was treated with chemoembolization without evidence of recurrence. In this article, we wish to highlight the use of minimally invasive percutaneous endovascular therapies such as transarterial chemoembolization (TACE) in the comprehensive management of the NAFLD spectrum and percutaneous transarterial embolization of the left gastric artery (LGA), a novel method, for the management of obesity.

CASE REPORT

CASE REPORT

A 68-year-old woman with a past medical history of morbid obesity, type 2 diabetes, and hypertension was referred to our clinic for evaluation of cirrhosis in January 2012. She weighed 81 kg with body mass index (BMI) 42. Review of previous labs reports revealed normal liver enzymes, elevated fasting glucose, and HbA1c. Serology for hepatitis viral infection and antinuclear antibodies were also negative. She had abdominoplasty at the time of C Section 27 years ago. Her primary physician had diagnosed her with nonalcoholic fatty liver disease (NAFLD) in 2010. US done in January 2012 revealed a cirrhotic liver (Figure 1a, b). Follow up US in July 2013 showed a 1.8 cm echogenic nodule in the left lobe (Figure 1c). Considering this picture in a non-alcoholic obese diabetic patient a diagnosis of hepatocellular carcinoma (HCC) from NASH cirrhosis was made. An MRI 3 months later confirmed changes of cirrhosis with a stable nodule in left lobe of liver showing enhancement features diagnostic of HCC (Figure 1d, e).

Based on Milan criteria for transplant in HCC (1), she could have been offered liver transplant. However, in view of morbid obesity she was not an ideal candidate and was not enlisted for transplant. To reduce weight she was advised to increase her physical activity and was referred to a nutritionist for dietary counseling. There was no change in her weight for next 7 months. At a multidisciplinary tumor board a decision was made to perform a lesser-known endovascular therapy, left gastric artery (LGA) embolization to help her in reducing the weight. The long-term plan was to reduce her weight of about 9 kg in the next 6 months, with subsequent loco regional therapy to control tumor growth.

Fundal branches of left gastric artery were embolized (right femoral artery access) until near stasis was achieved using Embosphere® Microspheres (Embosphere, Biosphere Medical, Rockland, MA, USA) (Figure 2). Post-embolization celiac angiogram confirmed absence of flow in the left gastric artery with patent common hepatic and splenic arteries. There was no complication during or after the procedure.

After 2 months, patient's weight was 74.5 kg with BMI 38. Even though the weight was steadily decreasing and the patient can be enlisted for liver transplant, we decided to control the growth of the tumor since liver transplants are hard to get. According to Barcelona criteria, first line treatment of HCC (<3cm) with associated disease is ablation. We decided to go against it since the tumor was very close to the liver capsule and performing a RF ablation would be painful if liver capsule was involved. Further, technically, it would be difficult to find an appropriate 'landing zone' for the shaft of the RFA probe. Also there is a theoretical chance of tumor seeding as there is no zone for tract ablation. We decided to treat HCC with transarterial chemoembolization (TACE) and the procedure was done twice to completely devitalize the tumor (Figure 3). A repeat CT scan revealed no viable tumor (Figure 3a).

Seven months after LGA embolization patient weighted 71.5 kg with BMI 36 without any lifestyle modifications like dietary changes or exercise. She said that she feels like a different person and unlike her past self, 'doesn't crave for food anymore'. Although HCC free, the transplant team placed her on the transplant list for elective surgery. Patient's timeline is graphically illustrated in Figure 4.

DISCUSSION

Etiology & Demographics

Nonalcoholic fatty liver disease, a global epidemic, represents a spectrum of disorders from simple steatosis to inflammation (NASH) leading to fibrosis, cirrhosis and even hepatocellular carcinoma.

Worldwide prevalence of NAFLD ranges from 6.3% to 33%, and NASH ranges from 3 to 5% (2). Obesity, diabetes mellitus, and hyperlipidemia are established risk factors for primary NAFLD (3). Simple hepatic steatosis, NASH, and advanced liver fibrosis all can progress to HCC. Although a majority remains stable, NAFL can progress to NASH in up to 25% of patients (4, 5). Of patients with NASH, 26%-37% of them progress to fibrosis and out of them 9-25 % progress to cirrhosis (2).

Clinical & Imaging features

Although some patients present with signs of liver disease, most patients with NAFLD are asymptomatic. They are usually associated with features of metabolic syndrome like obesity. Most cases are incidentally discovered when they are referred for workup of elevated liver transaminases. The definition of NAFLD requires that there is evidence of hepatic steatosis, either by imaging or by histology and there are no causes for secondary hepatic fat accumulation such as alcohol consumption or other causes of hepatitis. Prognosis depends on the severity of liver injury. Identification of early cirrhosis or advanced (bridging) fibrosis may alter management; hence, staging is important (2).

Liver biopsy remains the only reliable method for differentiating NASH from simple steatosis. However, it is expensive and carries some morbidity. Hence, its use is limited to only those patients who would benefit the most from the diagnosis in terms of prognosis and patient care (6). Various non-invasive imaging methods such as US, CT, MRI, and magnetic resonance spectroscopy (MRS) have been utilized to evaluate patients with NAFLD.

Characteristic findings on US are "bright liver" and loss of definition of the diaphragm due to posterior beam attenuation. US is a well-established and cost-effective imaging technique for screening subjects at risk of NAFLD, not effective in grading .At unenhanced CT, a normal liver has higher attenuation than a normal spleen. If lower, a diagnosis of hepatic steatosis may be considered. CT is not useful for detecting mild steatosis, but accurate for the diagnosis of moderate-to-severe steatosis. CT detects complication of cirrhosis like portal Hypertension and HCC. However, due to the potential radiation hazard, it is considered inappropriate for longitudinal follow-up (2, 7, 8).

Magnetic resonance (MR) imaging is one of the most sensitive modalities for detection and characterization of fatty liver. The degree of fat infiltration can be estimated by using either chemical shift imaging or MR spectroscopy. These techniques split the net MR signal into fat and water signal components, allowing the quantification of fat in liver tissue. In-phase and opposed-phase imaging sequences are used in MRI. In the in-phase sequence, fat in liver is brighter in signal intensity than the spleen and para-spinal muscles. In out-of-phase sequences there is a lower signal intensity of liver than on the corresponding in-phase images, this difference in signal intensity establishes the diagnosis of fatty liver (7).

However, imaging modalities are far less reliable at detecting NASH and the associated stages of fibrosis. Ultrasound imaging and ?-fetoprotein estimation play an important role in screening patient with cirrhosis for HCC. CT and MRI with contrast are useful in diagnosing and managing complications of cirrhosis and HCC. More recently, several imaging methods that measure liver stiffness have been investigated for their usefulness in assessing inflammation and fibrosis in patients with NAFLD. Innovative radiologic

modalities such as the US elastography (USE) and MR Elastography (MRE) are emerging as promising methods to diagnose NASH and/or advanced fibrosis in patients with NAFLD (8).

Management & Prognosis

The goal of managing NAFLD spectrum is by:

1. *Elimination of risk factors and preventing fibrosis:*

The primary approach to treat NAFLD involves elimination of the underlying risk factors. It has been shown that community-based lifestyle modification programs are effective in reducing and normalizing liver fat in NAFLD patients. This can be achieved either by hypo caloric diet alone or in conjunction with exercise (9).

Lifestyle interventions are often very difficult for patients to follow and sustain. Bariatric surgery has an increasing role in the management of patients with obesity. Various types of bariatric surgeries are available. In carefully selected patients, weight loss after bariatric surgery has demonstrated histological improvement in hepatic steatosis and fibrosis reducing long-term mortality (10, 11). However, bariatric surgery should be avoided in subjects with advanced cirrhosis, as there is a risk of hepatic decompensation with rapid weight loss, besides other risks of surgery (12). High mortality rates are also seen post-bariatric surgery (13, 14). A recent Cochrane review concluded that there is insufficient data to determine if bariatric surgery is an effective treatment for NAFLD (15).

2. *Management of complications of Cirrhosis and HCC:*

Patients with NASH cirrhosis are at risk of developing HCC similar to cirrhosis with any other etiology. Once HCC develops, management protocols are similar irrespective of etiology. NASH HCC have less-severe liver dysfunction and better overall survival after curative treatment compared to counterparts with hepatitis C and/or alcoholic liver disease (16). The best treatment option for NASH HCC is Liver transplantation, failing which locoregional therapies like Transarterial chemoembolization (TACE) or RF ablation can serve either as a bridge to transplant or as palliation (17).

Role of Left Gastric artery embolization:

Recent studies performed in animal models have demonstrated that body weight can be reduced by percutaneous, catheter-directed, transarterial embolization of the left gastric artery, the artery that preferentially provides blood flow to the fundus of the stomach (18, 19). Their hypothesis was that selective LGA embolization could cause relative ischemia in the mucosa of the gastric fundus, which could, in turn, suppress the production of the hormone ghrelin. Ghrelin acts at the level of hypothalamus to stimulate food intake (orexigenic effect) leading to weight gain in both animal and human models (20). Hence, suppression of ghrelin production through LGA embolization would help to reduce weight.

So far, only two studies have been done in humans using LGA embolization. Oklu et al. retrospectively reviewed the results of 15 patients who underwent LGA embolization for gastric hemorrhage in their institution. They reported that, three months after the procedure the decrease in body weight was more in LGA embolization (7.9%) as compared to embolization of other upper gastrointestinal arteries (1.2%) (22). Klipshidze et al. reported the results of a first-in-human prospective study of LGA embolization in five patients with 300-500-?m microspheres. The mean weight, body mass index, and ghrelin levels were decreased at 1 month, 3 months, and 6 months post-procedure (21). Similarly, in our patient we observed 10 kg (12%) decrease in body weight at the end of six months after LGA embolization.

Differential Diagnosis

Various imaging can diagnose fatty liver. However evaluation of etiology is based on clinical findings, laboratory investigation and histopathological correlation. The nutritional status of the individual including obesity or severe malnutrition including those individuals on total parenteral nutrition and patients on a starvation diet can cause fatty infiltration of the liver. Some of the drug induced causes include alcohol consumption as well as glucocorticoids, amiodarone, tamoxifen and methotrexate. Metabolic abnormalities like lipodystrophies, galactosemia glycogen storage diseases are also known to cause fatty infiltration of the liver. Other rarer causes include celiac sprue, wilson disease and inflammatory bowel disease (23).

TEACHING POINT

Minimally invasive percutaneous endovascular therapies such as transarterial chemoembolization (TACE) can be used in the comprehensive management of the NAFLD spectrum and percutaneous transarterial embolization of the left gastric artery (LGA), a novel method, for the management of obesity.

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FIGURES

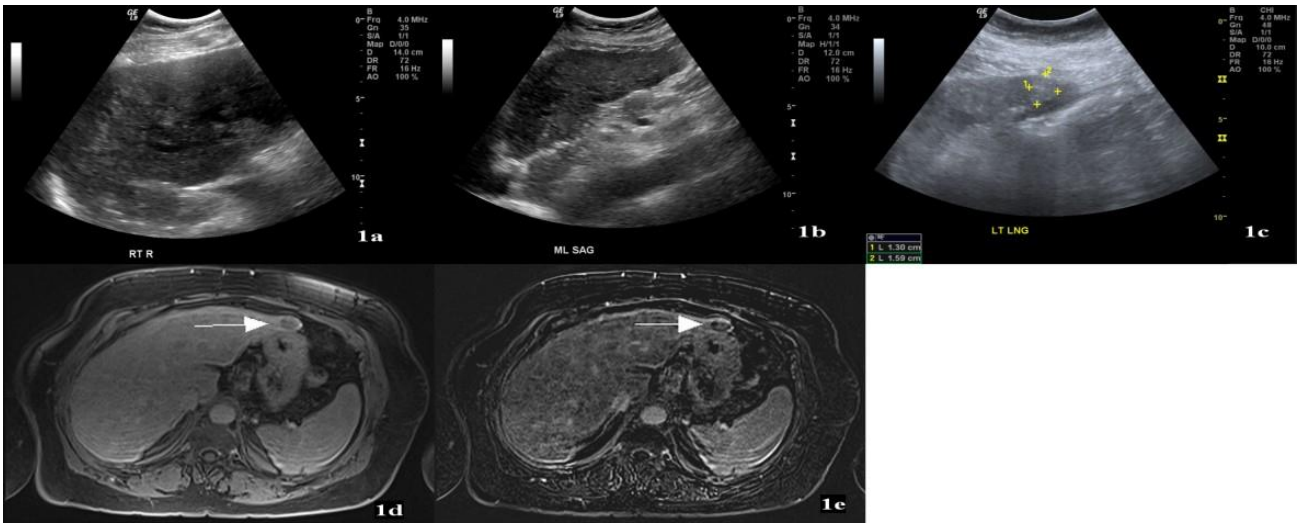


Figure 1: 68-year-old woman with a past medical history of morbid obesity, type 2 diabetes, and hypertension diagnosed with NAFL and later NASH Cirrhosis.

Findings: a) Gray scale US, oblique view in right hypochondrium, showing a coarse echo pattern of the liver with a nodular surface suggestive of cirrhosis. b) Gray scale US, longitudinal view in midline epigastrium shows similar echo pattern in the left lobe of the liver. c) Six months later , gray scale US, oblique view in midline epigastrium shows a well encapsulated echogenic nodule in left lobe of the liver(between yellow marks) . d)Triple phase contrast enhanced MRI axial views, upper abdomen showed a definite well-encapsulated enhancing lesion found on the lateral margin of the lateral segment of the left lobe of the liver measuring 1.8 cm in size (arrow)with arterial phase enhancement e) Definite washout was seen on delayed images (arrow) . Imaging features were consistent with a diagnosis of HCC.

Technique: Duplex ultrasonography with GE Logiq E9, 2.5- 4 MHz. MAGNETOM Symphony 1.5T, T1 weighted VIBE fat saturated axial sequence, TR 4, TE 2, post 12cc Omniscan contrast injection

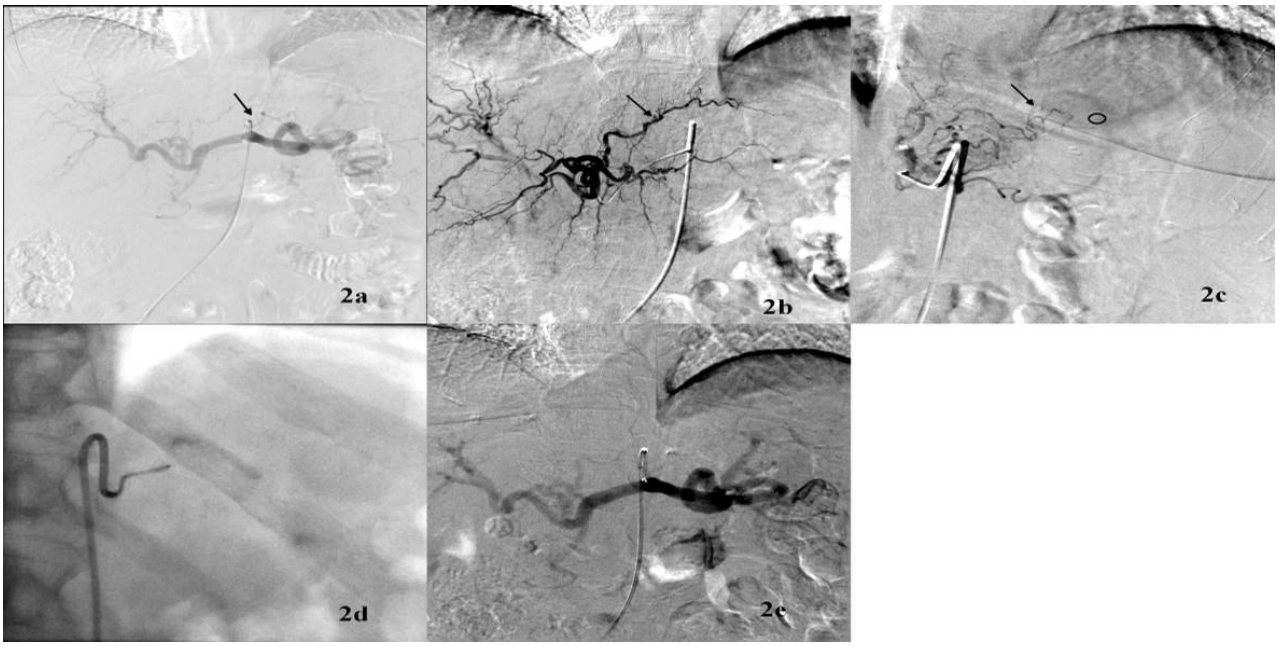


Figure 2: 68-year-old woman with a past medical history of morbid obesity, type 2 diabetes, and hypertension diagnosed with NAFL and later NASH cirrhosis.

Findings: Digital subtraction Angiogram (DSA), serial images in the upper abdomen frontal view. a) Celiac angiogram using a 5-Fr catheter showed a normal-appearing left gastric artery (arrow) in addition to tortuous hepatic arteries and a hypertrophic splenic artery. b) Left gastric arteriogram using a 2.4 French Progreat micro catheter (Progreat ®; Terumo, Tokyo, Japan) showed normal course and caliber of the left gastric artery (arrow) . c) Embolization of the fundal branches (arrow) was performed using 500-700 um Embosphere® Microspheres (Embosphere, Biosphere Medical, Rockland, MA, USA).Circle indicates anatomical location of fundus of stomach. d) Stasis of contrast was achieved with no forward flow in the left gastric artery. e) Post-embolization celiac angiogram showed absence of flow into the left gastric artery with normal flow in to common hepatic and splenic arteries.

Technique: DSA protocol: trans catheter injection of 12 ml contrast media at a flow of 3 ml/sec, Visipaque (Iodixanol) 320 (GE Healthcare, Waukesha, WI) performed on a clinical angiography system (Axiom Artis FA/BA; Siemens AG, Erlangen, Germany)

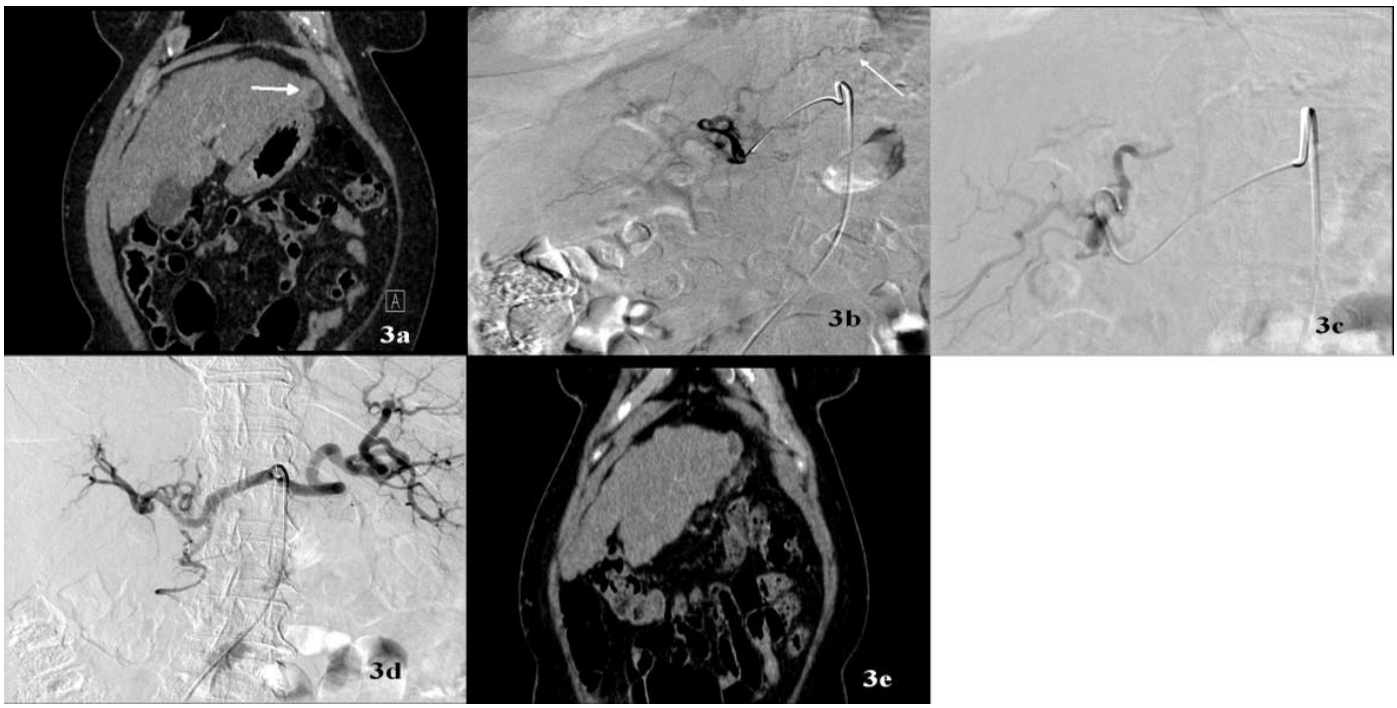
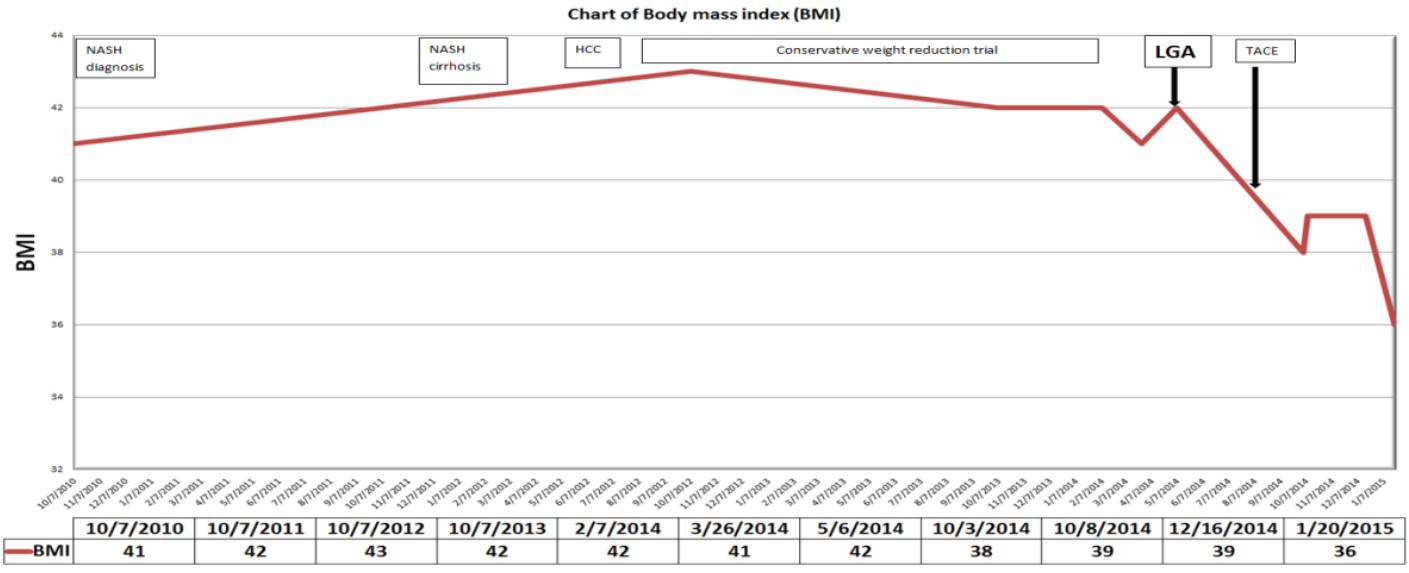


Figure 3: 68-year-old woman with a past medical history of morbid obesity, type 2 diabetes, and hypertension diagnosed with NAFL and later NASH Cirrhosis.
Findings: a) Arterial Phase CT scan, axial image in the upper abdomen after injection of intravenous contrast, reveals a hypodense lesion in segment II of the liver measuring 1.8 x 1.8 cm and containing a well-defined enhancing capsule (arrow) b) Digital subtraction Angiogram (DSA), serial images in the upper abdomen frontal view reveal , of the left hepatic artery reveals a small hypervascular blush (arrow). c) TACE was performed via segment 2/3 hepatic branches with 75mg of Doxorubicin 100-300um drug eluting beads. d) Post chemo-embolization left hepatic angiogram revealed no flow in the segment 2/3 hepatic branch with no hypervascular blush. e) Arterial Phase CT scan, after injection of intravenous contrast axial image in the upper abdomen reveals no enhancement in the previously seen left lobe of liver lesion.
Technique: CT scanner: Siemens Somatom emotion, 95 mAs, 130 Kv, slice thickness 2.5mm, intravenous contrast: 100 ml Omnipaque 300.
DSA protocol: transcatheter injection of 10 ml contrast media at a flow of 2 ml/sec, Visipaque (Iodixanol) 320 (GE Healthcare, Waukesha, WI) performed on a clinical angiography system (Axiom Artis FA/BA; Siemens AG, Erlangen, Germany)



	10/7/2010	10/7/2011	10/7/2012	10/7/2013	2/7/2014	3/26/2014	5/6/2014	10/3/2014	10/8/2014	12/16/2014	1/20/2015
BMI	41	42	43	42	42	41	42	38	39	39	36

Figure 4: Graphical illustration of patient's timeline

Etiology	Not definite, Metabolic syndrome (Obesity, diabetes mellitus, hyperlipidemia) has been established as risk factors for primary NAFLD. Pathogenesis: "3-hit hypothesis." "1st hit" consists of hepatic triglyceride accumulation combined with "2nd hit," such as proinflammatory cytokines leads to steatohepatitis and/or fibrosis. Cell death with impaired proliferation of hepatocyte progenitor cells represents the proposed "3rd hit"
Incidence	Worldwide prevalence of NAFLD ranges from 6.3% to 33%, NASH is 3 to 5% Simple hepatic steatosis, NASH, and advanced liver fibrosis all can progress to HCC. 25% NAFL can progress to NASH Of NASH, 26%-37% progress to fibrosis and up to 9-25 % progressing to cirrhosis.
Gender ratio	None established
Age predilection	None established
Risk factors	Metabolic syndrome (Obesity, diabetes mellitus, hyperlipidemia) have been established as risk factors for primary NAFLD.
Treatment and prognosis	Goal of managing NAFLD spectrum 1. Eliminate risk factors and preventing fibrosis : a. Lifestyle modification programs: Diet alone or in conjunction with exercise. b. Pharmacological treatment c. Bariatric surgery. 2. Management of complications of Cirrhosis and HCC: a. Complications of Cirrhosis: Management of ascites and varices. b. HCC: Management protocols are similar to that in viral etiology of HCC. Once HCC develops, the best treatment option is Liver transplantation, failing which loco regional therapies like TACE or ablation can serve either as a bridge to transplant or as palliation.
Findings on imaging	Liver biopsy: Gold standard in diagnosis and staging of NAFLD Non Invasive modalities : US, CT and MRI/ MRS are used for staging US : "bright liver", loss of definition of the diaphragm CT: On unenhanced scan, a lower attenuation of liver as compared to spleen. MRI: In-phase: fat in liver is brighter in signal intensity than the spleen and para-spinal muscles. Out-of-phase: lower signal intensity of liver than on the corresponding in-phase images; this difference in signal intensity establishes the diagnosis of fatty liver. MRS: Most of the identifiable peaks are derived from water and fat Emerging role of US and MR elastography in noninvasive detection of fibrosis

Table 1: Summary of Nonalcoholic fatty liver disease (NAFLD)

Causes of fatty liver	
Drugs	• Alcohol • Glucocorticoids • Amiodarone • Tamoxifen • Methotrexate
Metabolic abnormalities	• Lipodystrophy • Galactosemia • Glycogen storage diseases • Homocystinuria • Tyrosinemia
Nutritional status	• Over nutrition (Obesity) • Severe malnutrition • Total parenteral nutrition • Starvation diet
Others	• Celiac sprue • Wilson disease • Inflammatory bowel disease

Table 2: Differential diagnosis for causes of fatty liver

Modality	Imaging features	Role in NAFLD spectrum
US	Characteristic findings on US are "bright liver", loss of definition of the diaphragm	Well-established and cost-effective imaging technique for screening subjects NAFLD.
CT	At unenhanced CT, a normal liver has higher attenuation than a normal spleen. If lower, a diagnosis of hepatic steatosis may be considered.	Not useful for detecting mild steatosis .Due to the potential radiation hazard, inappropriate for longitudinal follow-up. Useful to detect complication of Cirrhosis like Portal Hypertension and HCC
MRI	*Chemical Shift Artifact* • In-phase: fat in liver is brighter in signal intensity than the spleen and para-spinal muscles. • Out-of-phase: lower signal intensity of liver than on the corresponding in-phase images, and this difference in signal intensity establishes the diagnosis of fatty liver. *MRS:* • Most of the identifiable peaks are derived from water and fat	One of the most sensitive modalities in the diagnosis, treatment, and follow-up of NAFLD.
Innovative radiologic modalities	Fibroscan, transient elastography (TE): sends a pulse through the skin, which is circulated through the liver. The velocity of the wave correlates with liver stiffness.	New imaging technologies evaluate liver stiffness by measuring the velocity of shear wave using US or MRI.

Table 3: Imaging in Nonalcoholic fatty liver disease (NAFLD)

ABBREVIATIONS

CT = Computed tomography
HCC = Hepatocellular carcinoma
LGA = Left gastric artery
MRE = MR Elastography
MRI = Magnetic resonance imaging
MRS = Magnetic resonance spectrography
NAFLD = Nonalcoholic fatty liver disease
NASH = Nonalcoholic steatohepatitis
TACE = Transarterial chemoembolization
US = Ultrasound

KEYWORDS

Nonalcoholic fatty liver disease; NAFLD; Hepatocellular carcinoma; HCC; Nonalcoholic steatohepatitis; NASH; Left Gastric artery embolization; Transarterial chemoembolization; TACE