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REVIEW

Imaging of cystic fibrosis manifestations in the abdomen

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Abstract

Cystic fibrosis is a common inherited autosomal recessive disease affecting 35,000 persons in the United States. It is caused by mutations of the cystic fibrosis transmembrane regulator (CFTR) gene, located on the long arm of chromosome 7. This protein carries chlorine in the membranes of epithelial cells of exocrine glands. Mutations in the CFTR gene results in production of abnormally viscous mucus. Although it primarily affects the lungs, cystic fibrosis is a multisystem disease with involvement of extra thoracic organs including the liver, pancreas, kidneys and digestive tract.

With advances in the management of cystic fibrosis resulting in improved life expectancy, cystic fibrosis patients are surviving into adulthood and extrapulmonary disease has become more commonplace. It is essential that radiologists are aware of the spectrum of potential manifestations of cystic fibrosis to allow accurate diagnosis.

The purpose of this manuscript is to provide an overview of the pathophysiology and imaging findings of abdominal entities unique to patients with cystic fibrosis. We will present a wide spectrum of renal, pancreatic, gastrointestinal, hepatobiliary and post-transplant cases describing the typical findings that will assist radiologists in providing a timely diagnosis for patients with cystic fibrosis.

Keywords Cystic fibrosis · Abdomen · Gastrointestinal · Renal · Pancreatic transplant

Introduction

Cystic fibrosis (CF) is the most common autosomal dominant recessive disease in the Caucasian population. The incidence of CF is approximately 1 in 3500 to 1 in 5000 live births in Northern Europe, Australia and North America. Approximately 35,000 persons in the United States have CF [1]. Ireland has highest rate of CF in the world with an estimated rate of 1 in every 1600 births [2].

CF is caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene and its product on chromosome 7. At least 2000 CFTR variants are known currently [3]. Deletion of three base pairs in CFTR leading to the loss of the amino acid phenylalanine at position 508 (F508del) of the protein is the most common cystic fibrosis–causing variant. 90% of cystic fibrosis–related mutations in the United States are F508del [4]. The frequency of less common variants can vary depending on geographical regions, with non-Caucasians having a higher proportion of rare CFTR mutations [3].

The CFTR gene product encodes an ion channel involved in the regulation of the water-electrolyte balance on the surface of many organs. Defective chloride transport across epithelial cells results in viscous secretions resulting in organ dysfunction [5]. Although the lungs are primarily affected, CF is a multisystem disease involving the abdominal organs including the kidneys, pancreas, GI tract and hepatobiliary system.

With improvements in the management and complications of CF, life expectancy in this population of patients is increasing. In 2022, adults accounted for 59.4% of the CF population, compared with 32.8% in 1992. For individuals born between 2018 and 2022, the median predicted survival age was 56.6 years compared to 37.5 years in 2007 [6]. In keeping with these improved survival rates, extra pulmonary complications of CF are more commonly encountered in adults and are an increasing cause of morbidity.

This paper aims to illustrate the abdominal manifestations of CF. There are many challenges in the clinical diagnosis of these manifestations with overlapping symptoms and

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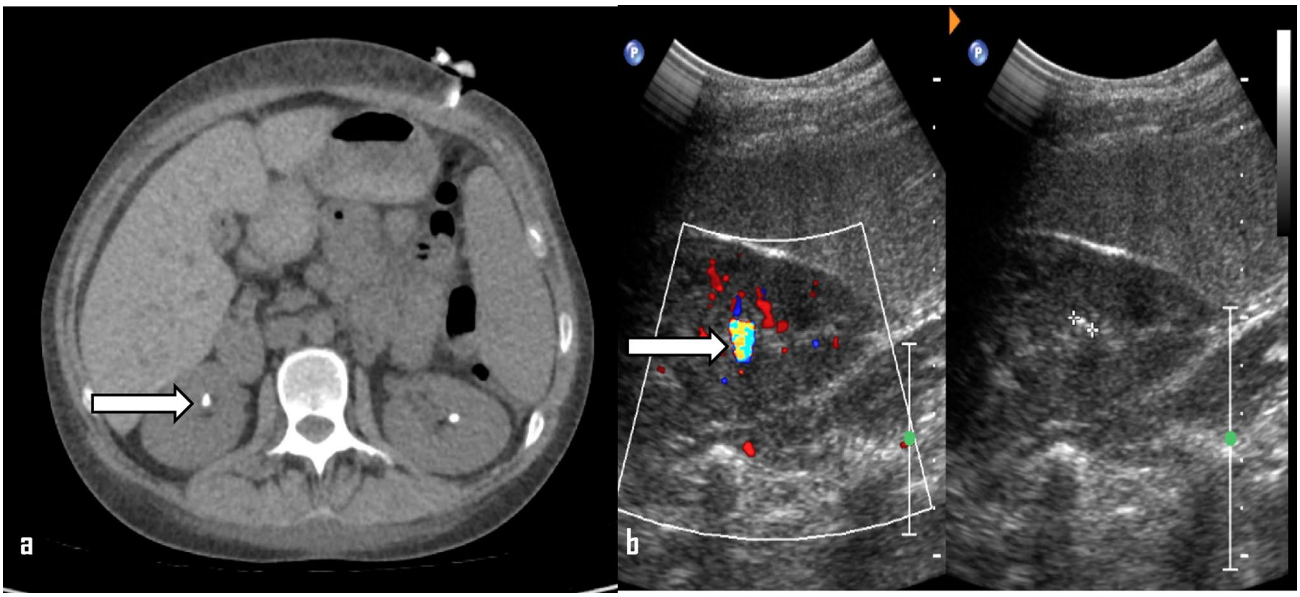

Fig. 1 Axial unenhanced CT **(a)** and US **(b)** of a 19-year-old female with non-obstructing renal calculi

a variation in presentation, therefore imaging plays a key role in identifying extra-pulmonary disease. In this review article we will describe the pathophysiology, clinical manifestations and imaging of the abdominal findings in adult patients with CF. We will present typical and atypical findings encountered in abdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and Positron Emission Tomography (PET).

Renal manifestations

Renal complications in adult cystic fibrosis patients are infrequent with a prevalence of 5% [7]. There is a wide spectrum of renal disease in adult patients with CF including renal stone formation and parenchymal disease.

Nephrolithiasis and nephrocalcinosis are the most common renal manifestations of CF with a prevalence of 2–4.6% (Fig. 1 and Fig. 2). The exact mechanism of stone formation is unclear, although it is known the CFTR protein is expressed in the kidney [8], possibly leading to urinary

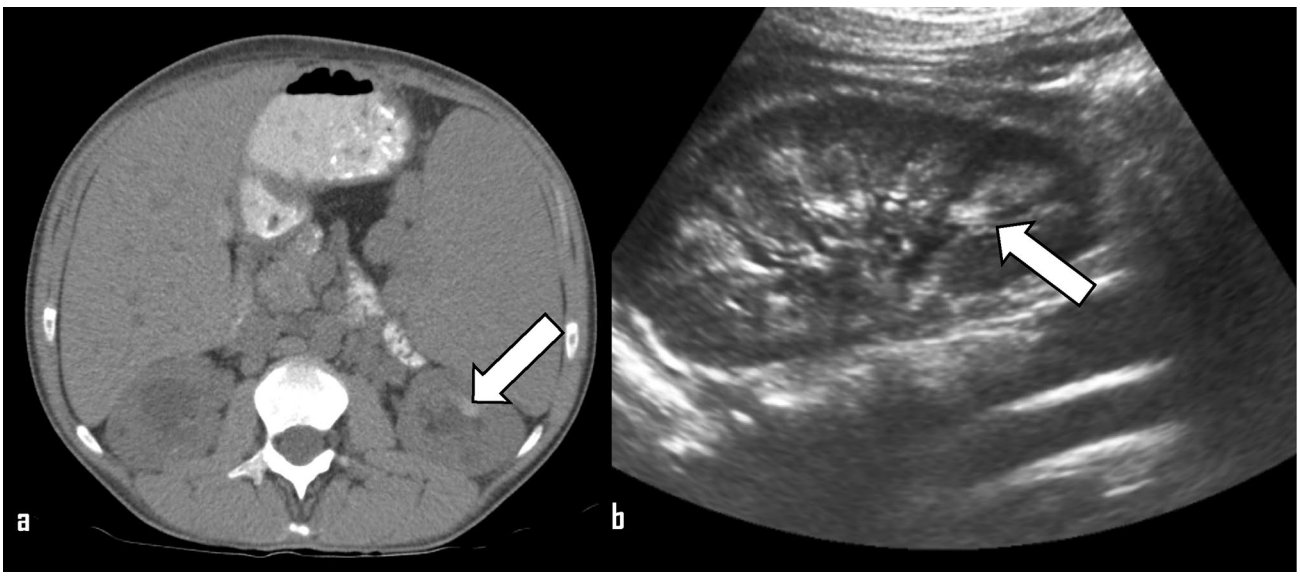

Fig. 2 Axial unenhanced CT **(a)** showing a dense renal medulla and US **(b)** showing increased medullary echogenicity typical of medullary nephrocalcinosis

abnormalities including hypercalciuria, hypocitraturia and hyperoxaluria [9, 10]. Urine of CF patients is saturated with calcium oxalate, the main component of renal calculi in patients with CF [11]. Chronic antimicrobial therapy resulting in altered gut flora which normally degrades oxalate is also believed to contribute to stone formation [12]. Ultrasound is frequently the first investigation of the urinary tract and can detect calculi. Typical findings of renal calculi on US include echogenic foci that show acoustic shadowing and twinkle artifacts on color doppler. CT is the most sensitive modality to detect urinary stones and typically appear as calcified densities in the renal collecting system, ureters, or bladder. Appearances of nephrocalcinosis can vary depending on the degree of cortical or medullary calcification. On US, medullary calcification, increased medullary echogenicity with possible posterior acoustic shadowing in more severe cases is typical of medullary calcinosis. On CT, increased attenuation of the medulla compared to the renal cortex is characteristic but not specific for nephrocalcinosis [12].

CF patients are at risk of acute kidney injury through chronic exposure to nephrotoxic agents such as aminoglycosides and immune suppressants [13], the main contributors to chronic kidney disease (CKD) in these patients. CKD is uncommon in patients with CF with a prevalence of 2.3%, doubling with every 10 years [14]. The incidence of moderate CKD rises to 11% in CF patients with a history of lung transplant. Patients with CKD are more likely to experience a longer cumulative effect of IV antibiotic cand chronic pulmonary infection [15].

Parenchymal disease is also reported in patients with CF. Amyloidosis as well as IgA nephropathy associated with chronic infections are associated with poor outcomes in patients with CF [13].

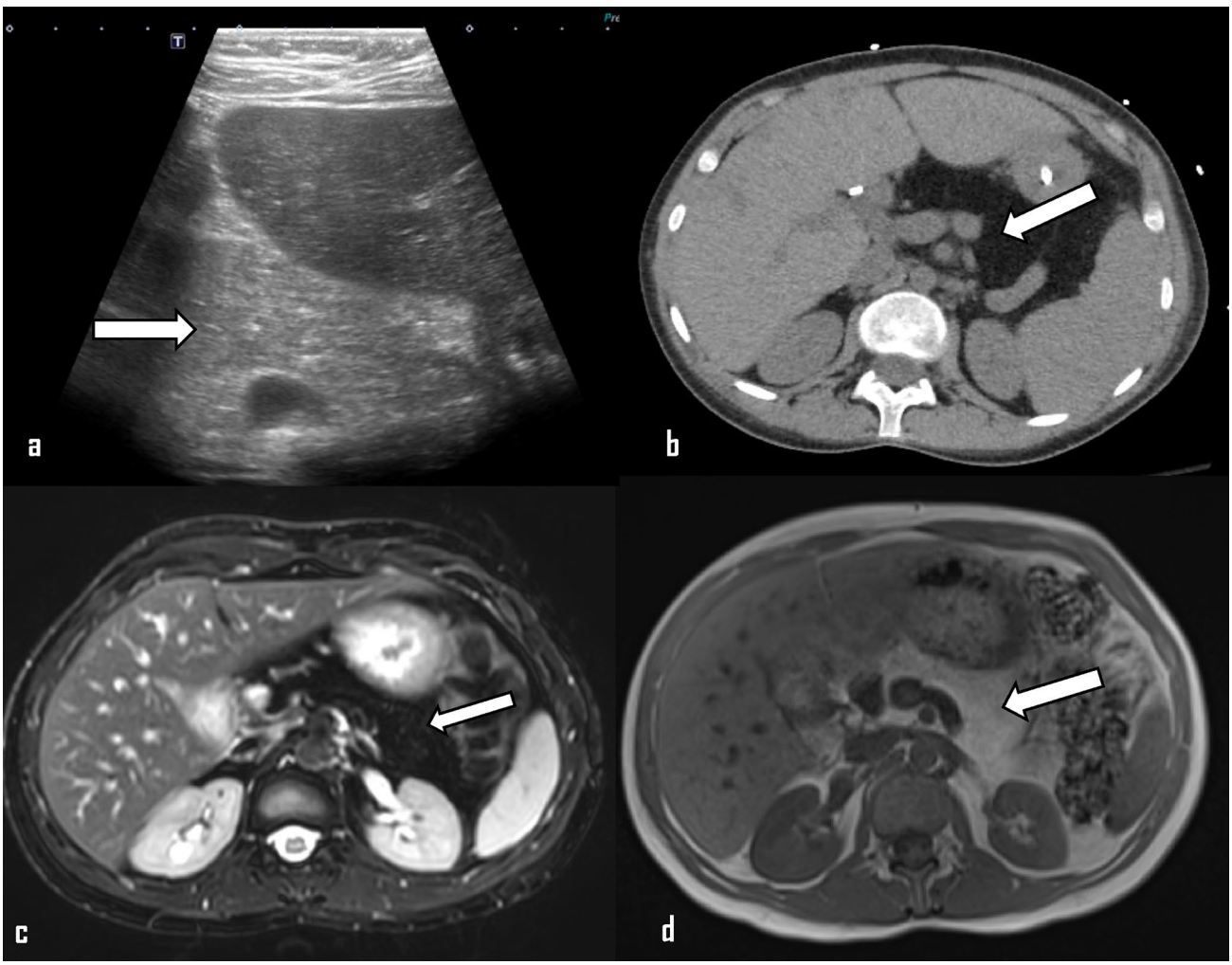

Fig. 3 US **(a)** and unenhanced CT **(b)** of a 30-year-old female showing with fatty replacement of the pancreas. MRI T2W fat suppressed **(c)** and T1W **(d)** demonstrates pancreas signal similar to retroperitoneal fat

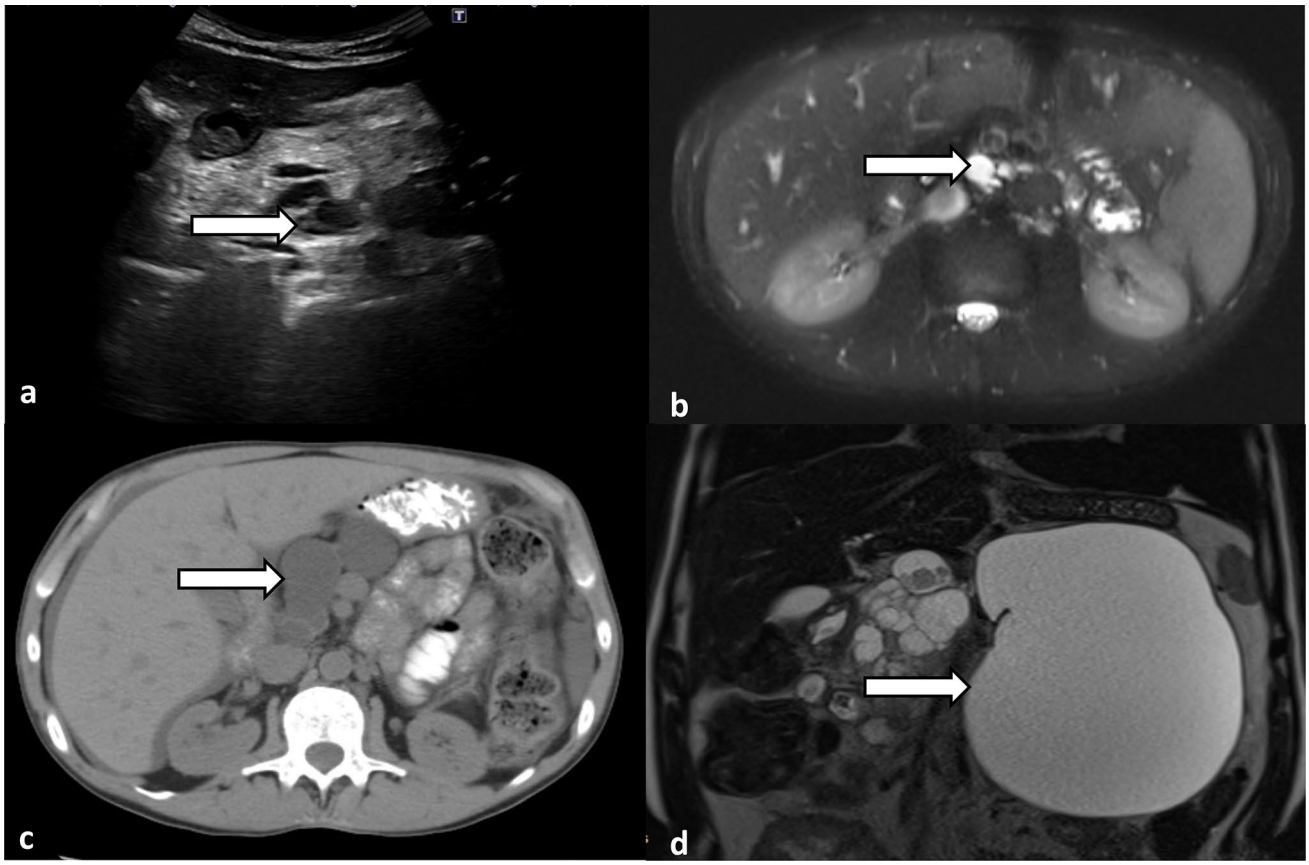

Fig. 4 US **(a)** and MRI T2W **(b)** showing multiple small cysts in the uncinate process of the pancreas. Axial unenhanced CT **(c)** and MRI coronal T2W **(d)** of a 58-year-old female, with 10-year interval between studies showing increased diffuse cystosis and replacement of the parenchyma with multiple large cysts measuring up to 12 cm

Pancreatic manifestations

The pancreas is the most affected abdominal organ in patients with CF. Inspissation of abnormally concentrated pancreatic secretions causes proximal duct obstruction. Continued secretion leads to pancreatic atrophy, inflammation and fibrofatty replacement resulting in a range of radiological findings (Fig. 3, Fig. 4 and Fig. 5). These appearances include fibrofatty replacement, lipomatous hypertrophy, pancreatitis as well as cyst formation [16–18].

Clinically, pancreatic dysfunction can present as endocrine and exocrine insufficiency. Exocrine insufficiency is secondary to impaired acinar cell function and is reported in 85% of CF patients. This leads to deficient pancreatic enzymes fat malabsorption, steatorrhea, malnutrition, and deficiency of fat-soluble vitamins. Endocrine insufficiency is secondary to pancreatic islet cell dysfunction and is less common, occurring in 30%–50% of patients. This can eventually progress to CF related diabetes mellitus [19].

Investigating pancreatic insufficiency involves a combination of investigations including fecal elastase-1 testing and direct assessment of pancreatic fluid collected during endoscopy. Noninvasive radiological investigations to quantify pancreatic exocrine function are also available, including secretin stimulated MRCP. Synthetic secretin administration leads to dilation of the pancreatic duct system and increased fluid volume in the duodenum. Qualitative assessment of the duodenal fluid can subsequently be performed and is a marker for pancreatic secretory function including in patients with CF [20]. Studies have demonstrated the accuracy of secretin induced MRI for the assessment of pancreatic function in patients with CF although high costs, technical complexity of analysis and increased examination time limits the use of secretin MRI in daily practice [21, 22].

The pancreas is typically atrophic in patients with CF. The atrophic pancreas may have complete fatty infiltration or partial fatty replacement. Complete fatty replacement is the most common radiological pancreatic with a mean age of replacement of 17 years [18, 23].

Typical US findings of the pancreas include loss of lobular pattern, hyperechoic and atrophic pancreatic parenchyma. Fatty replacement can also be seen on both CT and MRI (Fig. 3). The degree of fatty replacement varies, and the

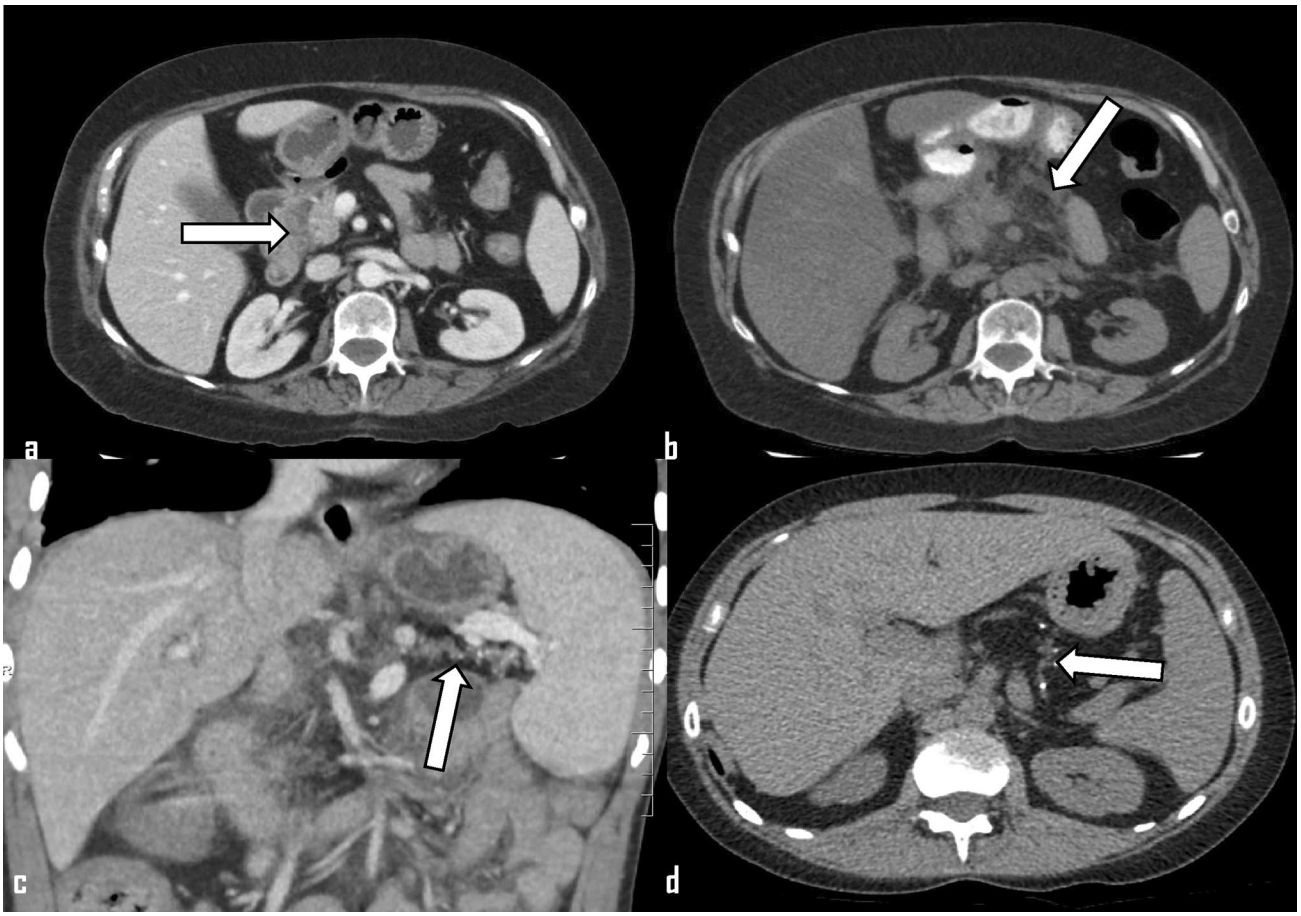

Fig. 5 Axial contrast enhanced CT **(a)** of a 64-year-old female with acute groove pancreatis and subsequently acute interstitial pancreatitis one year later **(b).** Coronal contrast enhanced CT of a 22-year-old female **(c)** and axial unenhanced CT **(d)** of 30-year-old female with pancreatic atrophy and calcification suggestive of chronic pancreatitis

pancreas is typically fat density on CT and fat signal intensity on MRI T1/T2 weighted sequences. Fibrosis in the pancreas manifests as low attenuation with decrease enhancement on CT. On MRI, intermixed low T1 and T2 signal is suggestive of fibrosis [24].

Complete replacement by fibrofatty tissue and enlargement of the gland are indicative of lipomatous pseudohypertrophy [18, 25].

Pancreatic cysts are a relatively common finding in adult CF patients (Fig. 4). The cysts can vary in size and number, typically a few millimeters in diameter. Pancreatic cystosis results in replacement of the pancreas with macroscopic cysts which can measure from 1 to 12 cm [26]. The cysts are lined by epithelium and thus represent true cysts [27, 28]. They are typically an incidental finding and asymptomatic, rarely causing symptoms through adjacent mass effect [29]. On US, the cysts are homogenous, hypoechoic and thin walled. The cysts are best demonstrated on MRCP or T2 weighted MRI. The cysts follow the signal of simple fluid including hypointense T1 and hyperintense T2 signal. They are usually unilocular with no internal septations or enhancement demonstrated.

Acute pancreatis is rare with a reported incidence of 1.2% and a mean age of first episode of 19.9 years [30]. Pancreatitis is typically seen in exocrine sufficient patients which predispose patients with CF to acute and recurrent cases of pancreatitis. Inflammatory changes associated with pancreatitis in patients with CF are less compared to the general population [31]. Calcification in also a reported finding and seen in 8% of patients [32] (Fig. 5.).

Gastrointestinal manifestations

The manifestations of the gastrointestinal tract often overlap, making a diagnosis difficult. Furthermore, non-CF related causes of abdominal pain may manifest atypically.

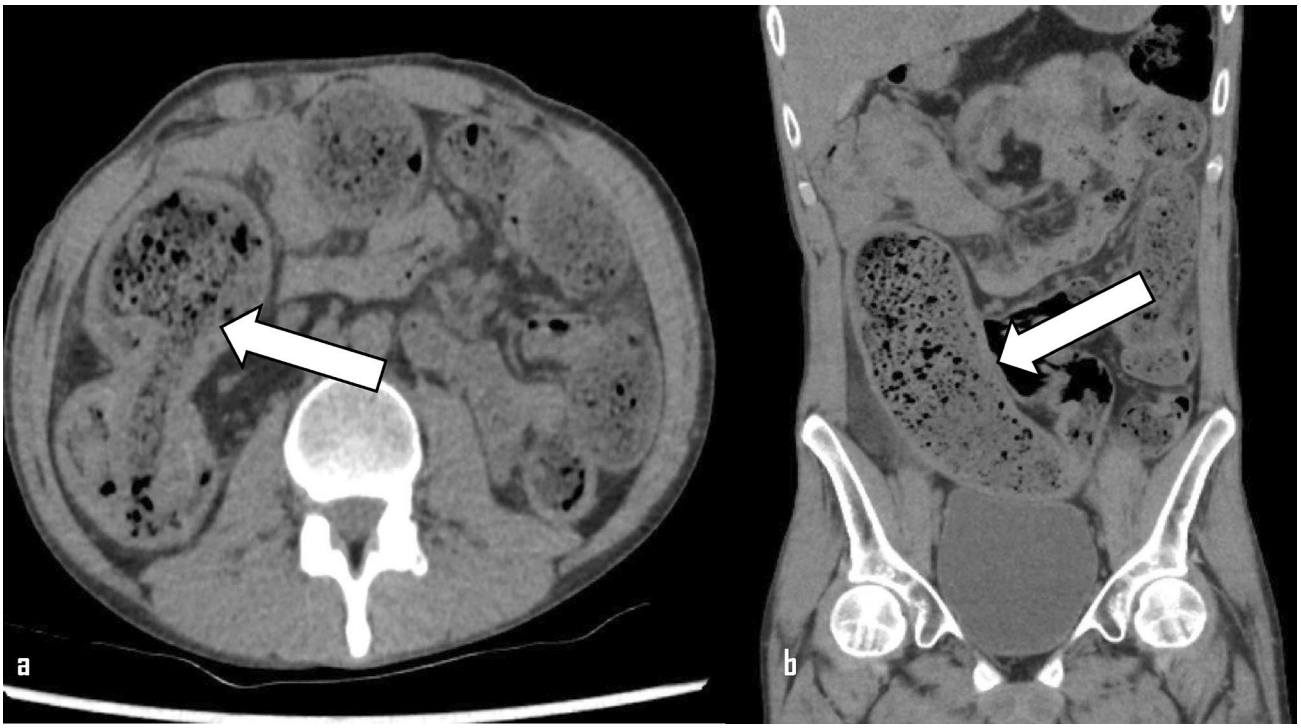

Fig. 6 Axial **(a)** and coronal **(b)** unenhanced CT of 24-year-old male with right lower quadrant pain showing fecalised content and distension of the distal ileum in keeping with DIOS

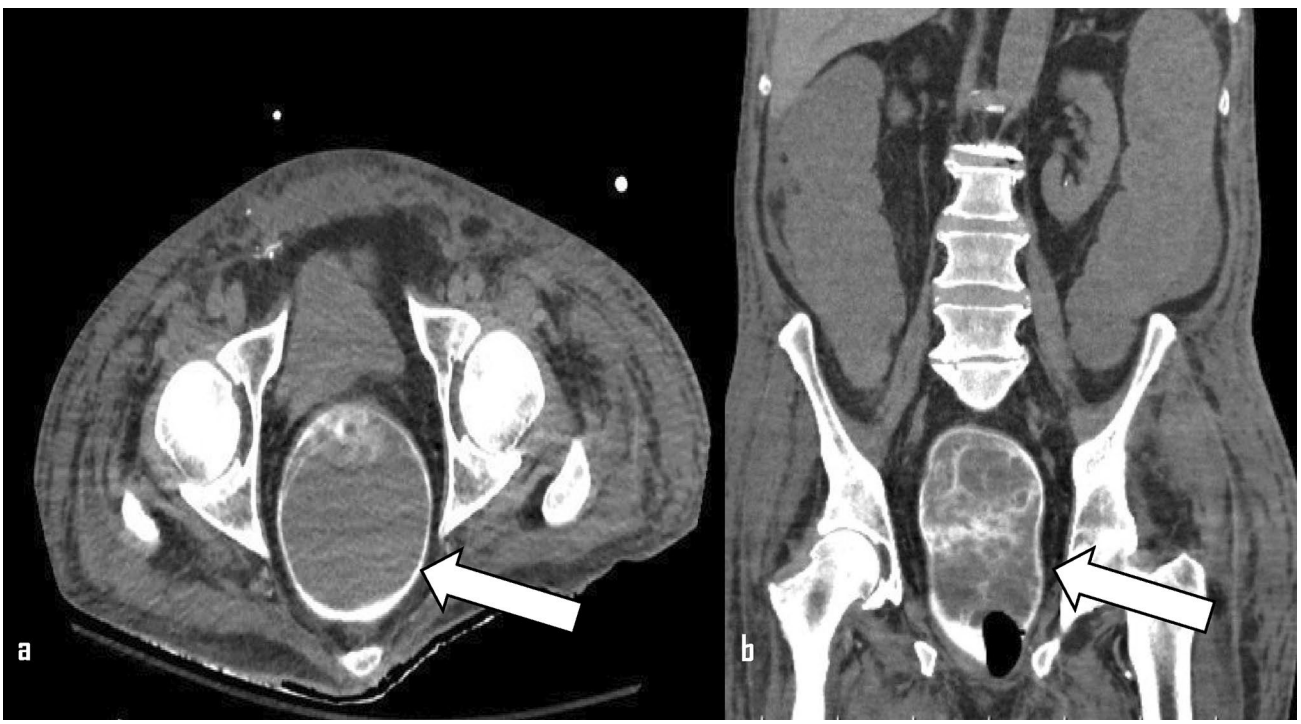

Fig. 7 Axial **(a)** and coronal **(b)** CT with PR contrast of a 69-year-old male with chronic constipation showing thickened inspissated material in the rectum and large bowel

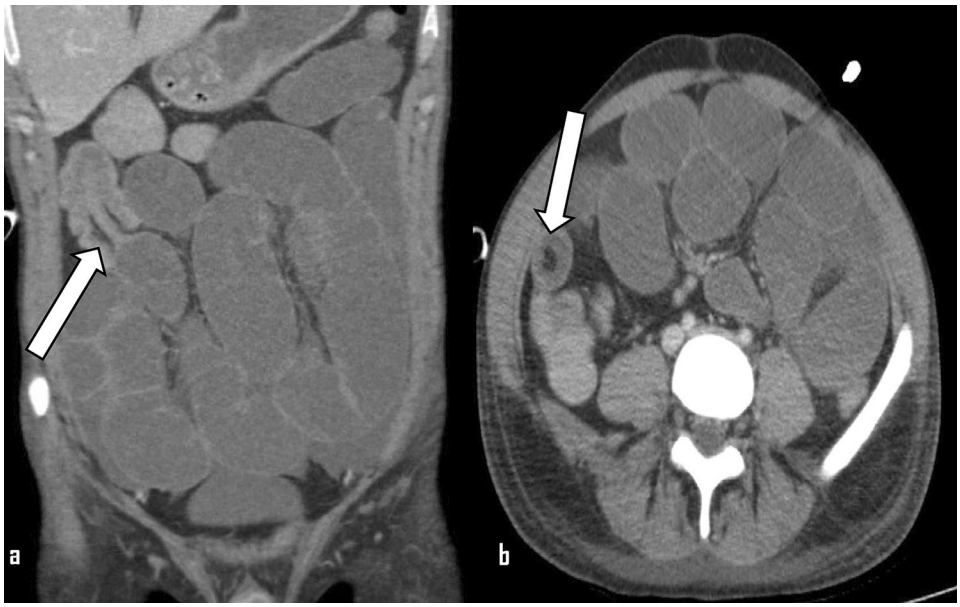

Fig. 8 Coronal **(a)** and axial **(b)** unenhanced CT of 27-year-old male with ileo-ileo intussusception and upstream obstruction 8 days following lung transplant

Treatment of chronic presentations may be improved by nutrition and an accurate diagnosis is essential for improving survival for patients with CF [33].

Distal ileal obstruction syndrome

Distal ileal obstruction syndrome (DIOS) or meconium ileal equivalent is reported to occur in 11–15% of adult patients and relatively unique to this patient population. DIOS is thought to be caused by a combination of thickened intraluminal secretions, delayed transit and undigested food [34]. This combination results in mucofeculent material impacting in the lumen of the bowel, typically in the distal ileum and the right colon (Fig. 6). Impaction of feculent material is also described in the distal colon and rectum leading to chronic constipation [35] (Fig. 7).

Clinically, DIOS can manifest as an acute intestinal obstruction or intermittent right lower abdominal pain and abdominal distension. A right lower quadrant mass may be palpable on examination. Differentiating between chronic constipation and DIOS clinically can be challenging however, the presence of subacute chronic abdominal symptoms with fecal material evenly distributed throughout the bowel favoring a diagnosis of constipation [36].

Risk factors for DIOS include pancreatic insufficiency, previous history of meconium ileus, dehydration and pancreatic insufficiency [33]. Patients with CF are also at increase of DIOS following lung transplant [37].

On imaging, the most common radiographic finding is a bubbly soft tissue mass in the right lower quadrant [23]. On CT, DIOS can depict the point of obstruction and dilated small bowel loops with feculent material [38]. Treatment is typically conservative, including increased hydration and stool softeners. Surgical intervention is rarely required.

Intussusception

Intussusception is more commonly seen in patients with CF compared to the general population, with a reported incidence of 1% [39]. It is most frequently ileocolic in distribution and lead points include inspissated material, a chronically distended appendix and lymphoid tissues [34]. It is found in 20% of CF patients presenting with acute obstruction and can also be a complication of DIOS [34, 40].

Often intussusception in the adult population is intermitted and resolves spontaneously without intervention. Clinically, symptoms include colicky abdominal pain, vomiting and a palpable mass. PR bleeding may not be seen in adult patients. As both intussusception and DIOS can present with acute abdominal pain and obstructive symptoms, accurate diagnosis is imperative as operative intervention may be required in the former.

Radiological findings are identical to those of the general population (Fig. 8 and Fig. 9). US may show a "target sign" or a "pseudo kidney sign". The "target sign" refers to the appearances of concentric alternative echogenic and hypoechoic bands on US. Echogenic bands are a result of the serosa and submucosa either side of a hypoechoic muscularis propria. A target sign can also be seen on CT [41]. The "pseudo kidney sign" is the longitudinal appearance of the intussuscepted segment of bowel and mesenteric vessels which mimics a renal hilum [42].

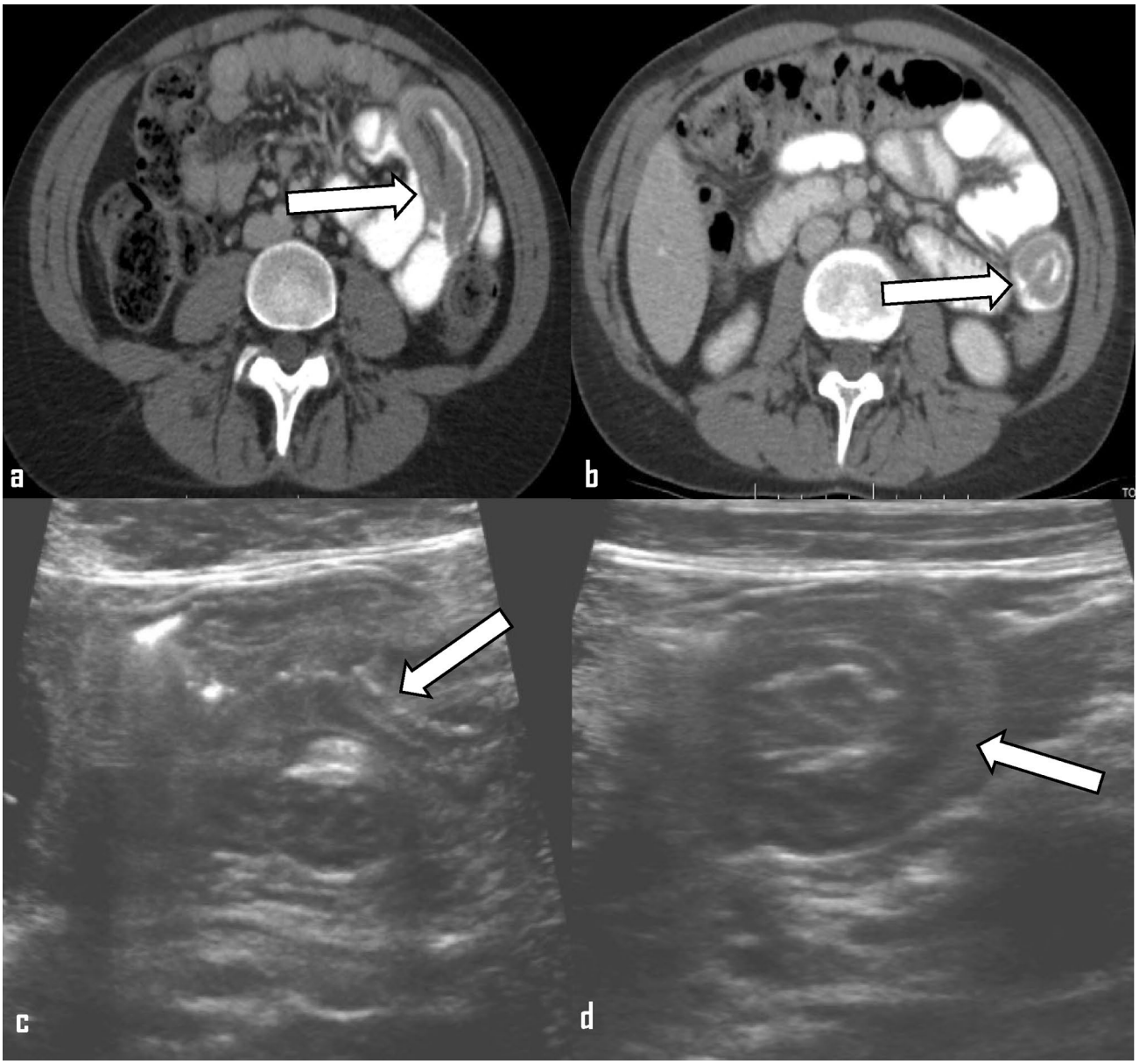

Fig. 9 Axial contrast enhanced CT **(a & b)** of 19-year-old female with asymptomatic jejeno-jejunal intussusception, treated conservatively. Follow up US demonstrates a pseduokidney sign **(c)** and target sign **(d)** consistent with persistent intussusception

Appendix

Appendiceal morphology in CF patients is a wide spectrum of appearances ranging from mucus distension, acute or chronic inflammation, perforation and abscess formation (Fig. 10). Appendicitis is uncommon in CF patients with a reported incidence of 1–2% of patients compared to 7% in the general population. The cause for this is uncertain but it is hypothesized that inspissated secretions have a protective effect against appendicitis [43].

Symptoms can be atypical, overlapping with DIOS and intussusception. Chronic antibiotic use can also mask typical symptoms potentially resulting in a higher incidence of perforation and abscess formation in patients with CF [44]. The appendix of CF patients is routinely enlarged (> 6 mm) as a result of mucoid impaction and appendix diameter is not a reliable parameter for assessment [45]. Therefore, identifying secondary signs of appendicitis is critical.

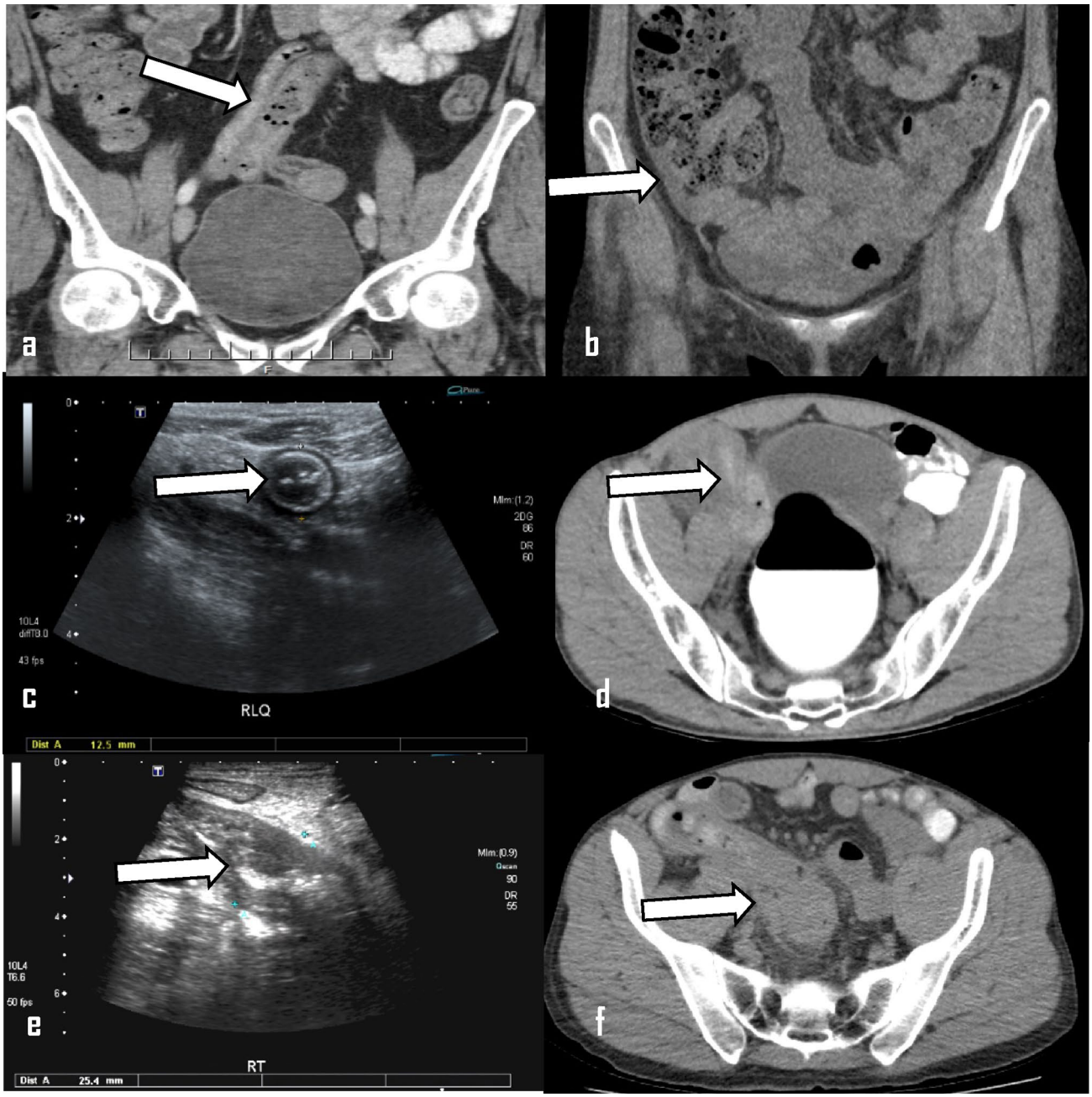

Fig. 10 Coronal CT **(a & b)** showing a distended appendix with mucus material. On CT, the appearance of the mucus material varies and can be high **(a)** or low **(b)** in attenuation. US **(c)** and axial CT with oral contrast **(d)** of 22-year-old male presenting with acute abdominal pain. US showing a distended and thickened appendix. CT confirmed appendiceal distension with high attenuation mucus secretions and associated inflammation. US **(e)** and axial CT with oral contrast **(f)** of a 43-year-old male presenting with chronic abdominal pain. US showing a significantly distended and thickened appendix. CT confirmed appendix distension with high attenuating mucus secretions and inflammation. Pathology confirmed chronic appendicitis

Colonic disease

The colon is commonly abnormal in patients with cystic fibrosis and demonstrates a wide spectrum of appearances. The CFTR is thought to play a role in epithelial permeability and interactions with bacteria, potentially predisposing patients with CF to varied bowel appearances [38, 46].

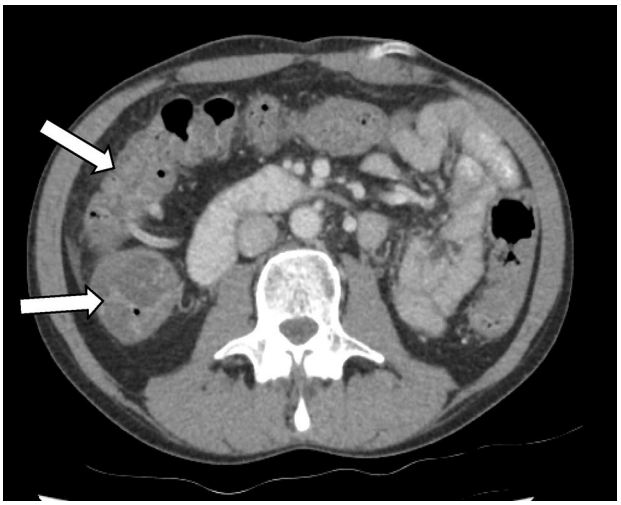

Fig. 11 Axial contrast enhanced CT of an asymptomatic 28-year-old male showed mural thickening of the ascending colon with no other associated inflammatory changes

Proximal bowel thickening and fibrofatty proliferation of pericolonic tissues has been described in patients with CF. This typically affects the right side of the colon with variable involvement of the transverse and descending colon (Fig. 11). Pathology specimens obtained at colonoscopy of these CF patients have revealed normal mucosa, non-specific inflammatory changes and microcolitis [40, 47]. These findings can be managed conservatively with colonoscopy reserved for worsening or persistent abdominal symptoms [38].

Colon wall redundancy, also known as jejunation of the colon, describes the "wrinkled" appearance of the proximal colon (Fig. 12). This results from the doubling or overlapping of the wall independent of the haustra of the colon, often mimicking the telescoping appearance of intussusception [48]. This has a reported incidence of 39% of CF patients with variation amongst different CFTR mutations. Mean thickness of the wall of the ascending colon is typically greater in patients with CF who have redundancy (4 mm) compared to both those CF patients without redundancy and the general population (1.8 mm and 1.2 mm respectively) [48].

Pneumatosis intestinalis (Fig. 13) has been reported in 5% of patients and is usually confined to the colon in patients with CF [34]. Development of pneumatosis is believed to be secondary to chronic lung disease and alveolar rupture. Air dissects the connective tissues into the peritoneum and mesentery with resultant sub serosal air [49]. It is typically benign and self-limiting. Although patients are often asymptomatic, a surgical consultation should be obtained in those CF patients with pneumatosis intestinalis presenting with an acute abdomen. CT findings included submucosal air lying along the dependent potion of the bowel.

Colon *Cancer*

Because of improved life expectancy in patients with CF, there is an increasing incidence of gastrointestinal malignances including the small bowel and biliary tract. Patients with CF are at an increased risk of colorectal cancer compared to age matched individuals without CF [50, 51]. Screening colonoscopy has demonstrated a high frequency of advanced adenomatous polyps in patients with CF [52] (Fig. 14).

The average age of onset of CRC in CF patients is approximately 40 years, 20–30 years younger than the in the non-CF population [51]. Although the overall risk of developing CRC is low in CF patients under the age of 30, the risk of CRC increases after lung transplantation, being 25–30 times

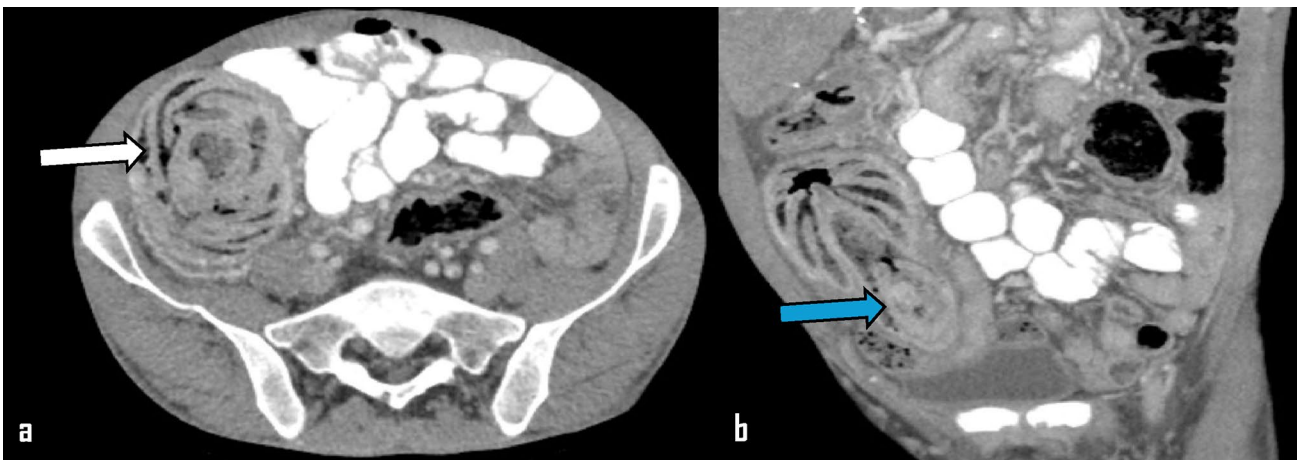

Fig. 12 Axial **(a)** and coronal **(b)** contrast enhanced CT of a 33-year-old male showing caecal redundancy (white arrow) and an incidental ileocolic intussusception (blue arrow)

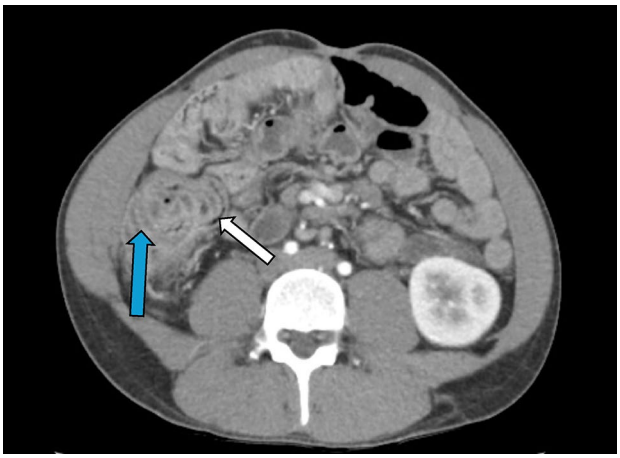

Fig. 13 Axial **(a)** and coronal **(b, c)** contrast enhanced CT on lung (a,b) and soft tissue (c) windows demonstrating asymptomatic benign transverse and ascending colonic pneumatosis in a 40-year-old female (blue arrows)

greater than the age adjusted baseline. Published recommendations suggests screening colonoscopy of CF patients beginning at the age of 40 and age of 30 in CF patients who have undergone successful transplantation [53].

The exact mechanism for the increased risk of CRC is unclear however, studies have shown the potential role of the CFTR gene acting as a tumor suppressor gene in the intestinal tract where loss of CFTR function leads to increased intestinal tumor formation [54, 55].

Hepatobiliary manifestations

CF associated liver disease (CFLD) is a term which describes a wide spectrum of hepatobiliary manifestations seen in patients with CF. Long thought to be predominantly an issue of childhood, CFLD incidence in adults is increasing as a result recent advances in life expectancy. The definition of CFLD remains controversial and a lack of consensus results in a wide variation of reported prevalence ranging from 30%-72% of adult CF patients [56, 57]. Although declining lung function remains the most common cause

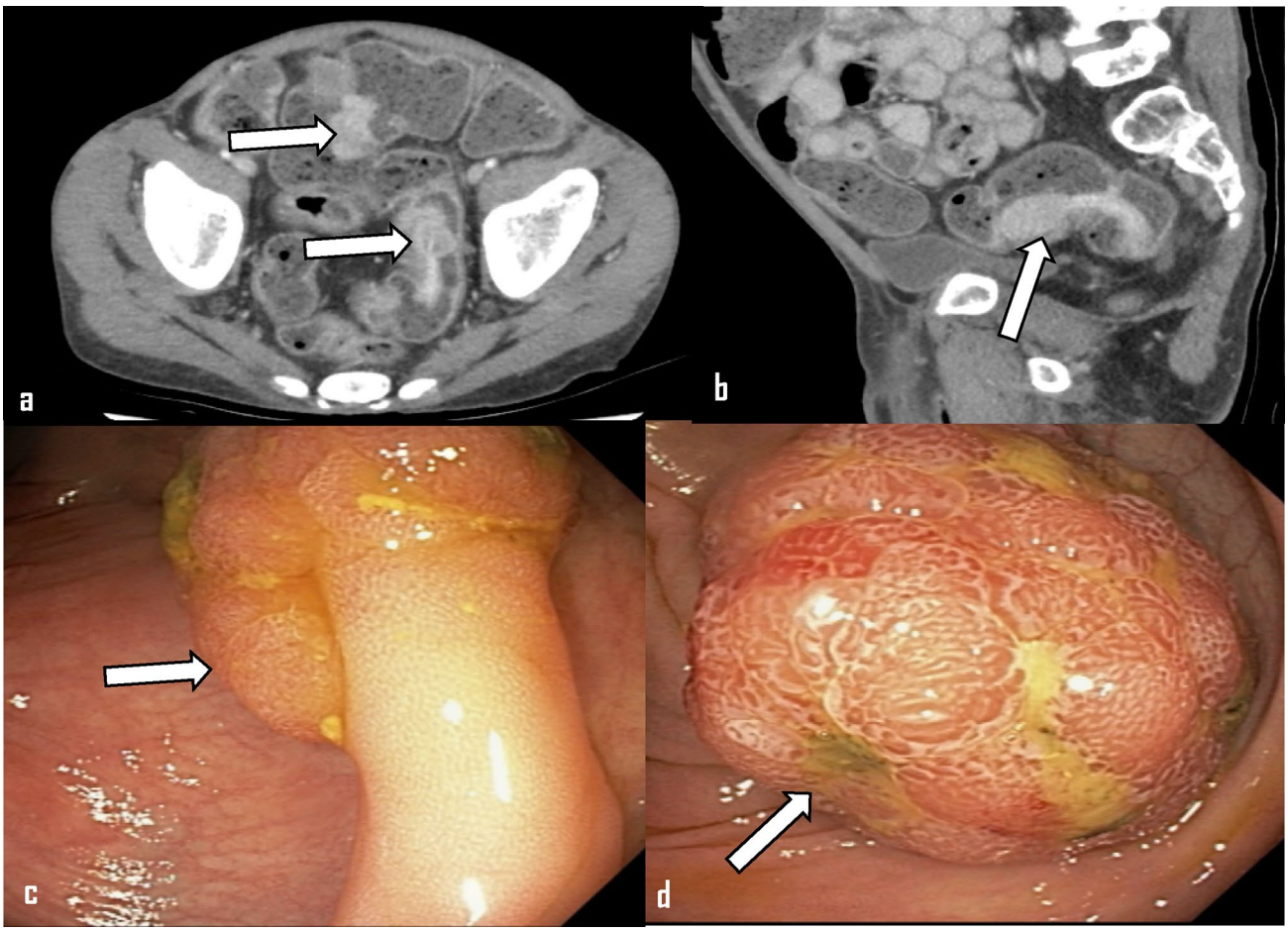

Fig. 14 Axial **(a)** and coronal **(b)** CT of a 36-year-old male showing multiple colonic polyps. These were further assessed and confirmed on colonoscopy **(c & d)**

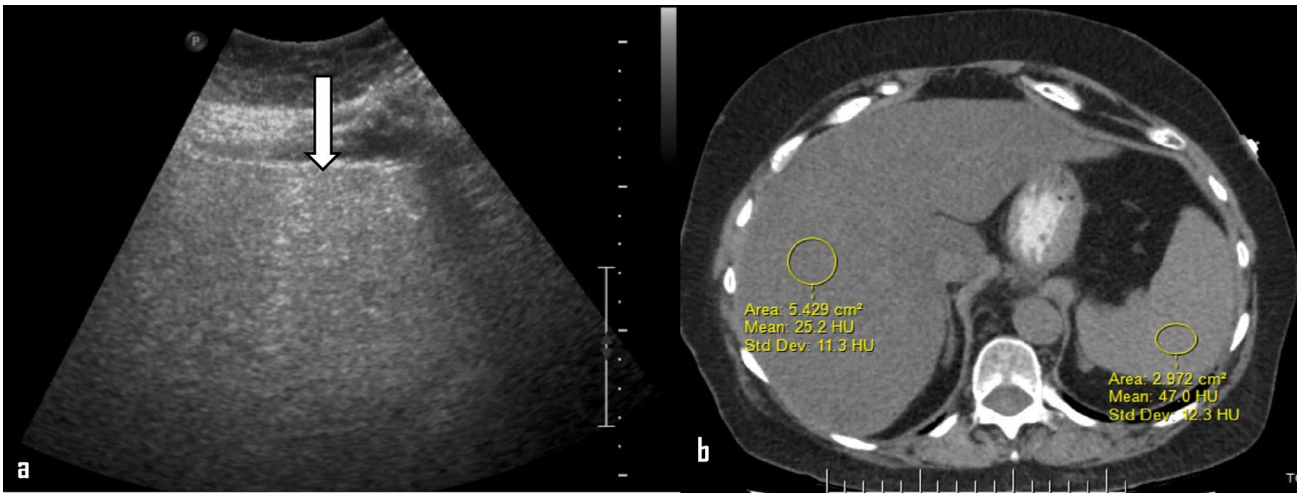

Fig. 15 US **(a)** and axial unenhanced CT **(b)** of a 66-year-old male with hepatic steatosis. US shows increased liver echogenicity and CT demonstrates liver attenuation is > 10HU less than the spleen and absolute attenuation < 40 HU

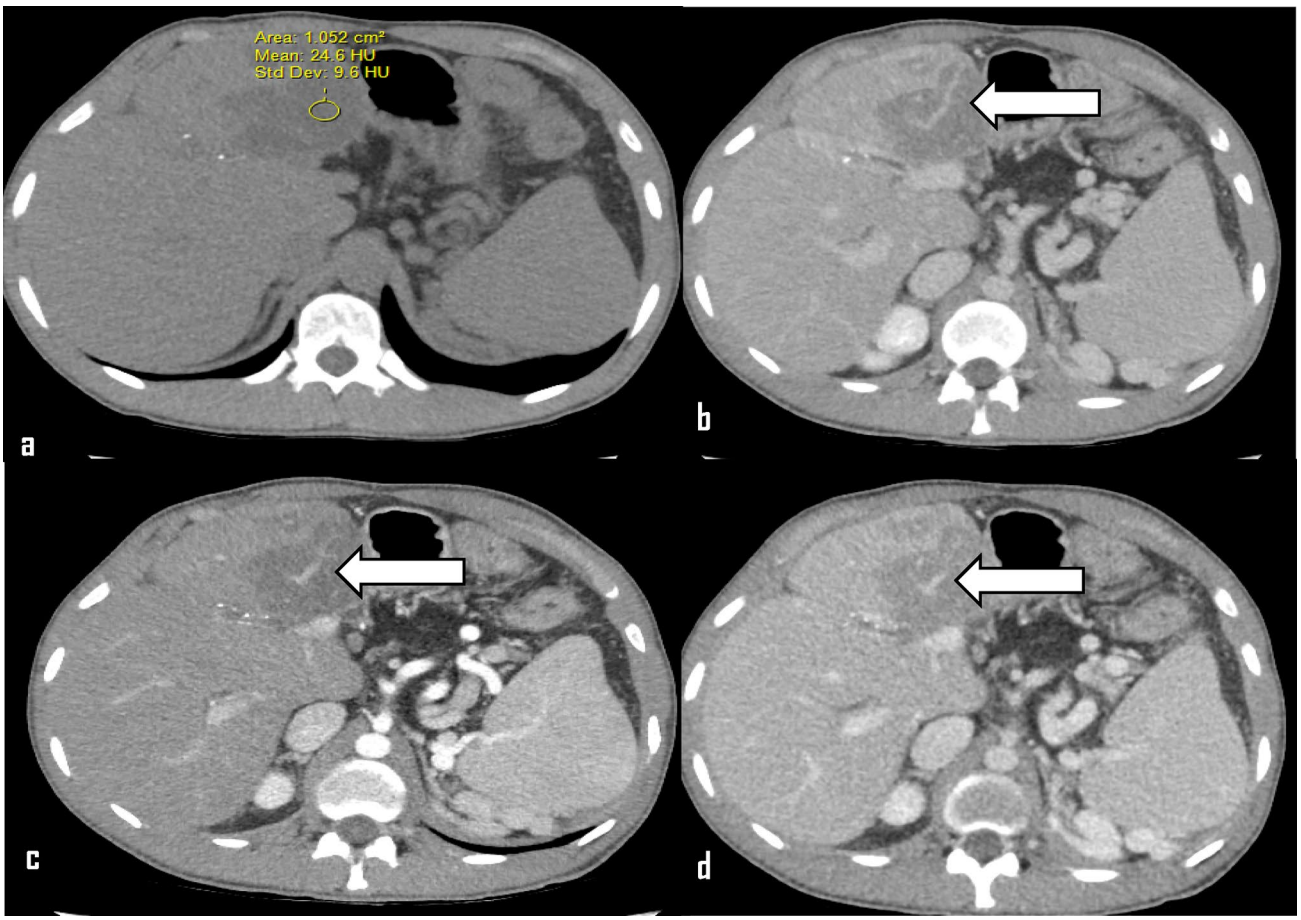

Fig. 16 Multiphase axial CT **(a–d)** of a 19-year-old male with known CF related cirrhosis. Unenhanced CT **(a)** shows a pseudo mass in the left lobe of liver with attenuation 24 HU. This remains hypoenhancing to adjacent liver tissue on all phases **(b–d)**. Note there is no mass effect on adjacent vessels, typical of focal fat (white arrows)

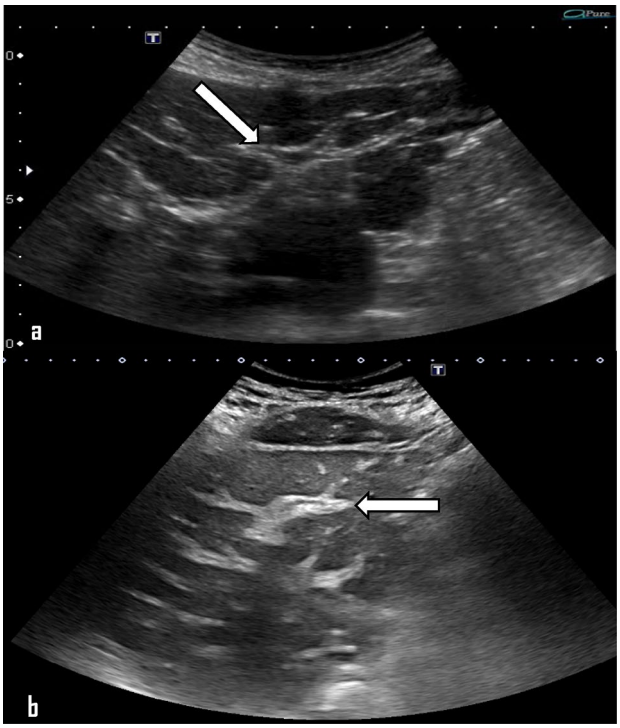

Fig. 17 US of a 46-year-old female **(a)** and 24-year-old male **(b).** US shows increased periportal echogenicity suggestive of focal biliary cirrhosis

of mortality in CF patients, liver disease is the third leading cause of death accounting for 2.5% of overall mortality [57].

The exact pathogenesis of CFLD remains poorly understood with CFTR expressed in bile ducts and the gallbladder but not hepatocytes. Absent CFTR functioning on the bile ducts causes impaired secretion of the biliary epithelium leading to increased viscosity, reduced bile flow, biliary obstruction and secondary mucoid impaction. Hyperviscous bile results in cell membrane injury, peribiliary inflammation and focal biliary cirrhosis [57, 58]. This can rarely progress to diffuse liver involvement and multilobular cirrhosis, the final stage of CFLD.

Hepatobiliary manifestations include hepatic steatosis, focal biliary cirrhosis, multilocular cirrhosis, portal hypertension and associated complications. CFLD is also characterized by biliary complications including cholelithiasis, micro gallbladder and sclerosing cholangitis.

Hepatic steatosis

Steatosis is the most common hepatic manifestation with a prevalence of 23–67% [59]. Like the general population, patients are often asymptomatic but may have intermittently deranged liver function tests. Hepatic steatosis has a variety of imaging appearances that can be diffuse or focal.

On US, steatosis is characterized as increased echogenicity and beam attenuation. Synchronous assessment of renal cortex echogenicity can be used as a marker of steatosis, the renal cortex appearing hypoechoic compared to the liver parenchyma. The resolution of vessel walls is typically reduced. On unenhanced CT, liver attenuation is > 10HU less than the spleen or absolute attenuation < 40 HU (Fig. 15). On MRI the liver is hyperintense on T1 and results in signal drop out on phase imaging. Diffuse steatosis can have a multilobulated pseudo mass appearance [60] (Fig. 16).

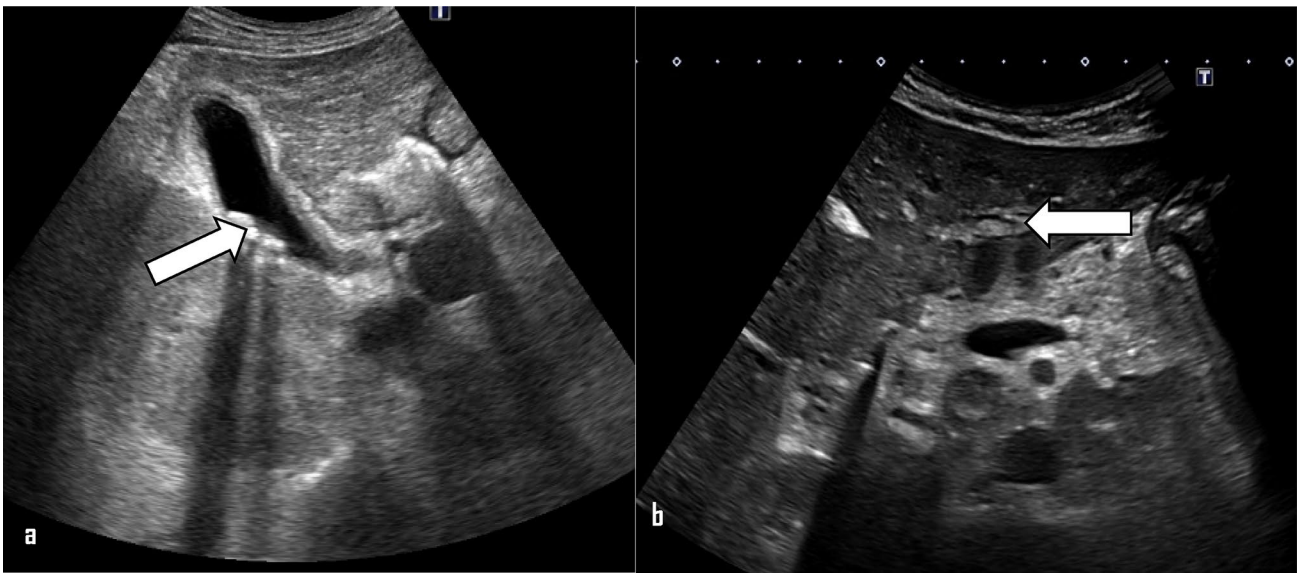

Fig. 18 US of a 31-year-old male showing gallbladder **(a)** and intraductal calculi **(b)**

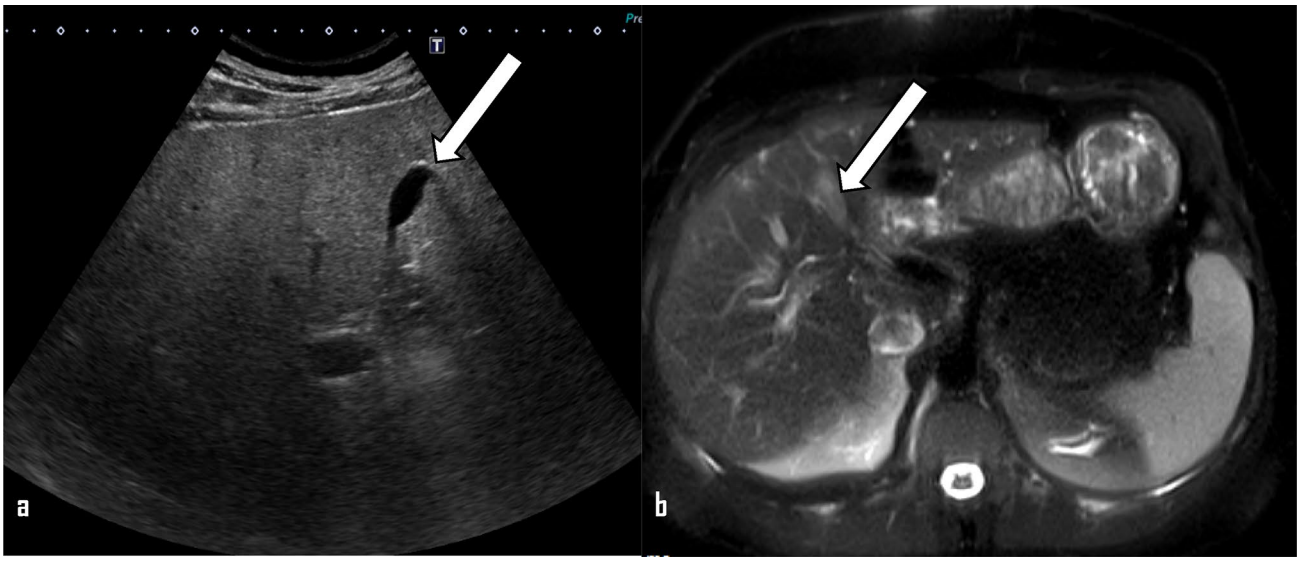

Fig. 19 US **(a)** and axial MRI T2W with fat saturation **(b)** of a 33-year-old showing a microgallbladder

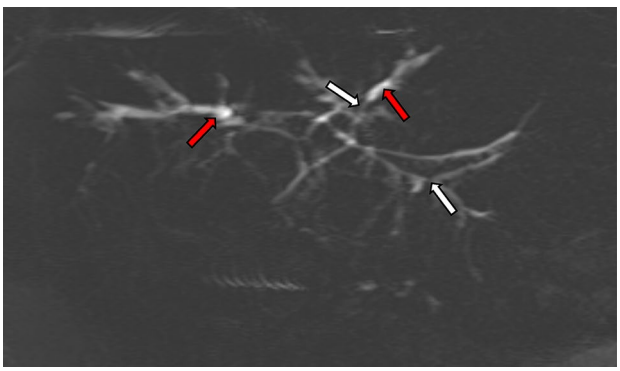

Fig. 20 T2W MRCP of a 39-year-old male showing multifocal stricturing (white arrow) and ductal dilation (red arrow) in keeping with CF related cholangitis

Focal biliary cirrhosis

Focal biliary cirrhosis is a result of chronic bile obstruction leading to periportal fibrosis. It is a characteristic lesion in patients with CF. Progressive periportal fibrosis can lead to multilobular cirrhosis and portal hypertension although this is rare. Focal biliary cirrhosis is predominantly a histological diagnosis with a reported incidence of 25%-72% of adult patients at autopsy [57]. On US, focal biliary cirrhosis is characterized by hyperechoic periportal thickening measuring greater than 2 mm (Fig. 17). On MRI, focal biliary cirrhosis is characterized by periportal high T1 signal [56].

Biliary tract disease

The biliary system can be involved in patients with CF but patients are often asymptomatic.

Cholelithiasis is common and can result from increased bile acid secretion in the setting of pancreatic insufficient which results in stone formation (Fig. 18). Cholelithiasis occurs in 12–24% of patients with CF [34]. Intrahepatic duct calculi have also been reported but are less common. Black pigmented stones are more commonly found in the CF population with cholesterol stones more prevalent in the general population. It was originally considered that cholesterol stones would be more prevalent in the CF population as fecal loss of bile acids secondary to pancreatic insufficiency would increase lithogenic bile and subsequent cholesterol stone formation. Black pigmented stones are believed to result from abnormal bile acidification due to the absence of the CFTR gene in the biliary epithelium. Gallbladder hypokinesia and biliary strictures may also contribute to stone formation [61].

Micro gallbladder is reported in 5–45% of CF patients (Fig. 19). This arises secondary to inspissated biliary secretions causing mucosal hyperplasia in bile ducts. As a result, there is increased sludge in the biliary tract, atresia and stenosis of the cystic ducts with subsequent atrophy of the gallbladder [33, 57].

CF cholangiopathy ranges from minor duct tapering to beading or stricture formation (Fig. 20). The pattern and the cholangiographic appearance of the strictures are similar to primary sclerosis cholangitis. Bile duct abnormalities have been reported in many CF patients both with and without clinically apparent liver disease [62].

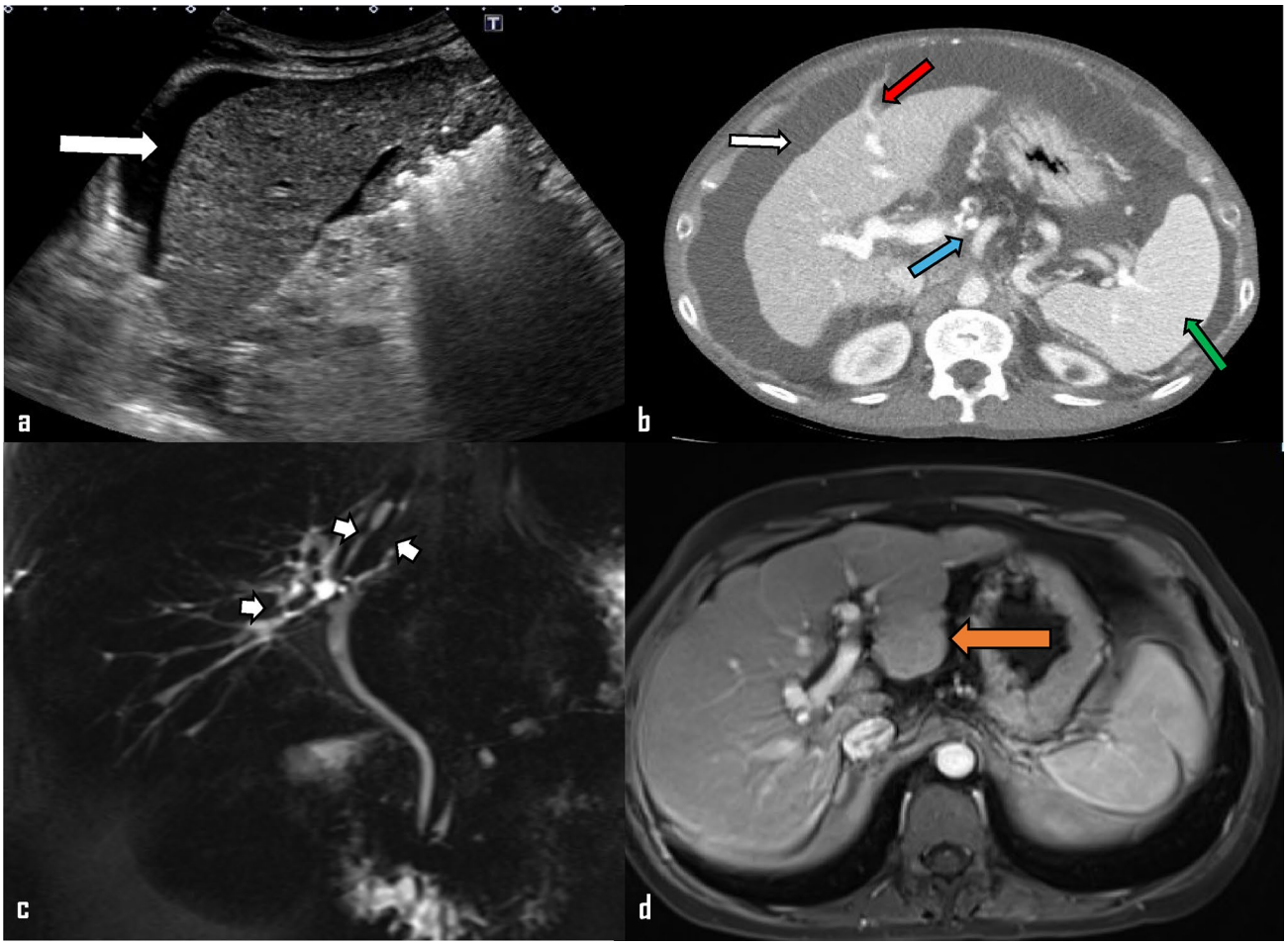

Fig. 21 US **(a)** and axial post contrast CT **(b)** of 36-year-old male with features of liver cirrhosis and portal hypertension. US shows a heterogenous echotexture, atrophy of the right lobe of liver and ascites (white arrow). CT confirms cirrhotic liver morphology and features of portal hypertension including ascites (white arrow), recanalization of umbilical vein (red arrow), varices (blue arrow) and splenomegaly (green arrow). MRI T2W MRCP **(c)** and post contrast enhanced T1 **(d)** of a 21-year-old female showing multifocal stricturing (white arrowheads) in keeping with CF related cholangitis and multilobular cirrhosis (orange arrow)

Multilobular cirrhosis

Multilobular cirrhosis in adult patients is rare and is typically encountered in pediatric patients with an estimated prevalence of 5.6% [57]. Improving life expectancy in CF patients means the number of cases in CF patients is expected to rise. Chronic CF liver disease can lead to liver fibrosis, and if left untreated, can progress to cirrhosis. Portal hypertension can eventually result from cirrhosis and is reported in 1%-8% of CF patients [63].

Clinically, multilobular cirrhosis is associated with a hard nodular liver that may or may not be enlarged. Complications such as splenomegaly, ascites and varices can occur secondary to portal hypertension. Portal hypertension may predate the onset of cirrhosis with some patients presenting with non-cirrhotic portal hypertension [57]. On imaging, the liver demonstrates an irregular liver edge and coarse heterogeneous parenchyma. Complications of portal hypertension are readily identifiable on US, CT and MRI (Fig. 21).

Although liver biopsy has been the reference standard for detecting liver fibrosis, many factors limit the clinical use of this procedure including potential complications, sampling error from small biopsy specimens or fibrosis heterogeneity. Noninvasive techniques for assessment for liver fibrosis have been developed including elastography. Elastography is an imaging technique that evaluates the mechanical properties of tissue. US or MRI are typically coupled with a device that generates shear waves. The shear wave velocity is then calculated, providing a direct correlation with the stiffness of the liver tissue. Compared to US, MRI elastography samples larger areas of the liver and is typically performed in conjunction with fat and iron quantification as well as a diagnostic MRI, resulting in a more comprehensive liver examination [64].

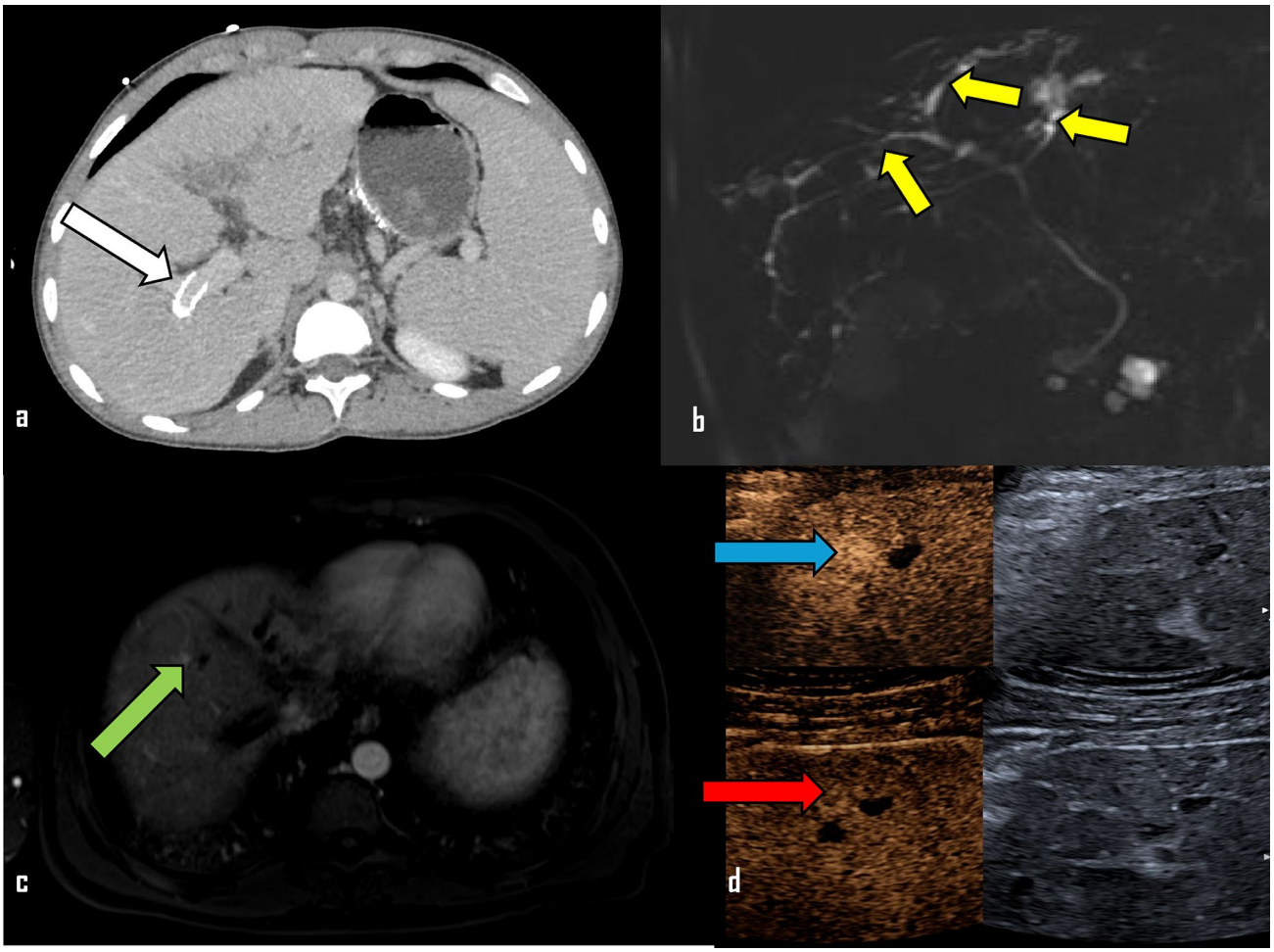

Fig. 22 Post contrast enhanced CT **(a)** 30-year-old male with history of lung transplant showing liver cirrhosis and features of portal hypertension including transjugular intrahepatic portosystemic shunt (white arrow). T2W MRCP **(b)** shows ductal irregularity and strictures consistent with CF related cholangiopathy (yellow arrow). Arterial phase MRI **(c)** showed an arterially enhancing lesion (green arrow) without venous washout (not shown). Subsequent contrast enhanced US **(d)** showed early enhancement (blue arrow) and non-peripheral rim washout (red arrow). Biopsy confirmed HCC

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and is strongly associated with cirrhosis of any etiology. As a result, patients with CF are at risk of developing HCC although this is rare and typically confined to case reports [65–68]. Biannual surveillance is recommended in all cirrhotic CFLD patients [33, 69].

On US, HCC typically appears hypoechoic compared to adjacent normal liver. Larger lesions can be heterogonous due to a combination of fibrosis, fat or necrosis. Diffuse HCC can be difficult to separate from background liver cirrhosis. On contrast enhanced US, HCC typically demonstrates arterial hypervascularity and "washout" (decreased echogenicity relative to background liver) [70].

CT and MRI findings can vary (Fig. 22 and Fig. 23). Typically, HCC enhances avidly in the arterial phase, washes out rapidly, becoming hypoattenuating to the rest of the liver in the venous phase compared. On T2 sequences, most HCC show mild–moderate hyperintensity. T1 signal can vary depending on content of the lesion including the presence of fat, glycogen, hemorrhage or high protein content [70, 71].

Rarely, benign lesions such as focal nodular hyperplasia and dysplastic nodules can simulate malignancy in cirrhotic patients (Fig. 24). The Liver Imaging Reporting and Data system was developed to standardize reporting and diagnoses of HCC. HCC is now typically diagnosed and treated on the basis of imaging without histopathological confirmation [72].

Post transplant manifestations

Lung transplantation is an important management strategy for end stage lung disease in patients with CF resulting in

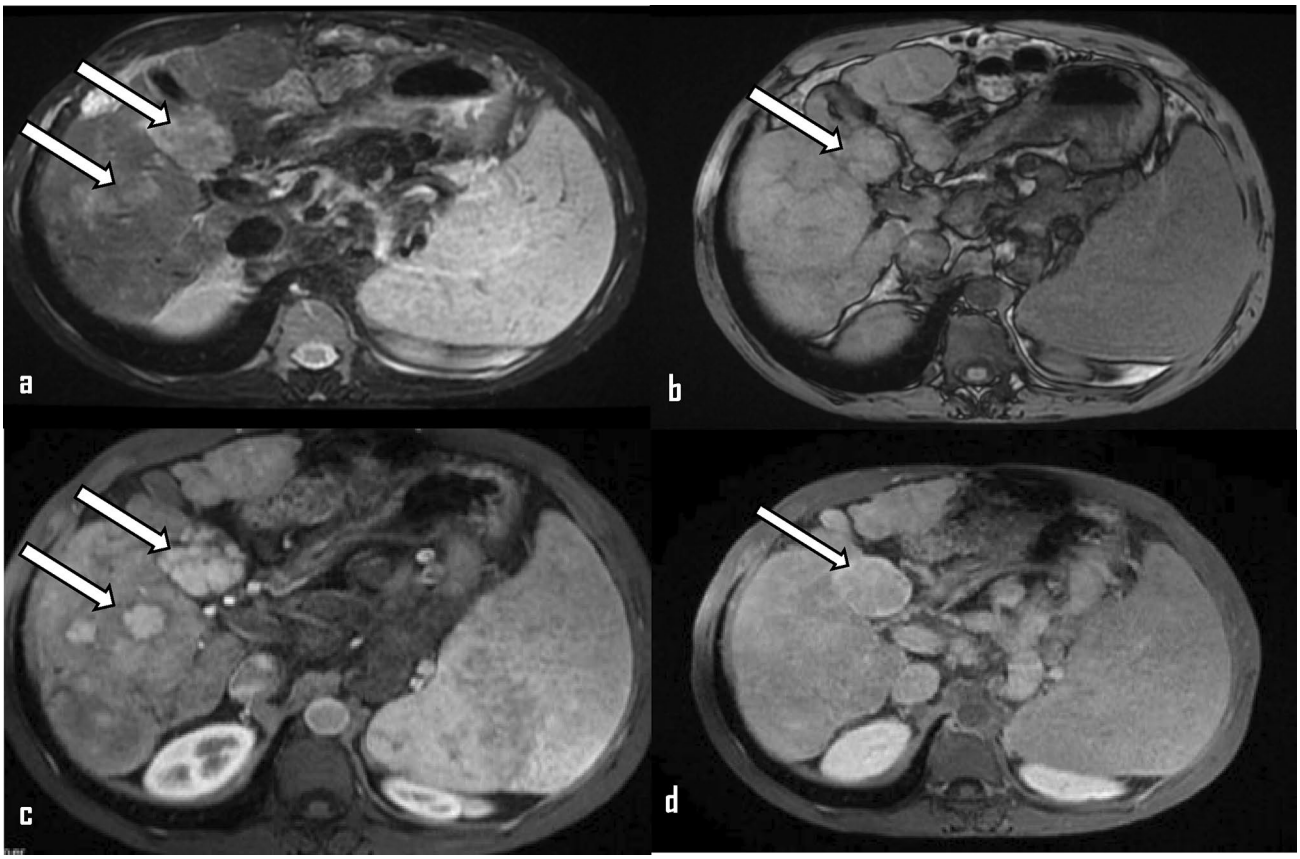

Fig. 23 Axial MRI of 25-year-old male with multilobular cirrhosis and multifocal lesions. The lesions return mild hyperintense T2 signal **(a),** isointense/mildy hyperintense T1 signal **(b)**, demonstrates arterial enhancement **(c)** and washout on venous phase **(d)**. Biopsy confirmed multifocal HCC

improved outcomes and quality of life [73]. Between 1995 and 2015, 7419 lung transplants were performed for CF worldwide, representing 16% of all lung transplants in that period [74].

Transplant recipients have significantly higher rates for developing cancer than the general population [75]. In lung transplant recipients, cancer represented the 2nd most common cause of death in recipients accounting for 17.3% of deaths in patients 5 to 10 years from transplant and 17.9% of deaths in those who were 10 years after the procedure [76]. Post-transplant chronic immunosuppressive therapy, impairment of anti-tumor immune surveillance and anti-viral activity is believed to play a central role in cancer development [77].

Post-Transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) is a group of lymphoid disorders that range from being lymphoid hyperplasia to aggressive poorly differentiated lymphoma, presenting as focal or disseminated disease. It is one of the most common cancers seen in organ transplant recipients with lung transplants reported at a particularly high risk with an incidence of approximately 5%. This is postulated to be related to higher levels of immunosuppression in thoracic organ transplantation compared to recipients of other solid organs [78].

In most cases, PTLD is thought to result from T Cell suppression in patients with latent Epstein Barr Virus (EBV) infection [79]. PTLD has a bimodal distribution with a peak in the first year of transplantation with a later peak 4–5 years after transplantation [80, 81]. In general,

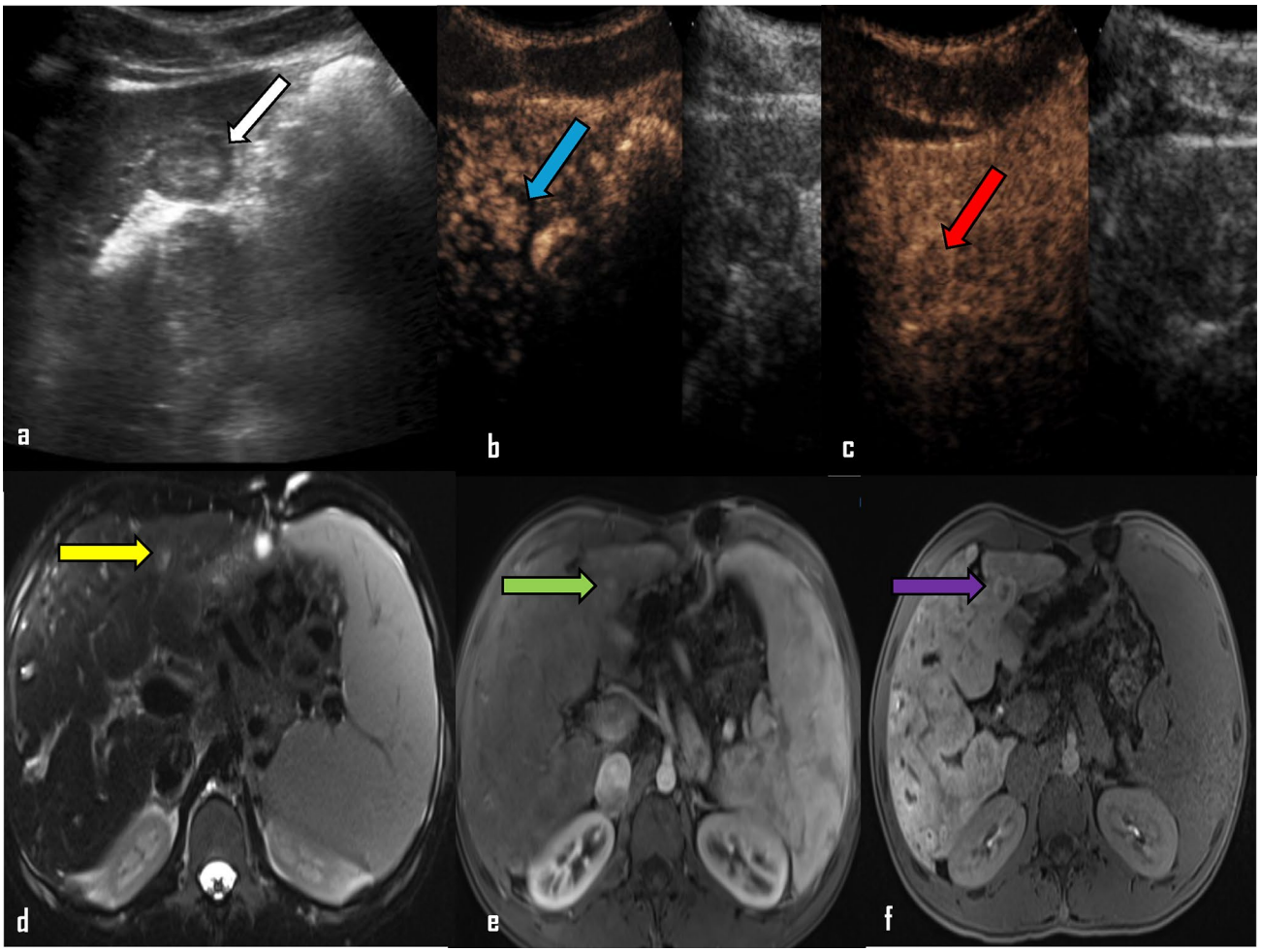

Fig. 24 23-year-old male with CFLD. US **(a)** shows a 2 cm hyperechoic lesion with peripheral hypoechoic halo segment 3 of the liver. CEUS showed arterial hypervascularity **(b)** and late central washout **(c)**. On MRI, this lesion demonstrates central T2 hyperintensity **(d)**, mild arterial enhancement **(e)** with retention on the 20-min delay hepatobiliary phase **(f).** Biopsy confirmed a FNH like nodule

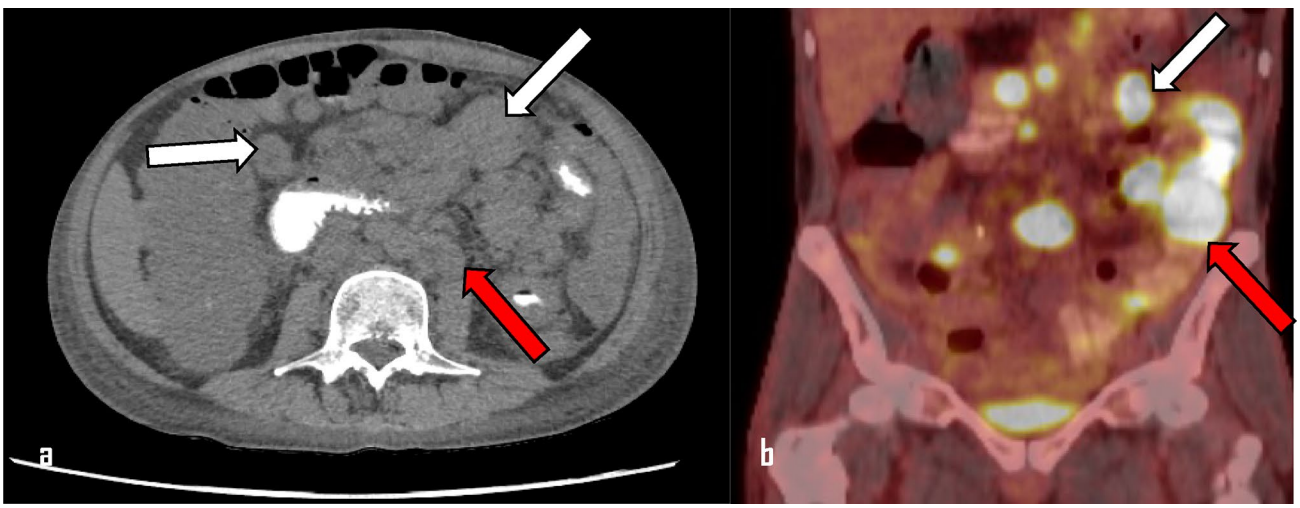

Fig. 25 40-year-old female with a history of lung transplant and multifocal nodal PTLD. Unenhanced axial CT **(a)** demonstrating multifocal enlarged abdominal (white arrow) and retroperitoneal lymph nodes (red arrow) with correlating tracer uptake on PET CT **(b)**

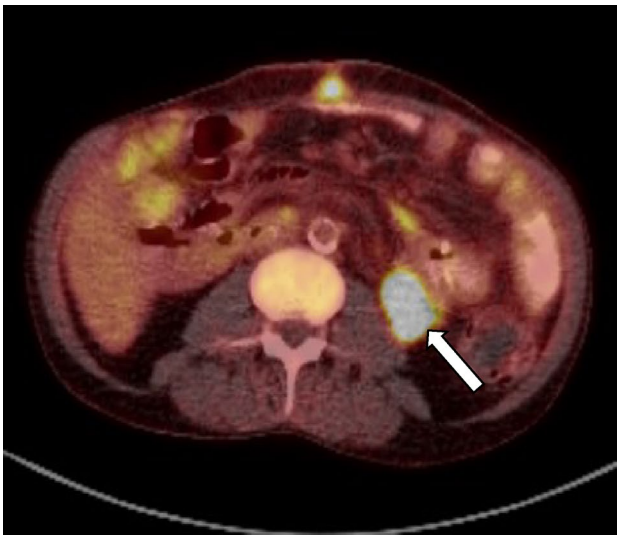

Fig. 26 56-year-old female with a history of lung transplant and isolated retroperitoneal nodal PTLD demonstrating tracer uptake on PET

the most common locations of PTLD involve lymph nodes, GI tract, CNS and liver [82, 83].

Nodal PTLD

Clinically, patients can be asymptomatic or present with nonspecific symptoms such as fevers and night sweats. Nodal PTLD may appear as multifocal lymphadenopathy (Fig. 25), isolated lymphadenopathy occurs in a minor number of cases (Fig. 26). The retroperitoneum is the most common location in the abdomen. On CT, lymph nodes are typically enlarged lymph (ranging from 2-6 cm), homogenously hypoenhancing and demonstrate loss of fatty hilum [84]. On PET, there is typically uptake of tracer with a median SUV 8.2–17.4 [85, 86].

Gastrointestinal PTLD

Clinically, symptoms are often vague and include abdominal pian. As with non-transplanted related lymphomas, mechanical obstruction from the tumor involving the GI tract is uncommon. A variety of gastrointestinal PTLD appearances have been described, often similar in appearance to lymphoma (Fig. 27). Typical gastrointestinal PTLD demonstrates circumferential mural thickening and aneurysmal dilatation. A discrete eccentric mass with or without ulceration or luminal narrowing is also described. On MRI, lesions are solid and demonstrate low T1/T2 signal intensity. Tumors related to PTLD are also hypoenhancing on CT and MRI. On PET, there is typically increased FDG uptake [87].

Hepatobiliary PTLD

Liver involvement can also have a varied appearance including discrete nodules or diffuse infiltrative disease. Discrete lesions are well circumscribed solitary masses or multiple scattered lesions through the liver (Fig. 28). PTLD nodules tend to have low signal intensity on both T1 and T2 imaging without significant contrast enhancement. In diffusely infiltrating disease, lesions are poorly marginated and appear as low-attenuation regions against a background of enhancing parenchyma. [87].

Ebstein Barr Virus associated smooth muscle tumor (EBV-SMT)

EBV-SMT is a rare oncology entity and typically reported in case reports or case series (Fig. 29 and Fig. 30). EBV is commonly associated with other malignancies including nasopharyngeal carcinomas and lymphomas. In few cases, it can trigger smooth muscle cell proliferation resulting in smooth muscle tumors.

To date, three types of (EBV-SMT) have been reported: 1) Post-transplant associated smooth muscle tumors 2) Human immunodeficiency virus (HIV) associated smooth muscle tumors 3) Congenital immunodeficiency associated smooth muscle tumors [88]. EBV-SMTs can arise in any organ, most commonly in the liver, lungs, central nervous system and gastrointestinal tract [89].

Post Transplant-SMT can be confused with PTLD as both result from the same virus and occur in immunocompromised patients. Clinically, EBV-SMT behaves with variable severity independent of their histological grade. Radiological findings cannot be used to separate the two entities as no characteristic imaging features have been reported. Instead, histopathology and immunochemistry are used to confirm diagnosis [90].

Liver transplantation

Currently, there is no available treatment that has proven to be efficacious or delays the progression of cystic fibrosis-associated liver disease and liver transplantation may be required in patients with advanced liver disease. Liver transplantation may be the ultimate treatment in patients with end-stage liver disease resulting in improved patient survival. Liver transplant is recommended in patients with CFLD and progressive liver failure, worsening jaundice or declining quality of life. Combined lung and liver transplant (CLLT) is considered for patients with advanced pulmonary and liver disease. Cystic fibrosis remains the most common indication for CLLT [91].

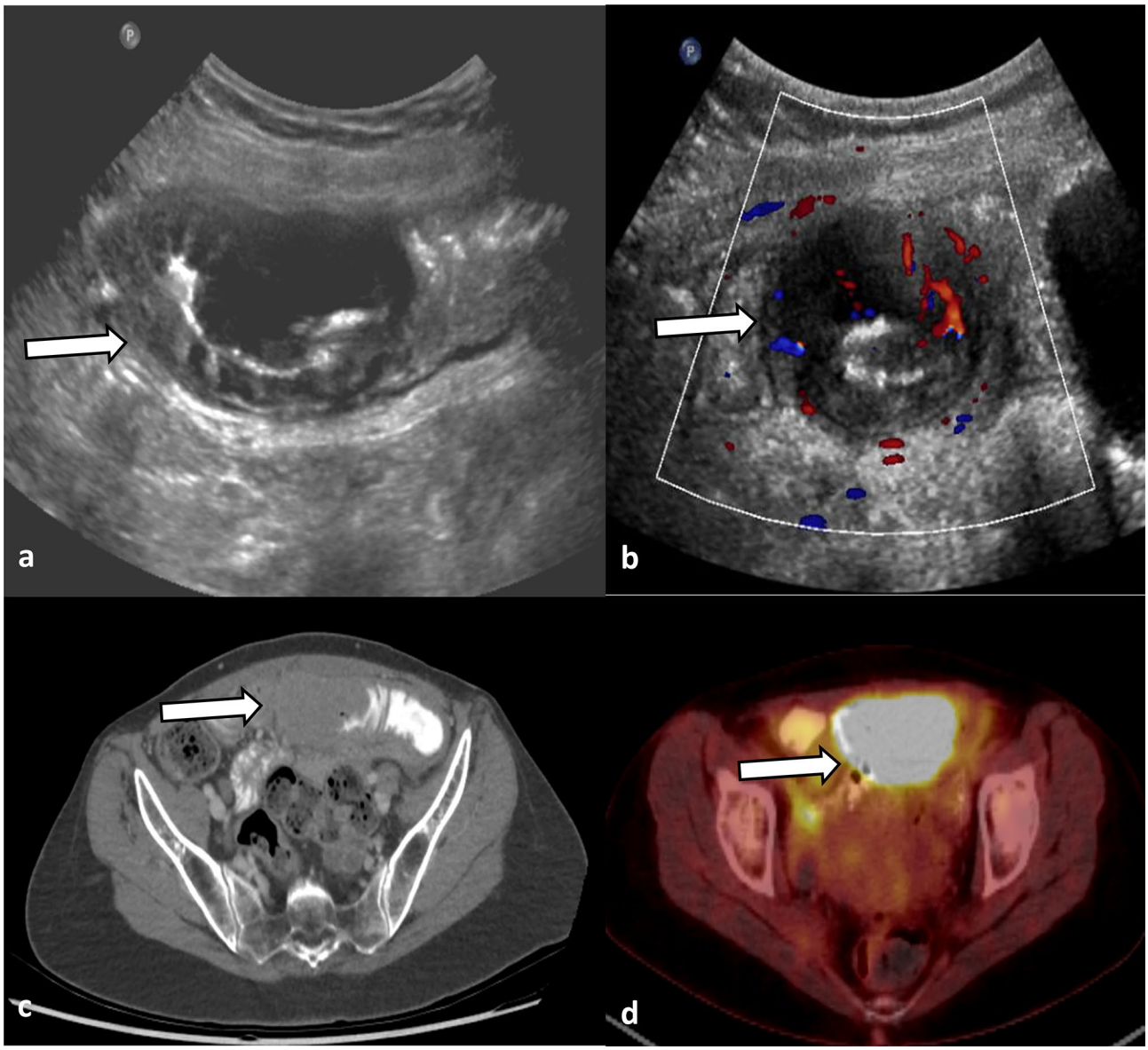

Fig. 27 34-year-old female with a history of lung transplant presenting with left lower quadrant pain. US **(a & b)** showing circumferential thickening of the proximal ileum, confirmed on contrast enhanced CT **(c)**. Correlating uptake on PET CT **(d)** is consistent with small bowel PTLD

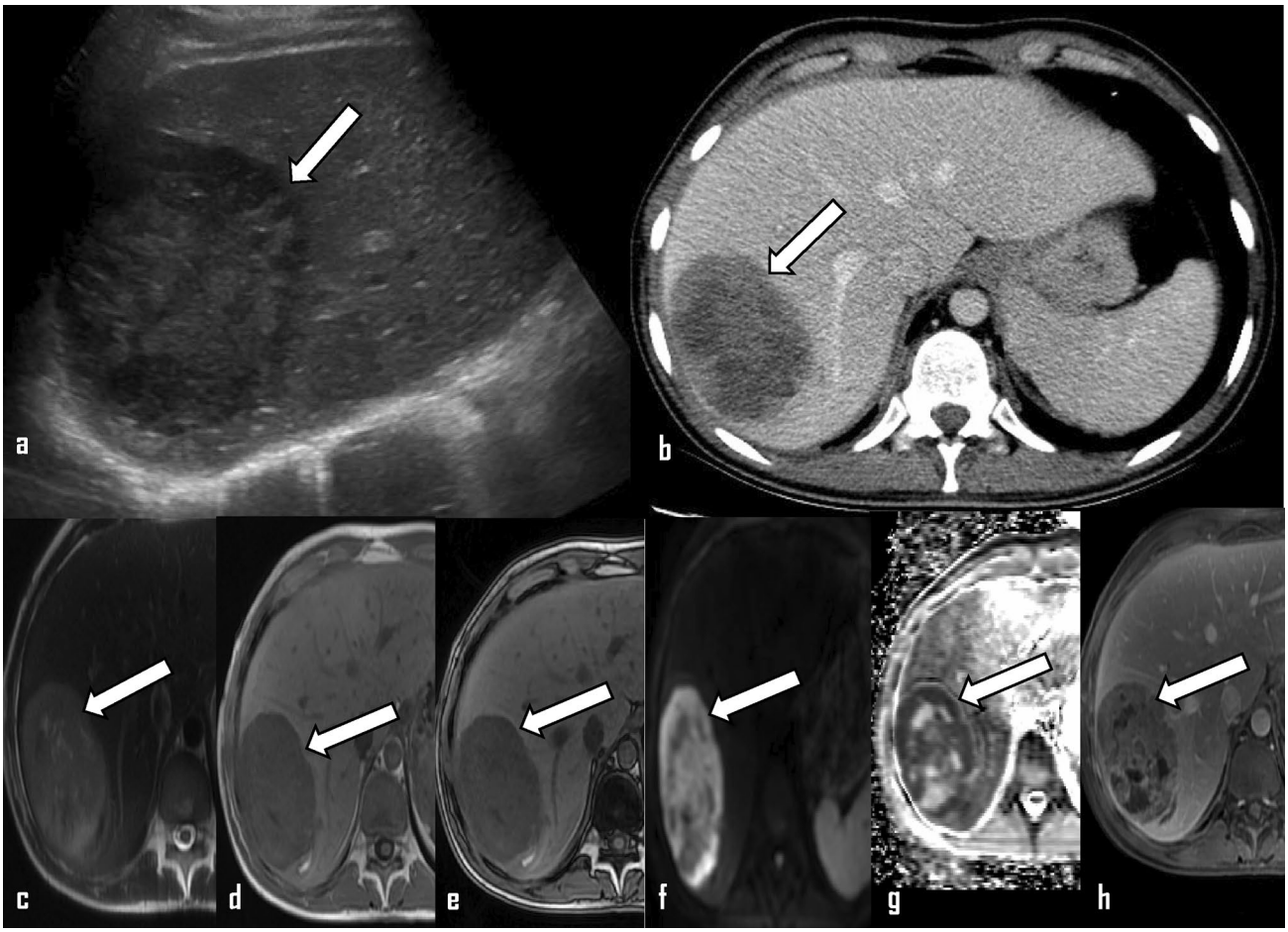

Fig. 28 26-year-old female with history of lung transplant. US **(a)** and contrasted enhanced axial CT **(b)** shows a heterogenous lesion in segment 7 of the liver. On MRI **(c–h)** the lesion demonstrates heterogenous mild hyperintense T2 signal **(c)** and hypointense T1 signal **(d).** No loss of signal was demonstrated on opposed phase to suggest intrinsic fat **(e)** or diffusion restriction **(f & g).** Following intravenous contrast, the lesion showed heterogenous enhancement **(h).** Biopsy confirmed PTLD and the patient was treated with reduction of immunosuppression

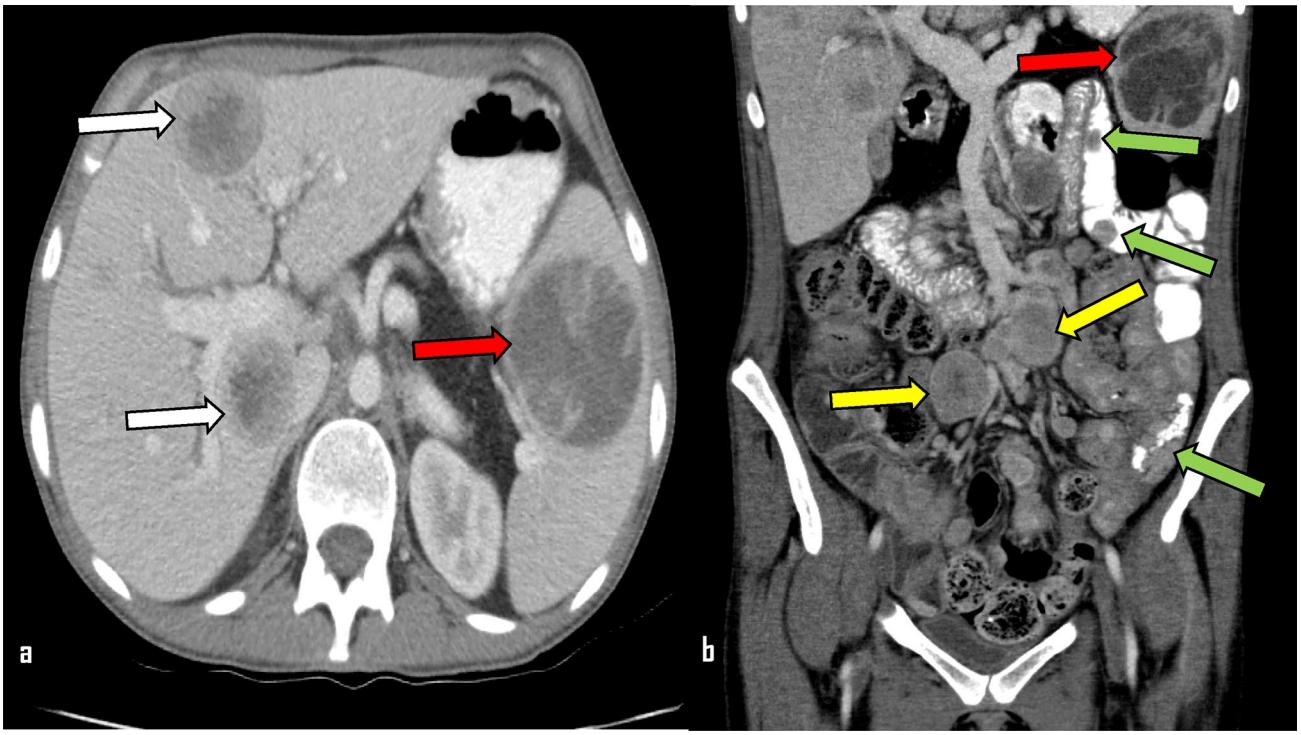

Fig. 29 The patient (described in Fig. 28) represented 3 years later for routine follow up CT. Axial **(a)** and coronal **(b)** contrast enhanced CT with new multifocal liver (white arrow), splenic (red arrow), mesenteric (yellow arrow) and small bowel (green arrow) polypoid lesions. Biopsy confirmed multifocal EBV smooth muscle cell tumors

Depending on the type of donor, there are two types of liver transplant including orthotopic liver transplantation, a whole lover transplant from a deceased donor or a living donor liver transplantation, where a portion of the liver (right or left lobe) is donated form a live donor. Conventional technique anastomosis between the donor and recipient includes a hepatic artery, portal vein, inferior vena cava and biliary anastomosis. It is important that radiologists are aware of common anastomotic techniques and expected postoperative imaging findings.

Conclusion

Advances in treatment have resulted in improved survival and an increasing adult population with cystic fibrosis. As survival improves, abdominal complications are becoming an increasingly important cause of morbidity and mortality in adult patients with CF. An awareness of their expected clinical presentation and imaging findings are essential for a timely diagnosis and appropriate management.

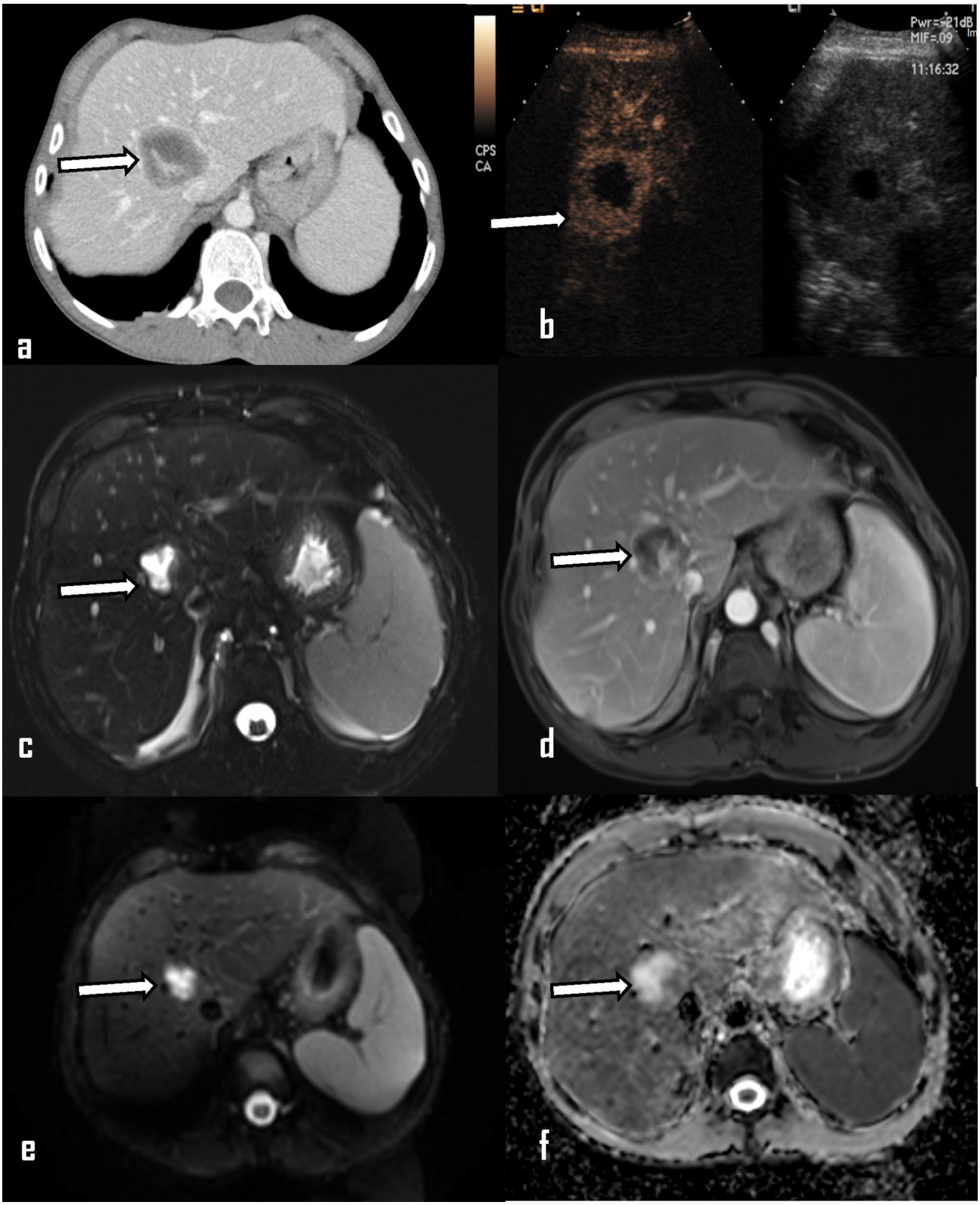

Fig. 30 24-year-old female with history of lung transplant, presenting with incidental liver lesion. Post contrast enhanced CT **(a)** and CEUS **(b)** showed a heterogeneously enhancing lesion. MRI **(c–f)** showed a solitary lesion which returns mildly hyperintense T2 signal **(c),** heterogeneous enhancement **(d)** with peripheral diffusion restriction **(e & f)**. Biopsy confirmed an EBV associated smooth muscle tumor

Author contribution A. wrote the main manuscript C. provided the concept and supervised the manuscript writing A. C. edited the manuscript B.D provided cases and input into the figures A.C. reviewed and edited the figures and cases suitable for publication.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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