Review

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Comments and illustrations of the WFUMB CEUS liver guidelines: Cystic fibrosis associated liver disease

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Abstract

In this series of articles with comments and illustrations on the World Federation for Medicine and Biology (WFUMB) guidelines on contrast-enhanced ultrasound (CEUS) the topics of very rare focal liver lesions (FLL) are discussed. Improving the detection and characterization of the most common FLL are the main topics of these guidelines. The focus of this review is on the many manifestations of cystic fibrosis-related liver disease (CFLD). These include focal biliary fibrosis, liver cirrhosis, vascular manifestations with nodular regenerative hyperplasia and portal hypertension with or without cirrhosis. This article describes the diverse changes of liver involvement in cystic fibrosis and their appearance on ultrasound, duplex sonography, and contrast enhanced ultrasonography. This knowledge and the imaging should help to recognize liver manifestations in time and enable a correct interpretation of ultrasound images in CF in the corresponding clinical situation.

Keywords: Cystic fibrosis liver disease; focal biliary cirrhosis; ultrasonography; CEUS

Introduction

The World Federation for Ultrasound in Medicine and Biology (WFUMB) has published guidelines on the use of contrast-enhanced ultrasound (CEUS) for the evaluation of focal liver lesions (FLLs) [1-5]. These guidelines provide accurate characteristics of the most common FLLs in CEUS. However, there is now a wide range of data on rare focal liver lesions, which are only mentioned here as examples. These are of benign [6-8] and malignant [4,9-11] origin, mesenchymal [12], vascular [13-15], autoimmune [16], sarcoidosis [17-19], infectious/parasitic pathogenesis [20-29], mucinous cystic neoplasms [30], lesions in liver cirrhosis [31,32], hepatic manifestations of amyloidosis [33], hematological diseases [34,35] and in pediatric patients [36].

This paper describes the diverse sonographic appearance of Cystic Fibrosis (CF) in the liver. Due to a mutation of the Cystic Fibrosis Transmembrane Conductance

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Regulator (CFTR), there is a dysfunction in the secretion of water in body secretions such as bronchial secretions, bile, pancreatic secretions and small intestinal fluid. In the lungs, this leads to bronchitis, bronchiectasis, pneumonia and infections with problem microbes. This in turn leads to pulmonary fibrosis, respiratory insufficiency and right heart disease. Cystic fibrosis is a disease that not only primarily affects the bronchopulmonary system. Many other organs are involved. In the pancreas, focal fatty replacement occurs with pancreatic atrophy and endocrine and exocrine pancreatic insufficiency. In the small intestine, the thickened secretion can lead to ileus. The altered composition of bile predisposes to gallstone formation.

The manifestation of CF on the liver is called cystic fibrosis-related liver disease (CFLD). The manifestations on the liver are manifold. The most important histological manifestation of CFLD is focal biliary fibrosis. In the course, liver cirrhosis may develop. Vascular obliterative changes may also occur and in this context nodular regenerative hyperplasia (NRH). The etiology of steatosis in the setting of CFLD is difficult to distinguish from metabolic and other causes.

This current article reviews the liver lesions of cystic fibrosis. An overview of disease patterns is also provided but the main focus is on the appearance on ultrasound (US) and contrast enhanced ultrasound (CEUS).

Focal biliary cirrhosis and portal sinusoidal vascular disease in Cystic Fibrosis Liver Disease

Cystic Fibrosis Liver Disease

CF is an autosomal recessive inherited disease. The disease is determined by a mutation in the gene encoding the CF transmembrane conductance regulator protein (CFTR) on chromosome 7 [37-41]. The CFTR gene encodes a protein located on the apical surface of gallbladder epithelia and gallbladder cells. This CFTR protein is responsible for the regulation of the fluid and electrolyte content of bile [39,41]. Mutations of the CFTR protein are causative for impaired bile acid homeostasis, decreased bicarbonate secretion with associated ph dysbalance and increased bile viscosity. These changes can lead to stagnation of bile, which in turn is causative for accumulation of toxic bile acids and more frequent infections [39,42].

After complications of CF lung disease and complications of lung transplantation, manifestations and complications of CF liver diseases (CFLD) are the third leading cause of death in these patients. It is known that up to 40% of pediatric patients develop signs of liver disease by 12 years of age [43] and 2-5% of all deaths are attributed to complications of CFLD [39].

In a comprehensive retrospective study of 3328 CF patients with exocrine pancreatic insufficiency, the incidence of CFLD increased by approximately 1% each year to reach 32.2% at the age of 25 years. The incidence of severe CFLD increased only after the age of 5 years and reached 10% at the age of 30 years [44]. Risk factors for severe CFLD were male sex, CFTR F508del homozygosity, and history of meconium ileus [44]. A history of exocrine pancreatic insufficiency and meconium ileus indicate a severe CF phenotype [45]. Meconium ileus increases the risk of CFLD fivefold [45].

The appearance of CFLD includes liver enzymes elevations, hepatomegaly, steatosis hepatis, focal biliary fibrosis/cirrhosis, multilobular cirrhosis, hepatolithiasis. Other typical manifestations include microgallbladder, cholecystolithiasis, dyskinesia of the gallbladder, and increased risk of gallbladder carcinoma [40,46,47] (Table I).

CFLD can be diagnosed according to the Best practice guidance from Debray et al provided two or more of the above characteristics are present [48]. Newer criteria including transient elastography, elevated fibrosis markers such as the aspartate transaminase (AST)/platelet ratio index (APRI) have been developed by Koh et al [49].

There are two main features of underlying CFTR defect associated CFLD. These may be independent of each other but may also coexist - focal biliary fibrosis and portal sinusoidal vascular disease [40].

Focal biliary cirrhosis

Focal biliary fibrosis is the main histologic feature [40]. It represents the pathognomonic histopathological liver lesion in cystic fibrosis [46]. An initial focal fibrogenic process may progress and lead to multilobular biliary cirrhosis [44,48]. This process is unpredictable. It does not depend on the age and duration of diagnosis of

Table I. Appearance of cystic fibrosis-related liver disease

Liver	Biliary system	Systemic changes in case of portal hypertension
Liver enzyme elevation	Micro gallbladder	Splenomegaly
Hepatomegaly	Cholecystolithiasis	Portal venous collaterals
Steatosis hepatis	Dyskinesia of gallbladder	Spontaneous (splenorenal) portosystemic shunts
Focal biliary fibrosis/cirrhosis	Increased risk of gallbladder carcinoma	Ascites
Multilobular fibrosis		Thickened hyperechoic omentum in children
Hepatolithiasis		

CFLD [40,50]. Multilobular cirrhosis is characterized by diffuse multiple nodules throughout the liver [46].

Portal hypertension is observed with and without pre-existing cirrhosis. Only 20-27% of CF patients with signs of portal hypertension have been confirmed to have underlying fibrosis or cirrhosis [51].

Portal sinusoidal vascular disease

When cirrhosis is not present, portal sinusoidal occlusion may be causative. NRH is again seen in association with vascular changes [52].

Histological changes in portal sinusoidal vascular disease in CFLD are summarized in Table II.

Most prominent histologic feature in the explants of CF children with portal hypertension without liver cirrhosis were obliterative portal venopathy and NRH (94 % of explants) [52]. The cause of obliterative portal venopathy is not fully understood. The involvement of the portal vessels in the pro-inflammatory status of the biliary system is thought a possible cause [40].

It is recommended [40] that the phenotype of CFLD to be assigned according to the criteria of the North American and European Societies for Paediatric Gastroenterology, Hepatology and Nutrition [54]: multilobular cirrhosis with or without portal hypertension or liver failure, liver involvement with or without portal hypertension but without cirrhosis, or no evidence of liver involvement [54]

Secondary, non-CFTR gene mutation related liver involvement

In addition, liver diseases not directly related to the CFTR gene mutation but related to CF disease still need to be considered. This is typically a congested liver secondary to right heart failure caused by pulmonary disease, but also steatosis hepatis owing to exocrine pancreatic insufficiency, malnutrition, deficiency of essential fatty acids and diabetes mellitus [39].

Surveillance

Liver enzymes may be elevated and a permanently elevated gamma glutamyl transferase (GGT) is a risk factor for the development of cirrhosis [55]. The changes in the liver are usually initially clinically unnoticeable. With regard to liver involvement of CF with CFLD, the European Societies recommend annual clinical examination, laboratory diagnosis, and sonographic monitoring. A corresponding flowchart with inclusion of elastography has been presented by Dana et al [40]. In patients with CFLD-related liver cirrhosis, HCC screening should be carried out using US and AFP determination [40].

Table II. Histological features of portosinusoidal disease in CFLD [51,53]

Vascular changes	Parenchymal changes
Obliterative portal venopathy	Incomplete septal fibrosis
Portal vein wall thickening Lumen narrowing of portal vein stenosis or sclerosis	Architectural disorganization • irregular portal vein tracts • centrilobular vein distribution • non-zonal sinusoidal dilatation • mild perisinusoidal fibrosis
Portal vein anomalies and increased arterialization, periportal vessels, deviated portal vessels	Nodular regenerative hyperplasia

Imaging of CFLD

US describes liver changes and features of portal hypertension with splenomegaly, shunts, and collaterals. In children, thickening of the hyperechoic omentum compared to the aorta is a sign of portal hypertension [40].

On US, the liver may be homogeneous, homogeneous hyperechoic, heterogeneous, and of nodular pattern [40,56,57]. A heterogeneous pattern is associated with an increased risk of developing multilobular cirrhosis [58]. An initially hyperechoic heterogeneous liver parenchyma image led to a nodular image in 23% of patients over a period of 4 years. However, this was not only due to cirrhosis, but also to NRH [58].

Diffuse parenchymal changes in CFLD in US are summarized in Table III and focal changes are shown in Table IV.

In an observation of 168 children with CF over duration of 9 years, 35% had abnormal liver texture find-

Table III. Diffuse changes of liver parenchyma on US [40,56,57]

Parenchyma on US	Importance
Homogeneous, normal echogenicity	• does not exclude fibrosis • does not indicate low risk for development of cirrhosis in a younger child [46]
Heterogeneous liver parenchyma	• Fibrosis may be present, • increased risk of developing multilobular cirrhosis
Hyperechoic/ Steatosis hepatis	• due to exocrine pancreatic insufficiency, malnutrition, chronic diarrhea, deficiency of essential fatty acids and diabetes mellitus
Multilobular cirrhosis	• in severe course of CFLD, • watch for signs of portal hypertension. • HCC monitoring is indicated

Table IV. Focal changes of liver parenchyma in CFLD on US [40,46]

Focal liver lesion	Appearance on US	Importance
Focal biliary fibrosis	Broad band-like hyperechoic changes of the periportal tissue	Differentiation from portal vascular thrombosis and liver lesions
Nodular regenerative hyperplasia	• multiple hyperechoic lesions or small, round isoechoic lesions with a thin hyperechoic rim • Portal vascular changes may be present	Differentiation from multilocular cirrhosis

ings in at least one ultrasound examination, and 23% had permanent findings [56]. Of 719 children with CF aged 3-12 years, 82.1% had homogeneous liver parenchyma on ultrasound, 8.9% had a heterogeneous ultrasound pattern of the liver, and 3.3% had signs of liver cirrhosis on ultrasound [59]. Of 106 children, 17.9% developed ultrasound changes in the liver over a 10-year period, half with portal hypertension [60].

Adult patients with CF have a higher incidence of an abnormal ultrasound pattern (45%) compared to non-CF patients (15%) [57]. Patients with CF were more likely to have a hyperechoic liver parenchyma compared with non-CF patients (22% versus 15%) and more likely to have a heterogeneous pattern (24% versus 0%) [57]. Liver stiffness assessment is a method to detect early forms of fibrosis as well as for disease progression monitoring [61-64].

As an US correlate for *focal biliary fibrosis*, wide (>2 mm) hyperechoic band-like periportal tissues may be seen adjacent to the portal tracts [46]. Magnetic resonance imaging (MRI) shows high signal intensity in the periportal areas on T1 weighting [46]. MRI, especially in combination with magnetic resonance cholangiopancreatography (MRCP), can detect changes in the bile ducts, periportal fibrosis and nodule formation in the paren-

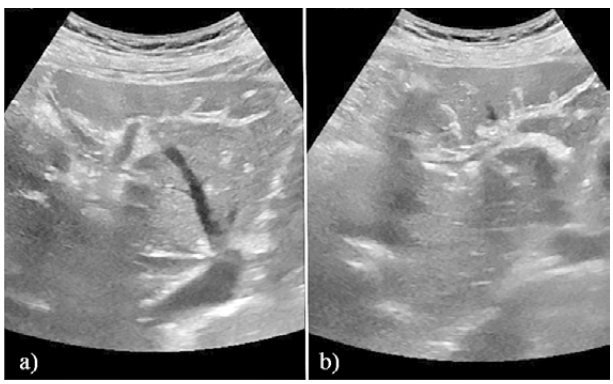

Fig 1. Wide hyperechoic changes periportally. 56 y/o male, care in adult outpatient clinic for cystic fibrosis. Abdominal US was performed for anemia. Unremarkable liver enzymes, no known CFLD. B-mode US reveals broad hyperechoic changes of portal walls and periportal region (a, b). These are an expression of periportal fibrosis. They are typical for focal biliary cirrhosis in CF but similar changes may be seen in other diseases associated with periportal fibrosis.

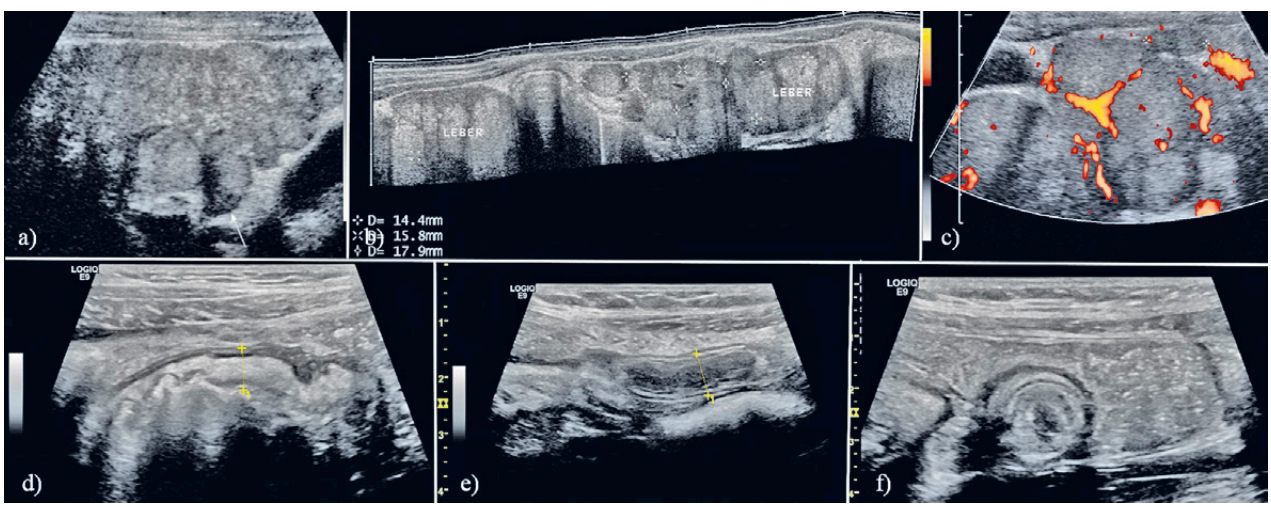

Fig 2. Multilobular cirrhosis in a child with Cystic fibrosis, exocrine pancreatic insufficiency, maximum-dose pancreatic enzyme substitution, colonic fibrosis, and appendiceal mucocele. Multiple large nodules in the liver on B-mode-US (a) and panoramic imaging (b). Power Doppler visualization of these large nodules with a destroyed vascular architecture (c). The colonic wall is gyriformly altered with hyperechoic thickened submucosa (d). The appendix is distended, outer diameter wider than 6 mm, shown longitudinally (e) and in cross-section (f). The examination is painless, and the findings are consistent with a mucocele.

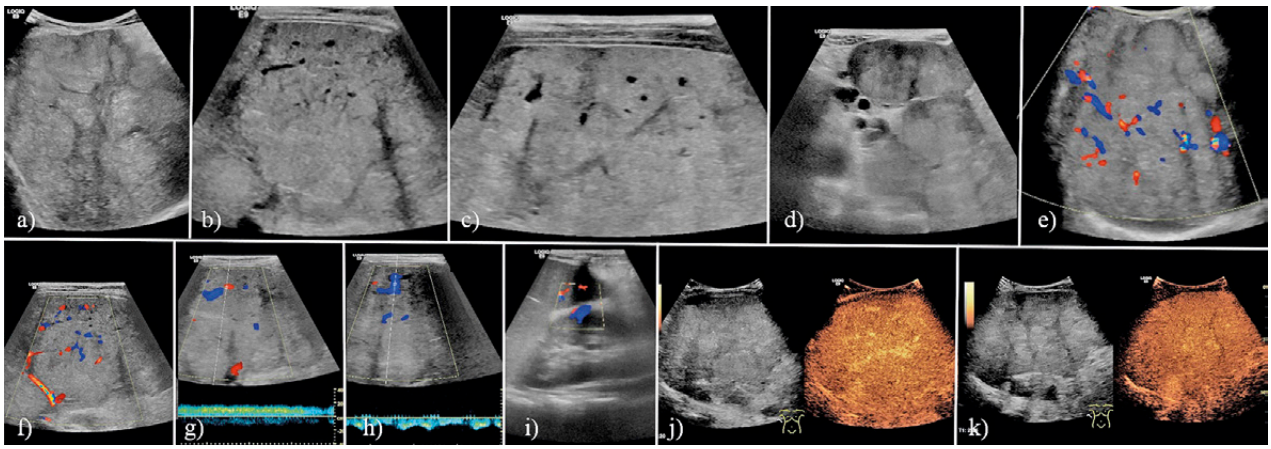

Fig 3. A 13 y/o, female. Cystic fibrosis liver disease. Planned for lung transplantation. Diabetes mellitus requiring insulin. Liver with diffuse macronodular hyperechoic regenerative nodules. B-mode US (a). Detection of small vascular structures in the regenerated nodules (b, c). Portal venous collaterals along the ligamentum teres (d). Irregular vessels in the macronodular regenerates suggesting collaterals and intrahepatic shunts (e, f). Subcapsular portal venous collaterals (Doppler) (g) and intrahepatic AV-shunts (h). Spontaneous splenorenal shunt at the renal capsule (i). On CEUS the nodules are isoenhanced in the arterial phase (j) and late phase (k).

chyma [46]. In nodular changes, it is necessary to differentiate between multilobular cirrhosis and NRH without cirrhosis [40]. NRHs present on US as multiple confluent hyperechoic liver lesions or as small, round isoechoic lesions with a thin hyperechoic rim [65] [fig 1-3].

Treatment of CFLD

The management of CFLD is based on symptomatic treatment, nutritional support, treatment of complications of portal hypertension with variceal band ligation and transjugular portosystemic shunt (TIPS). Treatment with ursodeoxycholic acid is controversial. While Colombo et al found no effect of UDCA treatment [66], Toledano et al reported a positive effect for survival in mild expression of CFLD [67]. The effect of norursodeoxycholic acid (NorUDCA) thus remains to be seen. This stimulates the secretion of bicarbonates while UDCA stimulates bile acid secretion [40]. Liver transplantation is an option in end-stage liver disease.

Conclusion

In CF it is important to detect possible liver involvement, to monitor patients, and to anticipate complications of liver disease with portal hypertension. Liver changes on US can be very discrete. These may be diffuse parenchymal changes in the setting of fibrosis, steatosis and multilocular cirrhosis. A homogeneous liver parenchyma with normal echogenicity does not rule out fibrosis. A heterogenic pattern of liver parenchyma is associated with an increased risk of developing liver cirrhosis. Similarly, it is possible that portal hypertension is not caused by cirrhosis but by obstructive portal venopathy. In this context, nodular changes can correspond to NRH. Focal changes can be focal biliary cirrhosis with broad hyperechoic periportal tissue, regenerated nodules, or NRH. Finally, screening for HCC is required in cirrhosis of the liver.

Conflict of interest: none

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