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ORIGINAL ARTICLE

Retrospective Study

Post-infantile giant cell hepatitis: A single center's experience over 25 years

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Abstract

BACKGROUND

Giant cell hepatitis in the adult population remains very poorly defined with only 100 case reports published in the literature over the last three decades.

AIM

To present our center's experience in an attempt to learn about the predisposing factors, outcomes and efficacy of proposed therapeutic interventions for giant cell hepatitis.

METHODS

A retrospective chart review was conducted through the electronic records of the University of Pittsburgh Medical Center. We queried 36726 liver biopsy reports from January 1, 1991 to December 6, 2016. Our search yielded 50 patients who were identified as carrying a definite diagnosis of post-infantile giant cell hepatitis (PIGCH) by pathology. The data collected included demographic information, laboratory data (liver function tests, autoimmune markers) and transplant status. In order to better analyze patient characteristics and outcomes, subjects were separated into a non-transplant (native) liver group and a post-liver transplant (allograft) group.

RESULTS

The incidence of PIGCH was approximately 0.14% of all biopsies queried in the

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25-year period. The mean age was 48 years with 66% females. Liver function tests were classified as 38.2% cholestatic, 35.3% hepatocellular and 26.5% mixed. Autoimmune hepatitis was found to be the most prevalent predisposing factor leading to PIGCH constituting 32% of cases. Management consisted mainly of immunosuppression, viral targeted therapy, supportive care and in six cases liver transplantations.

CONCLUSION
The diagnosis of PIGCH remains clinically challenging and requires a high index of suspicion as well as a thorough history, physical examination, serological workup and liver biopsy. Treatment of the underlying cause can result in clinical stability in a large number of cases.

Key words: Post-infantile giant cell hepatitis; Liver transplantation; Autoimmune hepatitis

Core tip: Post-infantile giant cell hepatitis is a rare disorder and very poorly defined in the literature. Our study aimed to present our center's experience in an attempt to shed more light about the predisposing factors, outcomes and efficacy of proposed therapeutic interventions for post-infantile giant cell hepatitis.

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INTRODUCTION

Giant cell hepatitis (GCH) is a relatively common histologic finding in neonates. It is believed to occur secondary to insults to immature hepatocytes. In children, it typically presents with cholestasis, conjugated hyperbilirubinemia and variable degrees of inflammation[1]. Idiopathic GCH refers to these histologic findings with a structurally intact biliary system as opposed to conditions where biliary abnormalities are present, such as biliary atresia[1]. The most commonly proposed patho-physiological hypothesis to account for the presence of giant cells includes an ineffective cytoplasmic division in the setting of cellular fission (endomitosis) in contrast to cellular hepatocyte fusion secondary to hepatic injury[2].

As common as GCH is in children, it is exceedingly rare in adults. GCH in the adult population remains very poorly defined with only 100 case reports published in the literature over the last three decades[3]. In adults the entity is referred to as post-infantile giant cell hepatitis (PIGCH), also known as syncytial or adult onset GCH. PIGCH represents a histologic diagnosis that has been associated with a myriad of medical conditions including infectious, hematologic, autoimmune disorders and drug reactions (Table 1)[3-13]. Pathological analysis is characterized by the presence of giant multinucleated syncytial hepatocytes. In particular, more than four to five nuclei in hepatocytes should be seen in a single lobule combined with other features of hepatitis such as lobular disarray, inflammation, Kupffer cell hypertrophy and spotty hepatocytes necrosis (Figure 1).

The clinical course of patients with giant cells on histology is widely variable, ranging from minimal symptoms without major clinical implications to acute liver failure that is often times fatal despite standard clinical care. In the current study, we aimed to present our center's experience with this very rare disease entity in an attempt to shed more light about its predisposing factors, outcomes and efficacy of proposed therapeutic interventions.

MATERIALS AND METHODS

After obtaining local institutional review board approval, we queried liver biopsy reports (36726) at the University of Pittsburgh Medical Center electronic records using

Table 1 Reported causes of post-infantile giant cell hepatitis

Infectious	Hepatitis A, B, C
	Epstein-Barr virus (EBV)
	Cytomegalovirus (CMV)
	Paramyxo-like virus
	Human immunodeficiency virus (HIV)
	Herpesvirus 6A
	Human papillomavirus (HPV)
Autoimmune	Autoimmune hepatitis (AIH)
	Ulcerative colitis (UC)
	Primary sclerosing cholangitis (PSC)
	Primary biliary cholangitis (PBC)
	Systemic lupus erythematosus (SLE)
	Rheumatoid arthritis (RA)
	Polyarteritis nodosa (PAN)
Drugs	Methotrexate
	6 mercaptopurine
	Amytriptyline
	P-aminosalicylic acid
	Vinyl chloride
	Chropromazine
	Methotrexate
Hematologic	Chronic lymphocytic leukemia (CLL)
	Lymphoma
	Sickle cell disease (SCC)
	Hypereosinophilia
	Autoimmune hemolytic anemia
Endocrine	Hypoparathyroidism
Infiltrative	Sarcoidosis
Post-transplant	-
Idiopathic	-

the keywords "giant cell hepatitis" from January 1, 1991 to December 6, 2016. Our search yielded 127 individual patient records, of which 45 were diagnosed prior to 18 years of age. The remaining 82 records were evaluated by three physicians (BM, SM, MM) after which 50 patients were identified as carrying a definite diagnosis of PIGCH based on liver biopsy. In order to better analyze patient characteristics and outcomes, subjects were separated into a non-transplant (native) liver group and a post-liver transplant (allograft) group.

RESULTS

The incidence of PIGCH was approximately 0.14% of all biopsies queried in the 25-year period. The mean age of the studied patient sample was 48 years with 66% females. Liver function tests were classified as follows: 38.2% cholestatic, 35.3% hepatocellular and 26.5% mixed; 73.5% of patients had bilirubin values exceeding 1.5 mg/dL at the time of diagnosis and 42% of patients had bilirubin values exceeding 5 mg/dL. Mean follow up of the entire cohort was over six years (79 mo; SD = 76.1). Patient demographics and liver function tests for patients are outlined in Table 2. Patients with GCH found in the native liver group were older, had higher aspartate aminotransferase, alanine aminotransferase and total bilirubin when compared to the allograft group.

Autoimmune hepatitis (AIH) was found to be the most prevalent predisposing factor leading to PIGCH constituting 32% of cases, while drugs accounted for 12% of cases. Other etiological associations included viral infections [hepatitis A, B, C (HCV), cytomegalovirus (CMV), Epstein-Barr virus], systemic autoimmune conditions (but not enough to give a diagnosis of AIH) and hematologic conditions. In nearly 1/3 of

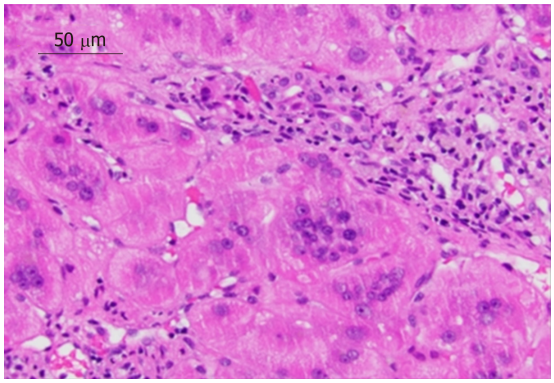

Figure 1 Liver biopsy of 44-year-old female with autoimmune hepatitis (hematoxylin and eosin stain 40 ×). Biopsy revealed chronic hepatitis with prominent giant multinucleated hepatocytes.

cases, no predisposing factor for PIGCH was found (idiopathic). In the post-transplant population, the most prevalent predisposing factor leading to PIGCH was AIH as well, accounting for 30% of cases.

Autoimmune markers related to liver disease were common: Anti-nuclear antibody in 34% of cases, elevated immunoglobulin G in 22% of cases, anti-smooth muscle antibody in 10% of cases, anti-mitochondrial antibody in 8% of cases and anti-liver kidney microsomal antibody in 2% of cases.

Drugs which were identified as the possible culprit for GCH development consisted of microdantin, ranitidine, omeprazole, moxifloxacin, ranitidine, plaquenil as well as chromium picolinate.

Notable pathological findings included diffuse necrosis in 24% of the patients, inflammation and acute hepatitis in 56% of patients and overt cirrhosis in 12% of patients. Of the ten patients with GCH post-liver transplant, five had concomitant features of acute cellular rejection.

Management of PIGCH consisted mainly of immunosuppression, viral targeted therapy, supportive care and in six cases liver transplantation. Management and outcomes are outlined in Table 3. Among the patients who were treated with immunosuppression, eight patients (53%) had improvement in their liver function tests. Of the patients treated with ganciclovir, two patients (100%) had improvement in their liver function tests.

Among the native group, five patients (13%) required liver transplantation, and one patient developed graft failure from post-transplant GCH and required a second transplant. Five (13%) patients died from liver-related complications in the native liver group compared to two (20%) in the allograft group. Among these seven patients, five died with acute liver failure. Patient #1 had received two liver transplants. The first transplant was for HCV cirrhosis and subsequently developed PIGCH in the allograft despite achieving a sustained virologic response after anti-viral therapy. This patient eventually developed allograft cirrhosis attributed to PIGCH and required a second transplant for this reason. The patient died of a spontaneous intracranial hemorrhage. Patient #2 had developed cirrhosis attributed to PIGCH and died of pneumonia and sepsis. The five remaining patients presented with acute liver failure. Patient #3 was urgently transplanted but developed infected necrotizing pancreatitis to which he succumbed. Patient #4 was found to develop a pneumothorax and died from hemothorax after placement of a thoracotomy tube. Patient #5 died after developing subcapsular hepatic bleeding following a liver biopsy. Patients #6 and #7 developed a massive variceal bleed and lower gastrointestinal bleeding (exact cause unknown), respectively, that led to their demise.

Of the 50 patients with GCH, 12 (6 native and 6 allograft) underwent a repeat liver biopsy of which 66% still had evidence of GCH despite treatment. Half of these patients had undergone liver transplantation (AIH, primary sclerosing cholangitis/AIH overlap, HCV, GCH, alcoholic and cryptogenic cirrhosis). These patients had persistent GCH on repeat biopsies despite immunosuppression. The patient with primary sclerosing cholangitis/AIH overlap had improvement of GCH findings on subsequent biopsy. One subject had evidence of acute cellular then chronic rejection on subsequent biopsies. Cirrhosis developed in a patient transplanted for alcoholic cirrhosis and GCH. Among the native liver group, six patients had recurrent GCH on biopsy. One had acute hepatitis B, while the rest did not have a specific predisposing factor.

Table 2 Patient characteristics and liver function tests

	GCH on native liver, *n* = 40	GCH on allograft, *n* = 10
Mean age in yr	50.4	43.4
Gender		
Male	14 (35%)	4 (40%)
Female	26 (65%)	6 (60%)
AST	433 ± 486	175 ± 158
ALT	488 ± 537	232 ± 206
Alkaline phosphatase	197 ± 151	296 ± 197
GGT	287 ± 582	246 ± 182
Bilirubin	10.9 ± 10.4	3.1 ± 3.8

GCH: Giant cell hepatitis; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-Glutamyl transpeptidase.

DISCUSSION

With only 100 cases reported in the adult literature, PIGCH remains poorly understood. The prevalence of this disease has been reported at 0.1% to 0.25%[3], which is consistent with the incidence in our cohort (0.14%). Given the rarity of this entity, outcomes and management are largely based on anecdotal evidence. There are no approved therapies and no consensus on management strategies[13].

The histological finding of giant cells in adults seems to be a manifestation of hepatic stress as opposed to a primary hepatic injury[3,10]. The diagnosis is made based on the presence of multinucleated giant cells usually evident in zones 1 and 3 of the Rappaport acinus. More than four to five nuclei in hepatocytes should be seen in a single lobule combined with other features of hepatitis such as lobular disarray, acinar inflammation, Kupffer cell hypertrophy and spotty hepatocytes necrosis. Other common features may include non-suppurative cholangitis, ductopenia and different stages of periportal fibrosis leading to cirrhosis[6,14]. Similar histological findings were observed among our patient cohort: The majority had notable inflammation on pathology, while a quarter of them exhibited evidence of hepatic necrosis (28% spotty necrosis, 48% bridging/confluent necrosis, 19% sub-massive necrosis and 5% massive necrosis), with 12% demonstrating overt cirrhosis, which is comparable to previous reported rates in the literature of about 13%[3].

Out of the six liver transplant recipients for PICGH, two died with recurrent disease. The first patient died in the early post-transplant period, and the second patient died 11 years later. Two patients required two more liver transplants each for recurrent decompensated cirrhosis despite being on standard immunosuppression. One patient developed cirrhosis with features of chronic rejection, which was thought to be related to recurrent hepatitis C, and another was related to CMV hepatitis.

Scant data exists on PIGCH in the post-transplant setting with prior observations indicating the need for re-transplantation in the majority of recipients due to recurrent disease. Pappo *et al*[15] examined the clinical and pathologic course of seven patients who developed GCH after liver transplantation. Five of these patients had GCH as their native liver disease. Two patients died. Two patients required re-transplantation because of recurrent GCH. One patient with recurrent GCH was still alive six years after transplantation. Similarly, in our study, ten patients developed GCH after liver transplantation. Two patients had GCH as their native liver disease. One patient died due to sepsis related to a second liver transplantation. Two patients developed recurrent GCH on the allograft; one of those patients had their immunosuppression increased and had survived at two years and the other patient required re-transplantation. Two patients developed *de novo* GCH that required an increase in immunosuppression; one patient eventually needed liver transplantation and the other one improved with medical management. One patient developed *de novo* GCH and CMV hepatitis and was treated with ganciclovir. The remaining four patients were lost to follow up.

Management strategies to treat recurrence mainly consisted of increasing immunosuppression and in rare cases the institution of ribavirin with variable success[16,17].

Our results were consistent with prior reports indicating a potential autoimmune link to the findings of PIGCH. We concluded that an autoimmune type hepatitis was seen in 1/3 of our patients; 34% of the patients had a positive anti-nuclear antibody,

Table 3 Predisposing factors, *n* (%)

Predisposing factors	GCH on native liver	GCH on allograft
AIH	13 (32)	3 (30)
Drug induced	6 (15)	0
No factor identified	12 (30)	3 (30)
UC	2 (5)	3 (30)
PSC	3 (7)	1 (10)
HCV	2 (5)	1 (10)
CMV	1 (2)	1 (10)
SLE	2 (5)	0
Lymphoma	2 (5)	0
HAV	1 (2)	0
HBV	1 (2)	0
EBV	1 (2)	0
Sjogren	1 (2)	0
Autoimmune hemolytic anemia	1 (2)	0
CLL	1 (2)	0
Peripheral eosinophilia	1 (2)	0
SCC	1 (2)	0
Celiac disease	1 (2)	0

GCH: Giant cell hepatitis; AIH: Autoimmune hepatitis; UC: Ulcerative colitis; PSC: Primary sclerosing cholangitis; HCV: Hepatitis C virus; CMV: Cytomegalovirus; SLE: Systemic lupus erythematosus; HAV: Hepatitis A virus; HBV: Hepatitis B virus; EBV: Epstein-Barr virus; CLL: Chronic lymphocytic leukemia; SCC: Sickle cell disease.

22% had an elevated immunoglobulin G, while 12 patients would fulfill at least a probable diagnosis of AIH based on the AIH scoring system[18] (Table 4).

The majority of our patients were female (66%), which is somewhat different to previous reports with approximately equal numbers between genders[3]. Idiopathic PIGCH was present in 30% of our cohort, which is much higher than prior published studies. A higher incidence of idiopathic PIGCH in our cohort compared to the published literature is likely a manifestation of publication bias, *i.e*. cases of PICGH where there is no clear link may be less apt to be reported[3]. Drug induced liver injury was the culprit in 12% of cases with all of the reported drugs being novel associations with PIGCH (Table 4).

Viral causes amongst our cohort seem to have been less frequent than previously reported. Outcomes of those with a viral cause was variable, although the cases where CMV infection was felt to be the culprit did respond well to ganciclovir, similar to cases reported in the literature[7,19].

The majority of deaths were in the group labeled idiopathic PIGCH, while only two out of sixteen patients with autoimmune like features died. Notably, all of the idiopathic patients were managed supportively while most of the autoimmune cases were managed with immunosuppression. One patient who died had chronic HCV in addition to AIH. HCV therapy (standard of therapy at the time was interferon-based treatment) was not offered given the patient's decompensated state. PIGCH has been described in both acute and chronically infected HCV patients (or co-infected with HIV) with a relatively good prognosis after treatment with interferon and ribavirin or immunosuppressive therapy when autoimmune features are present[19-22]. No studies have been published to date using the highly potent direct acting antivirals that might potentially prove to have even better outcomes with higher rates of viral eradication[23].

The presentations and outcomes of our patients coincide with previously reported observations in the literature of being highly variable. Some patients only manifested in mild elevations in liver function tests while others developed acute liver failure resulting in death or the need for liver transplantation (Table 2). Most patients responded well to immunosuppressive therapy that mainly consisted of intravenous hydrocortisone, prednisone, azathioprine and tacrolimus, especially with the presence of autoimmune features. One case (previously published) with PIGCH secondary to AIH complicating ulcerative colitis responded to prednisone with improved liver functions despite worsening ulcerative colitis (the patient ultimately required a

Table 4 Management and outcomes, *n* (%)

	GCH on native liver, *n* = 40	GCH on allograft, *n* = 10
Management		
Immunosuppression	11 (28)	4 (40)
Supportive care	10 (25)	0 (0)
Liver transplantation	5 (13)	1 (10)
Ganciclovir	1 (3)	1 (10)
Unknown	13 (33)	4 (40)
Outcomes		
Survived	25 (63)	4 (40)
Died	5 (13)	2 (20)
Unknown	10 (25)	4 (40)

GCH: Giant cell hepatitis.

colectomy)[12]. Several cases of PIGCH associated with chronic lymphocytic leukemia have been reported with largely favorable outcomes after being managed with intravenous immunoglobulins (in the events where immunoglobulins are low), rituximab or steroids[8,13]. This is similar to our patient with chronic lymphocytic leukemia who was managed successfully with prednisone but ultimately developed cirrhosis[24].

Our study has several limitations. It is based on retrospective chart review and is mainly descriptive. That being said, it includes the largest number of unique cases of PIGCH from a single institution included in a single manuscript.

The exact etiology of PIGCH and mechanism of injury remains unknown, and the histological findings are likely related to an idiosyncratic or cytopathic response to various hepatocyte stimuli. Our series suggested an autoimmune cause as the most common association. The diagnosis of PIGCH remains clinically challenging and requires a high index of suspicion as well as a thorough history, physical examination and serological workup, which should include viral, hematologic and autoimmune causes. Ultimately a liver biopsy is required as PICGH remains a purely histomorphological diagnosis. Treatment of the underlying cause (especially if it is autoimmune or viral) can result in clinical stability in a large number of cases. Treatment and monitoring should be done in close association with specialty centers including those capable of liver transplantation.

ARTICLE HIGHLIGHTS

Research background

Giant cell hepatitis in the adult population remains very poorly defined with only 100 case reports published in the literature over the last three decades. Pathological analysis is characterized by the presence of giant multinucleated syncytial hepatocytes. The clinical course of patients with giant cells on histology is widely variable, ranging from minimal symptoms without major clinical implications to acute liver failure that is often times fatal despite standard clinical care.

Research objectives

Our primary objective was to present our center's experience in an attempt to learn about the predisposing factors, outcomes and efficacy of proposed therapeutic interventions for giant cell hepatitis.

Research methods

A retrospective chart review was conducted through the electronic records of the University of Pittsburgh Medical Center. We queried 36726 liver biopsy reports from January 1, 1991 to December 6, 2016. Our search yielded 50 patients who were identified as carrying a definite diagnosis of post-infantile giant cell hepatitis (PIGCH) by pathology. The data collected included demographic information, laboratory data (liver function tests, autoimmune markers) and transplant status. In order to better analyze patient characteristics and outcomes, subjects were separated into a non-transplant (native) liver group and a post-liver transplant (allograft) group.

Research results

The incidence of PIGCH was approximately 0.14% of all biopsies queried in the 25-year period. The mean age was 48 years with 66% females. Liver function tests were classified as 38.2% cholestatic, 35.3% hepatocellular and 26.5% mixed. Autoimmune hepatitis was found to be the

most prevalent predisposing factor leading to PIGCH constituting 32% of cases. Management consisted mainly of immunosuppression, viral targeted therapy, supportive care and in six cases liver transplantation.

Research conclusions

The diagnosis of PIGCH remains clinically challenging and requires a high index of suspicion as well as a thorough history, physical examination, serological workup and liver biopsy. Treatment of the underlying cause can result in clinical stability in a large number of cases.

Research perspectives

This study reports our center's experience with PIGCH and the importance of thorough history, physical examination, serologic work up and liver biopsy in its diagnosis. Further research should aim at recognizing risk factors for progression from PIGCH to liver failure and further evaluation of therapeutic interventions (immunosuppression *vs* viral targeted therapy *vs* liver transplantation).

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ORIGINAL ARTICLE

Observational Study

Lumacaftor/ivacaftor therapy is associated with reduced hepatic steatosis in cystic fibrosis patients

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Abstract

BACKGROUND

Hepatic steatosis is a common form of cystic fibrosis associated liver disease (CFLD) seen in an estimated 15%-60% of patients with cystic fibrosis (CF). The pathophysiology and health implications of hepatic steatosis in cystic fibrosis remain largely unknown. In the general population, hepatic steatosis is strongly associated with insulin resistance and type 2 diabetes. Cystic fibrosis related diabetes (CFRD) impacts 40%-50% of CF adults and is characterized by both insulin insufficiency and insulin resistance. We hypothesized that patients with CFRD would have higher levels of hepatic steatosis than cystic fibrosis patients without diabetes.

AIM

To determine whether CFRD is associated with hepatic steatosis and to explore the impact of lumacaftor/ivacaftor therapy on hepatic steatosis in CF.

METHODS

Thirty patients with CF were recruited from a tertiary care medical center for this cross-sectional study. Only pancreatic insufficient patients with CFRD or normal glucose tolerance (NGT) were included. Patients with established CFLD, end

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stage lung disease, or persistently elevated liver enzymes were excluded. Mean magnetic resonance imaging (MRI) proton density fat fraction (PDFF) was obtained for all participants. Clinical characteristics [age, sex, body mass index, percent predicted forced expiratory volume at 1 s (FEV1), lumacaftor/ivacaftor use] and blood chemistries were assessed for possible association with hepatic steatosis. Hepatic steatosis was defined as a mean MRI PDFF > 5%. Patients were grouped by diabetes status (CFRD, NGT) and cystic fibrosis transmembrane conductance regulator (CFTR) modulator use (lumacaftor/ivacaftor, no lumacaftor/ivacaftor) to determine between group differences. Continuous variables were analyzed with a Wilcoxon rank sum test and discrete variables with a Chi square test or Fisher's exact test.

RESULTS

Twenty subjects were included in the final analysis. The median age was 22.3 years (11.3-39.0) and median FEV1 was 77% (33%-105%). Twelve subjects had CFRD and 8 had NGT. Nine subjects were receiving lumacaftor/ivacaftor. The median PDFF was 3.0% (0.0%-21.0%). Six subjects (30%) had hepatic steatosis defined as PDFF > 5%. Hepatic fat fraction was significantly lower in patients receiving lumacaftor/ivacaftor (median, range) (2.0%, 0.0%-6.4%) than in patients not receiving lumacaftor/ivacaftor (4.1%, 2.7-21.0%), $P = 0.002$. Though patients with CFRD had lower PDFF (2.2%, 0.0%-14.5%) than patients with NGT (4.9%, 2.4-21.0%) this did not reach statistical significance, $P = 0.06$. No other clinical characteristic was strongly associated with hepatic steatosis.

CONCLUSION

Use of the CFTR modulator lumacaftor/ivacaftor was associated with significantly lower hepatic steatosis. No association between CFRD and hepatic steatosis was found in this cohort.

Key words: Cystic fibrosis; Liver disease; Non-alcoholic fatty liver disease; Cystic fibrosis transmembrane conductance regulator; Lumacaftor/ivacaftor; Cystic fibrosis transmembrane conductance regulator modulator; Diabetes mellitus

Core tip: Hepatic steatosis is a common manifestation of liver disease in cystic fibrosis (CF). It remains unknown whether hepatic steatosis contributes to the development of cirrhosis in patients with CF. Lumacaftor/ivacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) modulator drug targeting the defective chloride channel that causes CF. In this cross-sectional study, CF patients receiving lumacaftor/ivacaftor had significantly lower magnetic resonance imaging proton density fat fractions than CF patients not receiving the CFTR modulator. CFTR modulator use should be included in future studies of CF liver disease.

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INTRODUCTION

The life expectancy for cystic fibrosis (CF) patients has improved dramatically over the past several decades, and continued improvement is expected with the widespread use of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies[1]. While pulmonary disease remains the leading cause of mortality in CF, extra pulmonary complications such as cystic fibrosis related diabetes (CFRD) and cystic fibrosis associated liver disease (CFLD) have emerged as important sources of morbidity in this population[2-4]. As the life expectancy for CF patients improves, determining the impact of CFTR modulator therapy on extra-pulmonary

disease is of critical importance.

Hepatic manifestations of CF are broad, including: Neonatal cholestasis, transaminase elevation, hepatic steatosis, focal biliary cirrhosis, multilobular cirrhosis and portal hypertension[3,5]. Cirrhosis with portal hypertension is the primary cause of morbidity and mortality from CFLD[6]. Debate regarding the optimal diagnostic criteria for CFLD is ongoing[6-9]. While older studies describe CFLD as a childhood-onset disease, recent data demonstrates that adult-onset CFLD is relatively common[8,10,11]. Multilobular cirrhosis with portal hypertension is the end stage manifestation of CFLD and is the third leading cause of death in CF patients[1,6].

Perhaps the most common manifestation of CFLD is hepatic steatosis, with prevalence estimates ranging from 15%-60%[7,12,13]. Historically, hepatic steatosis in CF patients was attributed to malnutrition and considered a benign finding that did not increase risk for hepatic cirrhosis[14]. Outside of CF, hepatic steatosis is strongly associated with obesity and type 2 diabetes[15]. Hepatic steatosis can progress to non-alcoholic steatohepatitis and cirrhosis, which is now a common indication for liver transplantation among the general population in the United States[16]. Little is known about the clinical implications of hepatic steatosis in CF and its relationship to other forms of CFLD[12,17,18].

CFRD is another common extrapulmonary manifestation of CF, with a prevalence of approximately 20% in adolescents and 40%-50% in adults[19]. CFRD is distinct from type 1 diabetes, which is characterized by absolute insulin deficiency, and type 2 diabetes in which peripheral insulin resistance predominates. CFRD is primarily a disease of insulin insufficiency, though insulin resistance occurs during illness and with increasing age[20,21]. Patients with CFRD typically have lower body mass index (BMI), reduced pulmonary function and higher mortality rates. These effects are at least partially mitigated by insulin therapy[22]. The prevalence of CFRD is also higher in CF patients with liver disease[23].

Both CFRD and CFLD are almost exclusively seen in patients carrying two pathogenic CFTR variants that severely limit the chloride channel function[24,25]. CFTR variants are generally categorized into five (or six) groups according to the underlying cause of channel malfunction. Class 1-3 variants result in little or no CFTR function while class 4-6 variants are characterized by residual CFTR function[26]. Individualized CF therapy relies on understanding the functional defect causing CFTR malfunction[27]. CFTR modulator therapies are a revolutionary class of small molecules targeting the underlying defect in CF[26]. Ivacaftor is a CFTR potentiator that increases chloride conductance only if CFTR is present in the cell membrane[28]. Lumacaftor and tezacaftor are correctors which redirect misfolded CFTR protein to the cell surface[29,30]. Lumacaftor/ivacaftor combination therapy was approved in 2015 for patients carrying two copies of the F508del (p.Phe508del, c.1521_1523delCTT) pathogenic variant.

While pulmonary effects of CFTR modulators have been meticulously examined, the extrapulmonary effects are not well characterized[28,30-33]. Two small studies demonstrated improved insulin secretion after modulator therapy; while two other studies failed to show improvement[34-37]. No studies have systematically examined the impact of CFTR modulator therapy on hepatic steatosis or other liver disease in patients with CF. Thus, we sought to determine the impact of CFRD on hepatic steatosis in CF patients and explore other factors associated with elevated hepatic fat, including CFTR modulator use.

MATERIALS AND METHODS

Patient characteristics

All studies were conducted according to the approved Institutional Review Board protocols at University Hospitals Cleveland Medical Center between January 1 and December 31, 2017. Thirty subjects with CF were recruited from the LeRoy W. Matthews Cystic Fibrosis Center at University Hospitals Cleveland Medical Center/ Rainbow Babies and Children's Hospital in Cleveland, OH, United States (Table 1 and (Supplemental Table 1). Eligible subjects were identified using the local CF database and were approached for study involvement during routine clinic visits or during hospitalization for a CF pulmonary exacerbation. All subjects were diagnosed with cystic fibrosis based on sweat chloride and genetic testing according to established guidelines[38]. Electronic medical records were reviewed to confirm eligibility. Inclusion criteria were age 10-40 years, pancreatic insufficiency and either normal glucose tolerance (NGT) or CFRD[39]. Pancreatic insufficiency was defined by a clinical need for pancreatic enzyme replacement. No fecal elastase testing was performed as part of this study. Subjects with established CFLD, persistent transaminase elevation

for greater than one year, low baseline lung function (*i.e.*, FEV_1 < 30% predicted) or an ongoing pulmonary exacerbation were excluded. Only subjects with two copies of a class 1-3 pathogenic CFTR variant were included in the final analysis. CFTR variants were classified into classes 1-5 using the CFTR 2 database and existing guidelines for functional classification[40,41]. Subjects with contraindications to MRI scanning (*i.e.*, metal implants, pregnancy) were also excluded. Informed consent was obtained in person prior to commencing study activities.

Clinical and laboratory evaluation

Clinical characteristics including BMI, percent predicted FEV1, diabetes status, insulin use and CFTR modulator use were collected from the electronic medical record. Fasting blood chemistries including lipids, hepatic function tests and hemoglobin A1C were assessed during a period of baseline health in ambulatory subjects or after completing treatment for a pulmonary exacerbation in hospitalized subjects. An oral glucose tolerance test (OGTT) was performed in NGT subjects who had not had an OGTT in the past six months. Glucose tolerance testing was performed according to standard guidelines. After an eight hour fast, subjects ingested 1.75 g/kg (maximum 75 g) of glucose dissolved in water. Plasma glucose was evaluated at baseline and 2 h post glucose ingestion[39]. Subjects whose study OGTT demonstrated impaired fasting glucose or impaired glucose tolerance as defined by standard criteria were excluded[42].

All serum chemistries were collected from peripheral venous samples according to standard technique[43]. Glucose, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase, and total bilirubin were analyzed using a Beckman AU 5800® analyzer. Hemoglobin A1C was analyzed using a BioRad-D-100® analyzer (University Hospitals Core Lab, Cleveland, OH, United States).

Hepatic fat fraction measurement

Proton density fat fraction (PDFF) was measured on a Siemens Skyra 3T magnetic resonance imaging (MRI) in the Imaging Research Core at Case Western Reserve University. Briefly, each subject was positioned supine within the MRI scanner. Spine and body array coils were used to obtain uniform images over the entire liver. A single-breathhold VIBE MRI acquisition was used to obtain axial liver PDFF maps for each subject (spatial resolution = 2 mm × 2 mm × 5 mm, 6 echoes). This MRI method also incorporates T2* correction to limit the effects of iron deposition and hepatic fibrosis[44]. All images were exported for offline analysis in Matlab (The Mathworks, Natick, MA, United States). Mean liver PDFF was determined for the central 6-8 imaging slices in each subject using a region of interest (ROI) analysis. The mean liver PDFF in each slice was then averaged over all slices to calculate the overall mean liver PDFF for each subject.

Data and statistical considerations

For this study, we considered a PDFF > 5% to be consistent with clinical hepatic steatosis[45]. We grouped subjects by the presence of hepatic steatosis > 5%, diabetes status, and CFTR modulator use to evaluate for significant associations. BMI percentiles were calculated for all subjects to account for age-related variation in BMI. Alkaline phosphatase measurements were standardized by subtracting the age and sex specific mean and dividing by the respective standard deviation. The resulting values were in units of standard deviation. Continuous variables were described with medians and ranges and nominal variables with frequencies and percent. Continuous variables were analyzed with a Wilcoxon rank sum test and nominal variables were analyzed using Chi square test or Fisher's exact test. Statistical analysis was performed using SAS software version 9.4 (SAS Institute, Cary, NC, United States). The level of significance was set at 0.05. The statistical analyses were performed by MaryAnn O'Riordan PhD, biomedical statistician.

RESULTS

Participant characteristics

We recruited 30 participants of whom 20 completed the study (Figure 1). Exclusions related to progression to impaired glucose tolerance on OGTT (n = 3), inability to perform breath hold for MRI (n = 2), failure to schedule or complete the MRI (n = 4) and presence of a class 4 CFTR pathogenic variant (n = 1). Participant characteristics are summarized in Table 1. The study population was primarily Caucasian, which is consistent with the demographic of the CF population overall. Eighty percent of the

Table 1 Demographics for all subjects and stratified by modulator (lumacaftor/ivacaftor) use

	All subjects (*n* = 20)	CFTR modulator (*n* = 9)	No CFTR modulator (*n* = 11)	*P* value
Age at MRI (yr)	22.3 (11.3-39.0)	26.4 (16.3-39.0)	21.9 (11.3-36.1)	0.29
Genotype				
F508del/F508del	10	9	1	< 0.01
F508del/other	9	0	9	< 0.01
Other/other	1	0	1	< 0.01
Male sex	16 (80%)	7 (78%)	9 (82%)	1.00
BMI percentile	39 (2-96)	51 (3-77)	23 (2-96)	0.21
% predicted FEV1	77 (33-105)	73 (33-89)	77 (48-105)	0.24
CFRD	12 (60%)	7 (78%)	5 (45%)	0.20
Insulin therapy	10 (50%)	6 (67%)	4 (36%)	0.37

Data presented as median (range) or frequency (percent) as appropriate. BMI (percentile): body mass index percentile adjusted for age; FEV1: forced expiratory volume at 1 s; CFRD: cystic fibrosis related diabetes.

study subjects were male. Median subject age at the time of MRI was 22.3 years with a range from 11.3 to 39.0 years. All participants had two severe class 1-3 CFTR pathogenic variants. Twelve subjects (60%) had CFRD and 8 subjects (40%) had NGT. Ten CFRD subjects (83%) were prescribed insulin therapy. Nine subjects (45%) had received the CFTR modulator lumacaftor/ivacaftor (Orkambi®) for more than 12 mo at the time of MRI. No subject received lumacaftor/ivacaftor for fewer than 12 mo.

Hepatic steatosis

The median hepatic fat fraction for all subjects was 3.0% with a range from 0.0%-21.0%. Six subjects (30%) had hepatic steatosis, defined as PDFF > 5%. Subjects with hepatic steatosis showed a trend toward younger age that did not reach statistical significance. Alkaline phosphatase and age-adjusted alkaline phosphatase (z-score) were higher in subjects with hepatic steatosis, $P = 0.01$ and $P = 0.03$. LDL and HDL were both higher in patients with hepatic steatosis, $P = 0.05$ and $P = 0.02$. Total bilirubin, AST, ALT and GGT did not differ significantly between subjects with and without hepatic steatosis (Table 2). Missing data for alkaline phosphatase, AST, ALT, total bilirubin (1 missing), LDL, HDL, triglyceride (4 missing), and GGT (3 missing) were excluded from all analyses.

CFTR modulator

Hepatic fat fraction was significantly lower in the 9 subjects receiving CFTR modulator therapy (2.0%, 0.0%-6.4%) than in the 11 subjects not receiving CFTR modulators (4.1%, 2.7%-21.0%), $P = 0.002$ (Figure 2). Two CFRD subjects receiving CFTR modulators had exceptionally low hepatic fat fractions of 0.0%. Subjects receiving CFTR modulator therapy were not significantly different in terms of age, BMI percentile or diabetes status from subjects not receiving modulators. Absolute BMI was higher in the CFTR modulator group, which likely reflects expected age-related change in BMI, $P = 0.05$ (Table 3).

CFTR modulator use was associated with lower total bilirubin than no CFTR modulator use, $P = 0.003$. Alkaline phosphatase levels were also lower in the CFTR modulator group, but this difference may relate to younger age in the no CFTR modulator group, $P = 0.01$. Although age-adjusted alkaline phosphatase (z scores) were numerically lower in the CFTR modulator group than the no CFTR modulator group, this did not reach statistical significance, $P = 0.07$ (Table 3).

Diabetes

The median hepatic fat fraction was not statistically different between subjects with CFRD (median, range) (2.2%, 0.0-14.5%) and NGT (4.9%, 2.4-21.0%), $P = 0.06$. Subjects with CFRD were older (28.2 years, 17.0-39.0) than NGT subjects (18.0 years, 11.3-30.6), $P = 0.04$. As expected, the older CFRD cohort demonstrated a higher BMI, $P = 0.05$, but not BMI percentile, than NGT subjects. Patients with CFRD demonstrated lower percent predicted FEV1, which is known to be associated with CFRD, $P = 0.001$. Subjects with CFRD also demonstrated higher hemoglobin A1C levels, $P = 0.002$. Alkaline Phosphatase was lower in the CFRD group compared to the NGT group, $P = 0.04$; however, age adjusted alkaline phosphatase (z-score) was not different between groups (Table 2).

Importantly, CFTR modulator use was more common among patients with CFRD

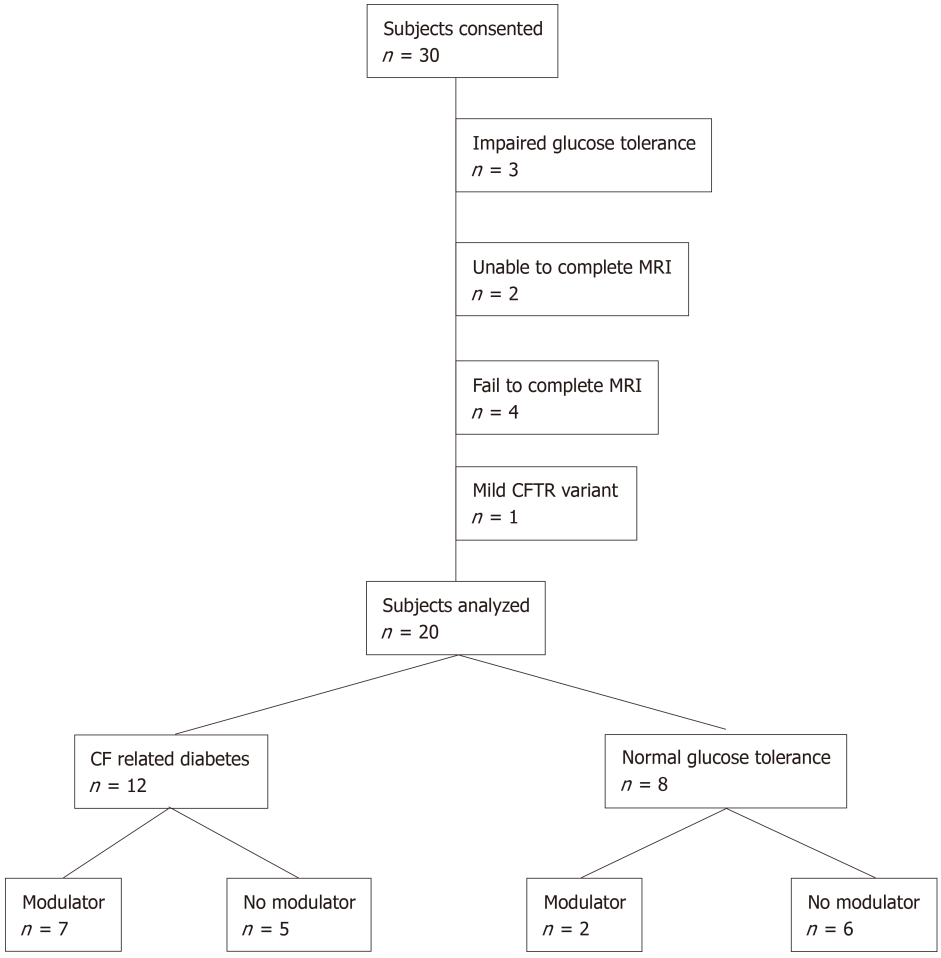

Figure 1 Consort diagram. Consort diagram for the study. Modulator refers to lumacaftor/ivacaftor use. CF: Cystic fibrosis, MRI: Magnetic resonance imaging; CFTR: Cystic fibrosis transmembrane conductance regulator.

(7 of 12, 58%) than patients with NGT (2 of 8, 22%). Because we demonstrated that CFTR modulator use is associated with lower hepatic fat, we repeated the fat fraction analysis by diabetes status after excluding subjects receiving CFTR modulator therapy. The median hepatic fat fraction for the 5 CFRD subjects not receiving CFTR modulator was 4.1% (range 2.8%-14.5%) and for the 6 NGT subject not receiving CFTR modulators was 4.9% (range 2.7%-21.0%), which were not significantly different, $P = 0.92$.

DISCUSSION

In this cross-sectional study of 20 CF patients aged 11-39 years with either NGT or CFRD, we demonstrate a statistically significant association between use of the CFTR modulator lumacaftor/ivacaftor and reduced hepatic fat. CFTR modulator use was also associated with lower total bilirubin and a trend toward lower age-adjusted alkaline phosphatase levels (z-score). Interestingly, CFRD patients on lumacaftor/ivacaftor demonstrated particularly low hepatic fat fractions (0.0% in two cases), suggesting a particular sensitivity to modulator effects in patients with CFRD (Supplemental Table 1). CFRD was not found to be associated with increased hepatic steatosis as was originally hypothesized. In contrast, patients with CFRD showed a trend toward lower PDFF, which most likely reflects higher rates of CFTR modulator use in the CFRD group. Given the small number of subjects not receiving lumacaftor/ivacaftor, we cannot exclude a relationship between CFRD and hepatic steatosis in CF based on this study.

The multifactorial pathogenesis of hepatic steatosis has not been fully elucidated. While strongly associated with obesity and insulin resistance in the general population, hepatic steatosis has historically been attributed to nutritional deficiencies in CF patients. In 1999, Lindblad reported an association between hepatic steatosis and linoleic acid deficiency in a cohort of 41 CF patients[14]. Others have proposed that

Table 2 Summary of data stratified by presence of steatosis, use of modulator (lumacaftor/ivacaftor), and diabetes status

	Normal Range	All subjects (*n* = 20)	Steatosis (*n* = 6)	No Steatosis (*n* = 14)	*P* value	CFTR modulator (*n* = 9)	No CFTR modulator (*n* = 11)	*P* value	CFRD (*n* = 12)	NGT (*n* = 8)	*P* value
Hepatic Fat Fraction	--	3.0 0.0-21.0	9.5 6.0-21.0	2.4 0-4.1	0.01	2.0 0.0-6.4	4.1 2.7-21	0.002	2.2 0.0-14.5	4.9 2.4-21	0.06
Age	--	22.3 11.3-39.0	16.7 13.4-36.1	26.0 11.3-39.0	0.08	26.4 16.3-39.0	21.9 11.3-36.1	0.29	28.2 17.0-39.0	18.0 11.3-30.6	0.04
Sex (male)	--	16 80%	5 83%	11 78%	1.00	7 78%	9 82%	1.00	8 67%	8 100%	0.12
BMI	--	21.0 16.9-32.4	20.5 16.9-32.4	21.0 18.8-25.7	0.6	22.4 18.8-25.7	20.0 16.9-32.4	0.05	21.0 18.8-32.4	19.6 16.9-22.4	0.05
BMI percentile	--	39 2-96	50 2-96	30 3-77	0.77	51 3-77	23 2-96	0.21	39 3-96	37.5 2-73	0.62
FEV1 %	--	77 33-105	86 62-105	74.5 33-97	0.22	73 33-89	77 48-105	0.24	63.5 33-105	88 65-97	0.001
CFTR modulator	--	9 45%	1 17%	8 57%	0.16	9 100%	11 100%	--	7 58%	2 25%	0.20
Hemoglobin A1C (%)	< 5.8	5.8 5.2-8.2	5.7 5.4-6.4	6.3 5.2-8.2	0.30	6.3 5.3-8.2	5.7 5.2-7.4	0.21	6.4 5.4-8.2	5.6 5.2-5.7	0.002
AST (U/L)	9-39	23 11-45	27 11-45	23 11-42	0.93	20 11-42	27 11-45	0.39	20 11-42	26 11-45	0.87
ALT (U/L)	10-52	22 10-58	24.5 12-58	22 10-45	0.57	18 10-45	29 12-58	0.19	18 10-58	26 14-47	0.46
GGT (U/L)	5-64	14 9-29	19 14-25	13.5 9-29	0.10	12 9-24	19 10-29	0.07	13.5 9-29	19 11-24	0.30
Alk Phos (U/L)	33-120	110 44-310	172 146-310	90 44-234	0.01	66 44-178	155 103-310	0.01	90 44-178	157 71-310	0.04
Alk Phos SD	-2-2	1.2 -1.5-4.8	3.1 -0.6-4.8	-0.3 -1.5-4.7	0.03	-0.3 -1.5-4.7	1.8 -0.6-4.8	0.07	0.6 -1.5-4.8	1.4 -0.6-3.2	0.65
Total Bili (μmol/L)	0-20.5	6.8 3.4-20.5	8.5 3.4-15.4	5.1 3.4-20.5	0.47	5.1 3.4-6.8	8.6 3.4-20.5	0.003	5.1 3.4-18.8	8.6 5.1-20.5	0.06
Triglyceride (mmol/L)	< 1.7	1.02 0.36-2.55	1.25 0.69-2.55	0.68 0.36-1.54	0.07	0.9 0.64-2.55	1.25 0.36-2.35	0.79	0.68 0.64-2.35	1.28 0.36-2.55	0.15
LDL (mmol/L)	< 3.4	1.7 0.8-2.4	1.4 0.9-1.6	1.7 0.8-2.4	0.05	1.6 0.8-2.2	1.7 0.9-2.4	0.53	1.7 0.9-2.4	1.6 0.8-2.0	0.71
HDL (mmol/L)	> 1.0	1.03 0.53-2.03	0.84 0.53-1.41	1.09 0.91-2.03	0.02	1.04 0.86-2.03	0.98 0.53-1.54	0.31	1.01 0.53-2.03	1.05 0.84-1.53	0.73

Data is stratified by steatosis (MRI proton density fat fraction >5%) or no steatosis (MRI proton density fat fraction <5%), use of CFTR modulator lumacaftor/ivacaftor, and diabetes status. Data are presented as median and range. To convert total bilirubin from μmol/L to mg/dL multiply by 0.0585.To convert triglycerides from mmol/L to mg/dL multiply by 88.5. To convert LDL from mmol/L to mg/dL multiply by 38.7. To convert HDL from mmol/L to mg/dL multiply by 38.7. CFRD: cystic fibrosis related diabetes. NGT: normal glucose tolerance; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyltransferase; LDL: Low density lipoprotein; HDL: High density lipoprotein; BMI: Body mass index.

carnitine and choline deficiency cause hepatic steatosis in CF[5,46]. In contrast, more recent data suggests that hepatic steatosis in CF is associated with higher BMI and better lung function[13]. Importantly, one case report suggests that CFTR dysfunction may be responsible for hepatic steatosis in CF. Hayes *et al*[47] reported rapid resolution of severe hepatic steatosis in a 17 year old female (F508del/G511D genotype) after initiation of ivacaftor therapy. Our results further support a role for CFTR dysfunction in the pathogenesis of hepatic steatosis in CF.

We have considered possible explanations for our findings. As CFTR is not expressed in hepatocytes, improvements in hepatic steatosis with CFTR modulators must be mediated by CFTR expression in other tissues[48]. In CF, biliary stasis and impaired enterocyte function contribute to persistent fat malabsorption, even with

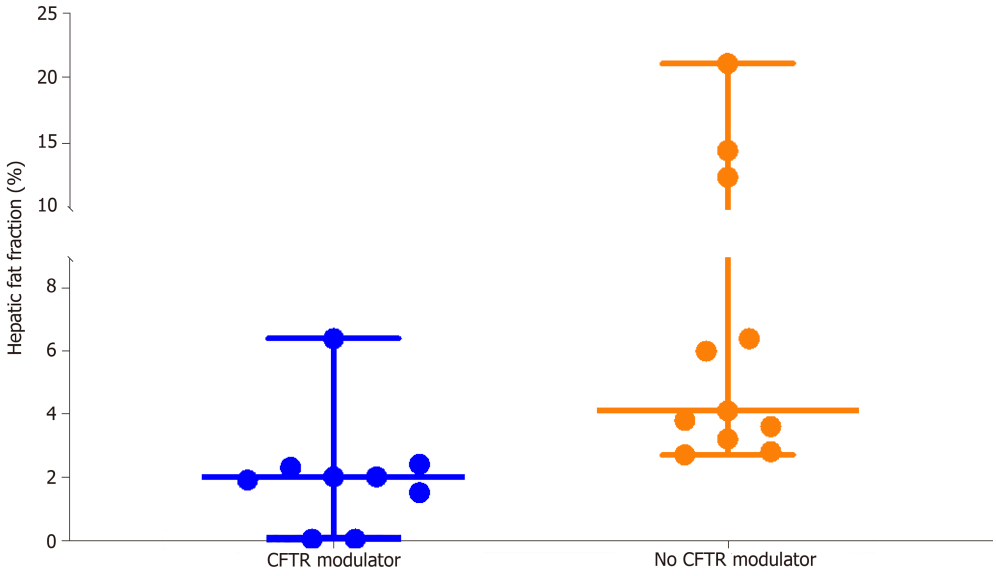

Figure 2 Hepatic steatosis (proton density fat fraction) stratified by lumacaftor/ivacaftor use. Subjects receiving cystic fibrosis transmembrane conductance regulator (CFTR) modulator (lumacaftor/ivacaftor) had a median proton density fat fraction of 2.1%. Subjects not receiving CFTR modulator had a median proton density fat fraction of 4.1%. Each dot represents one subject. Horizontal lines indicate the minimum, median and maximum for each group. $P = 0.002$. CFTR: Cystic fibrosis transmembrane conductance regulator.

adequate pancreatic enzyme replacement[49,50]. Chronic fat malabsorption can lead to deficiencies in fat soluble nutrients including linoleic acid and choline-which have previously been associated with hepatic steatosis[46]. Therefore, we theorize that CFTR modulator therapy may lead to resolution of hepatic steatosis by reversing nutritional deficiencies. Further mechanistic studies are needed to test this theory.

It is also possible that lumacaftor/ivacaftor therapy reduces hepatic steatosis through an off target, non-CFTR mediated, mechanism. Additionally, the extremely low hepatic fat seen in subjects receiving lumacaftor/ivacaftor may be secondary to the F508del/F508del genotype itself, rather than the modulator. Although the single F508del/F508del homozygous subject not on lumacaftor/ivacaftor had significant hepatic steatosis, a single observation cannot exclude a genotype effect. Ultimately, longitudinal study is needed to demonstrate that CFTR modulator therapy causes reduced hepatic steatosis and elucidate the mechanism behind this observation.

Prior studies of hepatic steatosis in CF patients have compared varied, qualitative measures of hepatic fat[13,14]. Ours is the first study to utilize a single, precise, quantitative measure of hepatic fat, the MRI PDFF. Other strengths of our study include the collection of detailed biochemical and clinical information. We acknowledge important limitations. As this study utilized a cross sectional design, we can only demonstrate an association between lumacaftor/ivacaftor therapy and reduced hepatic fat. Moreover, we are unable to exclude the possibility that the F508del/F508del genotype, rather than CFTR modulator use, is associated with reduced hepatic steatosis. Prospective, longitudinal study of modulator therapy in patients expressing different pathogenic CFTR variants will help clarify this question. The relatively small sample size limited our power to detect differences in hepatic fat between CFRD and NGT subjects. This study does not eliminate a possible association between CFRD and hepatic steatosis in CF. Further longitudinal study is needed to understand how hepatic steatosis influences insulin sensitivity and risk for progression to CFRD.

In conclusion, we found no evidence that CFRD is associated with increased hepatic steatosis. We provide strong preliminary data suggesting that lumacaftor/ivacaftor is associated with reduced hepatic steatosis in CF patients. This finding raises many questions about the impact of CFTR modulator therapy on nutrient absorption and on the mechanisms of hepatic steatosis in CF patients. Our study raises the possibility that CFTR modulator therapy may impact other forms of CFLD and adds to the small but growing literature on the extrapulmonary impact of CFTR modulator therapy. CFTR modulator status should be included in future studies of hepatic steatosis or CFLD.

Table 3 Magnetic resonance imaging proton density fat fraction and biochemistry for all subjects and stratified by modulator (lumacaftor/ivacaftor) status

	Reference range	All subjects, *n* = 20	CFTR modulator, *n* = 9	No CFTR modulator, *n* = 11	*P* value
PDFF (%)	< 5%	3.0 (0.0-21.0)	2.0 (0.0-6.4)	4.1 (2.7-21.0)	0.002
HbA1C (%)	< 5.8%	5.8 (5.2-8.2)	6.3 (5.3-8.2)	5.7 (5.2-7.4)	0.21
Alk Phos (U/L)	[1]	110 (44-310)	66 (44-178)	155 (103-310)	0.01
Alk Phos (SD)	-2.0-2.0	1.2 (-1.5-4.8)	-0.3 (-1.5-4.7)	1.8 (-0.6-4.8)	0.07
Total bilirubin (μmol/L)[2]	0-20.5	6.8 (3.4-20.5)	5.1 (3.4-6.8)	8.6 (3.4-20.5)	0.003
AST (U/L)	9-39	23 (11-45)	20 (11-42)	27 (11-45)	0.39
ALT (U/L)	10-52	22 (10-58)	18 (10-45)	29 (12-58)	0.19
GGT (U/L)	5-64	14 (9-29)	12 (9-24)	19 (10-29)	0.07
Triglyceride (mmol/L)[3]	< 1.7	1.02 (0.36-2.55)	0.9 (0.64-2.55)	1.25 (0.36-2.35)	0.79

[1]Reference range is age dependent;
[2]To convert from μmol/L to mg/dL multiply by 0.0585;
[3]To convert to mg/dL multiply by 88.5. Results of magnetic resonance imaging proton density fat fraction and key laboratory parameters for all subjects and stratified by cystic fibrosis transmembrane conductance regulator modulator (lumacaftor/ivacaftor) use. Data presented as median (range) or number (percent) as appropriate. CFTR: Cystic fibrosis transmembrane conductance regulator; PDFF: Proton density fat fraction; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyltransferase.

ARTICLE HIGHLIGHTS

Research background
Hepatic steatosis is a common form of cystic fibrosis associated liver disease (CFLD). The journal has published previous manuscripts regarding CFLD.

Research motivation
Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators are a revolutionary therapy which target the underlying cause of CF for the first time. Currently, very little is known about the impact of CFTR modulator therapy on hepatic disease in CF, despite liver failure being the third leading cause of death in CF patients.

Research objectives
The objectives of this study were therefore to determine whether CF related diabetes (CFRD) is associated with hepatic steatosis and to identify predictors of hepatic steatosis in CF.

Research methods
Patients with established CFLD, end stage lung disease, or persistently elevated liver enzymes were excluded. Mean magnetic resonance imaging (MRI) proton density fat fraction (PDFF) was obtained for all participants. Clinical characteristics and blood chemistries were assessed for possible association with hepatic steatosis. Hepatic steatosis was defined as a mean MRI PDFF > 5%. Patients were grouped by diabetes status and CFTR modulator use (lumacaftor/ivacaftor, no lumacaftor/ivacaftor) to determine between group differences. Continuous variables were analyzed with a Wilcoxon rank sum test and discrete variables with a Chi square test or Fisher's exact test.

Research results
Twelve subjects (60%) had CFRD and 8 subjects (40%) had normal glucose tolerance (NGT). The median hepatic fat fraction for all subjects was 3.0% with a range from 0.0%-21.0%. Six subjects (30%) had hepatic steatosis, defined as PDFF > 5%. Hepatic fat fraction was significantly lower in the 9 subjects receiving CFTR modulator therapy (2.0%, 0.0%-6.4%) than in the 11 subjects not receiving CFTR modulators (4.1%, 2.7%-21.0%), $P = 0.002$. The median hepatic fat fraction was not statistically different between subjects with CFRD (median, range) (2.2%, 0.0-14.5%) and NGT (4.9%, 2.4-21.0%), $P = 0.06$.

Research conclusions
In the enclosed manuscript, we demonstrate that lumacaftor/ivacaftor therapy is associated with reduced hepatic fat in CF patients. While hepatic steatosis has historically been considered a benign finding in CF, the spreading epidemic of liver failure from non-alcoholic steatohepatitis makes this doubtful.

Research perspectives
It suggests a previously unrecognized effect of CFTR modulators of CFLD. CFTR modulator status should be included in future studies of hepatic steatosis or CFLD.

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CASE REPORT

Intrahepatic and intra-abdominal splenosis: A case report and review of literature

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Abstract

BACKGROUND

Splenosis is defined as the process by which tissue from the spleen disseminates through the body and grows in an ectopic location following trauma or a splenectomy. Visceral sites of splenosis are rare.

CASE SUMMARY

We report a case of intrahepatic splenosis in a 57-year-old man with a history of trauma over 40 years ago who initially presented with chest pain. Findings initially mimicked malignancy but a diagnosis of intrahepatic splenosis was confirmed using computed tomography and scintigraphy with technetium-99m heat-denatured red blood cells (Tc-99 DRBC).

CONCLUSION

Scintigraphy with Tc-99 DRBC is a reliable technique to diagnose splenosis and should be performed before using more invasive procedures are carried out. Splenosis should be considered as a possible differential diagnosis for a hepatic nodule in any patient with a history of abdominal trauma, previous splenectomy or atypical radiological features on imaging.

Key words: Intrahepatic splenosis; Abdominal splenosis; Computed tomography; Scintigraphy; Hepatocellular carcinoma; Case report

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Core tip: Intrahepatic splenosis is rare. On imaging it is difficult to distinguish splenosis from hepatic malignancy, particularly hepatocellular carcinoma. We report a case of a patient with intrahepatic and intra-abdominal splenosis diagnosed using scintigraphy with technetium-99m heat-denatured red blood cells. To the author's knowledge, this is the first case where hepatic splenosis was confirmed without using invasive procedures such as biopsy or surgery. Splenosis should be considered as an important differential for a hepatic lesion in a patient with a history of trauma or splenectomy, particularly if the lesion is located near the capsule and associated with multiple abdominal deposits.

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INTRODUCTION

Splenosis is a benign acquired condition. Following trauma or a splenectomy, splenic tissue may autotransplant in an ectopic location. Common sites include the serosal surface of the small or large intestine, greater omentum or the peritoneum[1]. Less frequently, splenic nodules may be found in the liver[2], stomach[3], pancreas[4] and following rupture of the diaphragm in the thorax[5]. The kidneys[6], ovaries[7] and subcutaneous tissue[8] are even rarer sites of splenosis. Splenosis is usually asymptomatic and when incidentally discovered can be difficult to distinguish from malignancy using computed tomography (CT) or magnetic resonance imaging (MRI).

CASE PRESENTATION

Chief complaints

A 57-year-old male presented to the Emergency Department with severe right-sided pleuritic chest pain radiating to his back. There was no associated breathlessness, fever, cough, haemoptysis, dizziness, syncope, numbness, paraesthesia or weakness.

History of present illness

The patient reported that the symptoms began abruptly two days ago and progressively worsened, without any triggers. The pain settled following the administration of morphine after admission to hospital.

History of past illness

In 2015 he was diagnosed with benign prostatic hypertrophy and had suffered traumatic injury following a road traffic accident over 40 years ago. Of note, he had no history of hepatic disease.

Physical examination

There was marked tenderness on inspiration on the right side of the chest, but otherwise physical examination was unremarkable. The patient's vital signs were normal with a temperature of 37.0 °C, heart rate of 74 bpm, blood pressure of 125/75 mmHg, respiratory rate of 15 breaths/min and oxygen saturations of 98% in room air.

Laboratory testing

Routine blood tests were within normal ranges including liver function tests, alpha-fetoprotein, prothrombin time and a normal D-Dimer.

Imaging examinations

A CT angiogram was performed to rule out aortic dissection due to his acute presentation. No evidence of the latter was seen but there was a 3-cm large arterially enhancing lesion in segment IV of the liver (Figure 1A). The lesion was arterialised with faint hypoenhancement in the portal venous phase (Figure 1B and C). Multiple arterially enhancing peritoneal, lesser sac and retroperitoneal nodules were additionally seen following the same enhancement pattern. The patient's spleen was observed to be lobulated and the right inferior ribs and right iliac crest had an abnormal appearance suggestive of previous trauma.

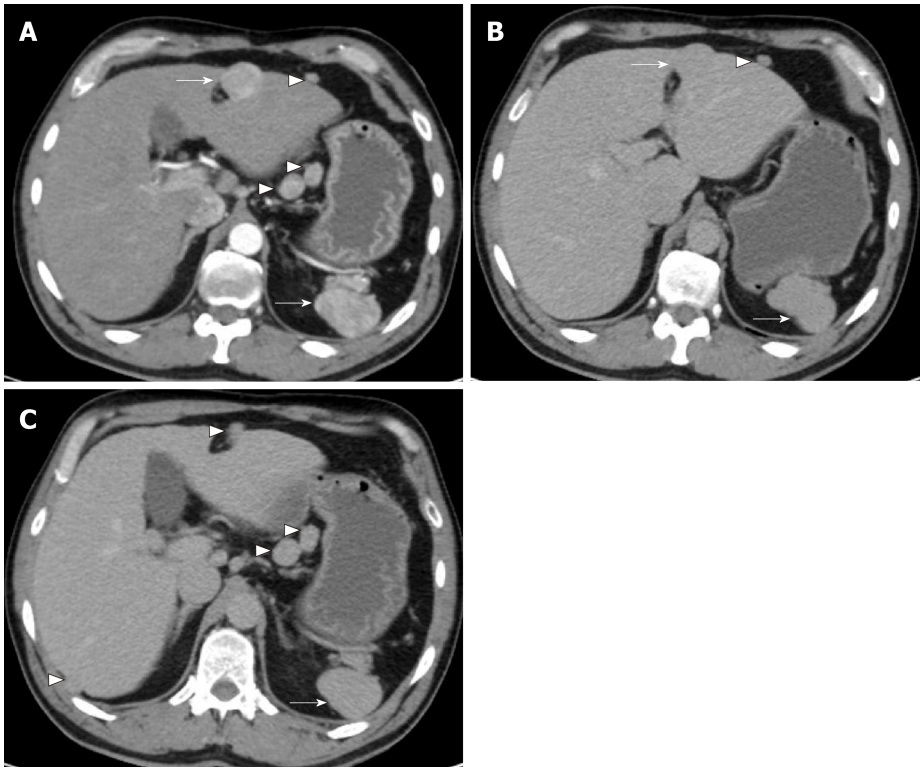

Figure 1 Computed tomography axial images from a patient with intrahepatic splenosis. A: arterial phase; a heterogenously enhancing left lobe liver lesion is present 3 cm in diameter (thick arrow). Similar heterogeneously enhancing peritoneal and lesser sac nodules are seen (arrowhead). The deformed spleen shows typical heterogenous "zebra stripe" arterial enhancement; B and C: portal venous phase; the liver lesion (thick arrow) and the peritoneal and retroperitoneal nodules (arrowhead) are isodense and the same density as the spleen (thin arrow).

FINAL DIAGNOSIS

Following discussion of these imaging findings and the patient's history in a specialist multidisciplinary team meeting, the possibility of intrahepatic splenosis with additional intra-abdominal splenosis was considered. This diagnosis was confirmed using scintigraphy with technetium-99m heat-denatured red blood cells (Tc-99 DRBC), which demonstrated uptake of the radiolabelled red blood cells by the multiple peritoneal nodules, as well as the lesion within the liver and the anterior abdominal wall (Figure 2).

OUTCOME AND FOLLOW UP

Due to the extensively reported benign nature of this condition, treatment was not required. The patient was informed of the incidental imaging finding and reassured. He was also informed that his chest pain was likely to be musculoskeletal in nature.

DISCUSSION

We describe a case of intrahepatic splenosis diagnosed radiologically, in a patient with a history of trauma. To the authors' knowledge, this is the first case of intrahepatic splenosis diagnosed without the need for histological analysis, thereby avoiding the potential risk of complications secondary to invasive investigations such as a liver biopsy or laparoscopic surgery.

To date, 21 case reports of intrahepatic splenosis have been described in the literature. We specifically review 13 cases which include CT and MRI (Table 1). Nine cases describe solitary lesions[9-17], whilst four cases involved multiple lesions[18-21]. The nodules ranged in size from 1.5-5.0 cm and were primarily found in the left lobe of the liver. Additional abdominal splenic nodules were reported in four cases to be located in close proximity to the upper pole of the left kidney[19], pancreatic tail[19], mesentery of the colon[20], paravesical space[21], caecum[21] and abdominal wall[15].

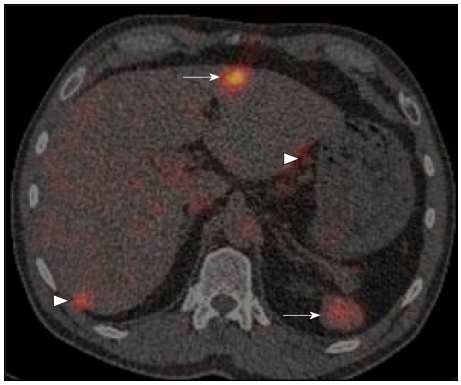

Figure 2 Denatured red cell scan with fused computed tomography images. The liver lesion (thick arrow), peritoneal and retroperitoneal nodules (arrowheads) and spleen (thin arrow) show uptake in keeping with multiple areas of splenic tissue.

All patients except one[14] had undergone a splenectomy in the past. Notably, a wrong diagnosis was made in all but one case[21], primarily of hepatocellular carcinoma (HCC)[9,13-18,20], leading to unnecessary surgery with the correct diagnosis only being made following post-operative histological analysis. This is partly due to the fact that splenosis is rare and hence is often not considered amongst the differential diagnosis. Additionally, six of the patients included in the literature review had chronic liver disease[9,13-16,18] including hepatitis B; a major risk factor for the development of HCC and four patients had raised tumour markers[9,14,15,18]. In such cases, HCC presents a more likely diagnosis rather than hepatic splenosis. In the isolated case where splenosis was correctly suspected, percutaneous biopsy was still carried out for confirmation[21].

Imaging is a useful diagnostic tool to distinguish splenosis from other lesions such as HCC, hepatic metastasis, haemangioma and focal nodular hyperplasia (FNH). CT and MRI provide panoramic imaging of the abdomen and can identify the size, location and enhancement characteristics of all lesions. Critically, all the splenic deposits exhibit an enhancement pattern identical to the native spleen on all imaging, with a heterogenous classical striped arterial hyperenhancement. However, this may be difficult to characterise if the native spleen is small or has been removed.

Classically, on unenhanced CT splenic tissue appears hypointense relative to the liver, whilst on MRI it appears hypodense on T1 and hyperintense on T2-weighted images. Five and six cases in the literature review exhibited these CT[14-17,19] and MRI[10,11,16,18,19,21] findings respectively (Table 1). On administration of contrast, splenic nodules are hyperintense in the arterial phase[9,10,13-20] often with a striated appearance as seen in our patient. They vary in appearance in the portal venous phase and may be hypointense[10,14,15,17,20], isointense[19] or hyperintense[9,13,16,18].

HCC has a variable appearance on both CT and MRI depending on biological characteristics including their degree of differentiation[22]. Since their blood supply is derived from the neoangiogenesis of non-triadal arteries, HCC, like splenosis typically appear hyperenhancing in the arterial phase with portal venous washout[22] (Table 2).

Hepatic metastasis also varies widely in appearance depending on the location of the primary tumour. They may appear hypo or hypervascular but typically show portal venous washout[23]. Haemangioma, FNH and adenoma are benign lesions which typically show arterial hyperenhancement[24-26] and hence may be mimicked by splenosis.

Of note, MRI using superparamagnetic iron oxide contrast instead of gadopentetate dimeglumine has been used to distinguish hepatic splenosis from malignancy[27]. Following intravenous administration, these particles are removed from the circulation specifically by the reticuloendothelial cells of the liver and spleen, leading to a reduction in signal intensity of the hepatic and splenic parenchyma on T2-weighted MRI. Such a reduction in signal intensity is however not seen in malignant lesions except some well differentiated HCCs[[18,28]. Splenic nodules still have a higher intensity than the hypointense liver as they take up more contrast. Nonetheless, uptake of contrast still occurs in FNH and so the specificity of this technique is limited in isolation[29].

Scintigraphy using Tc-99 DRBC is the current diagnostic tool of choice. This is due to its high specificity in identifying splenic tissue. It involves intravenous injection of heat denatured erythrocytes labelled with Tc-99. The majority, as many as 90% of the

Table 1 Characteristics of previous cases of intrahepatic splenosis identified in our literature review

Ref.	Age/sex	Blood results	Liver disease	Existing malign-ancy	Initial diagnosis	CT	MRI-T1	MRI-T2	Enhance-ment	Technique for diagnosis
[9]	60/M	Abnormal LFTs, ↑AFP	Chronic HepC	None	HCC	NA	NA	NA	A: Hyper V: Hyper	Laparosco-pic surgery
[10]	54/M	Normal	None	None	NA	NA	Hypo	Slightly hyper	A: Hyper V: Hypo	Laparotomy
[11]	54/M	Normal	None	Gastric cancer	Liver metastasis	ND	Hypo	Slightly hyper	NA	Laparotomy
[12]	52/M	Normal	None	None	Neurendo-crine tumour	NA	NA	NA	Hypervas-cular	Surgery
[13]	53/M	↑γGT	NASH	None	HCC/ hepatic adenoma	NA	NA	NA	A: Hyper V: Hyper	Laparosco-pic surgery
[14]	58/M	↑AST, ↑ALT ↑AFP, ↓PT, +HepC	Chronic HepC	None	HCC	Hypo	NA	Hyper	A: Hyper V: Hypo	Surgery
[15]	67/F	Slightly abnormal LFTs, ↑AFP	Chronic HepC	None	HCC	Hypo	Slightly hyper	Slightly hyper	A: Hyper V: Hypo	Surgery
[16]	42/M	+HepB +HepC	NASH	None	HCC	Hypo	Hypo	Hyper	A: Hyper V: Hyper	Laparotomy
[17]	54/M	Normal	None	None	HCC	Slightly hypo	Slightly hypo	Slightly hypo	A: Hyper V: Hypo	Surgery
[18]	32/M	↑AFP, ↑AST, +HepB	Chronic HepB	None	HCC	NA	Hypo	Hyper	A: Hyper V: Slightly hyper	Laparotomy
[19]	39/M	Normal	NA	None	Renal malignancy	Hypo	Hypo	Slightly hyper	A: Hyper V: Iso	Surgery
[20]	49/F	Normal	None	None	Hepatic malignancy	NA	NA	NA	A: Hyper V: Hypo	Laparotomy
[21]	69/M	Normal	None	None	Intrahepatic, abdominal splenosis	NA	Hypo	Slightly hyper	Hypovasc-ular	Percutane-ousbiopsy

M: Male; F: Female; AFP: Alpha-fetoprotein; AST: Aspartate transaminase; ALT: Alanine transaminase; γGT: Gamma-glutamyltransferase; PT: Prothrombin time; LFTs: Liver function tests; Hep B+: Hepatitis B positive; Hep C+: Hepatitis C positive; NASH: Non-alcoholic steatohepatitis; HCC: Hepatocellular carcinoma; A: Arterial phase; V: Portal venous phase; Iso: Isointense; Hypo: Hypointense; Hyper: Hyperintense (relative to the liver parenchyma); ND: Lesion not detected; NA: Not available.

erythrocytes are sequestered in splenic tissue, whilst normal liver tissue or malignant lesions have relatively modest uptake of the radioactive isotope[30]. This technique is therefore a reliable means of distinguishing splenic tissue from other hepatic lesions and avoids subjecting a patient to invasive procedures such as biopsy or surgery which are associated with their own risks.

Patients with splenosis are typically asymptomatic. Hence, surgery is only indicated if rare complications such as infarction[31], bleeding[32] or adhesions resulting in bowel obstruction occur[33]. It is suggested that splenosis may even be beneficial, providing some degree of immunological protection[13]. As it is a benign condition, it is often only diagnosed incidentally decades after the initial trauma following imaging for an unrelated condition. It is therefore difficult to ascertain the time taken for splenosis to occur. However, the process of splenic cells seeding in and growing on the serosal surface of the liver after recruiting nearby hepatic vasculature is likely to take several years. In the literature cases of intra-hepatic splenosis were diagnosed from a range of 5 to 46 years after trauma or splenectomy[17].

CONCLUSION

In conclusion, splenosis should be considered as a possible differential diagnosis for a hepatic nodule in any patients with a history of abdominal trauma or previous splenectomy, especially when the nodules are located near the capsule of the liver and are associated with multiple intra-abdominal deposits. Scintigraphy using Tc-99

Table 2 Typical enhancement characteristics of ectopic splenic tissue and other hepatic lesions

	Enhancement pattern
Splenosis	Arterially hyperenchancing; variable venous enhancement
HCC	Arterially hyperenhancing; venous hypoenhancement
Hepatic metastasis	Arterially variable enhancement; venous hypoenhancement
Haemangioma	Arterially peripheral nodular enhancement; venous infilling
FNH	Arterially hyperenhancing; venous iso/hyperenhancing with late enhancement of scar on MRI
Hepatic adenoma	Arterially hyperenhancing; variable venous enhancement

HCC: Hepatocellular carcinoma; FNH: Focal nodular hyperplasia; MRI: Magnetic resonance imaging.

DRBC is a reliable technique to diagnose splenosis and should be carried out in all patients suspected of the condition before more invasive diagnostic procedures are considered. Greater awareness of this condition could reduce the high incidence of unnecessary invasive interventions in these patients.

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