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Quarterly Medical Review - Sickle cell disease

The liver in sickle cell disease

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ABSTRACT

Liver involvement in SCD patients is frequent but often misdiagnosed or underestimated, except in case of advanced liver diseases. Because of so far poorly recognized forms of chronic SCD-related vascular injury that can silently evolved towards end stages or facilitate ACLF, any persisting liver function tests abnormalities should be carefully investigated, following the above proposed algorithm. Work up and management must be considered multidisciplinary in relationship with a Hepatologist. Early SCD hepatopathy should prompt revision of SCD management to prevent further liver injury and decompensation, discussing transfusion exchanges and hydro urea when not yet initiated, and control for any cofactor of liver injury. The role of HSCT in early SCD hepatopathies also deserves evaluation. In advanced SCD hepatopathies, liver transplantation, which has been rarely performed so far, is the only therapeutic option associated with improved survival. It should definitely be discussed- either electively in case of decompensation in SCD cirrhosis or jaundice/recurrent cholangitis in cholestatic diseases, with excellent outcome, - or emergently in case of ALF or ACLF with more mitigate results.
To improve knowledge and management of SCD liver diseases, creation of national and international registries, as well as longitudinal observational cohorts are encouraged.

1. Introduction

Liver involvement in sickle cell disease (SCD) is frequent but often asymptomatic. In patients presenting with vaso-occlusive crisis, elevation of ALT and/or conjugated bilirubin > 17 μmol/L happen in 10 to 40 % of cases [1,2]. However, the spectrum of liver injury in SCD is broad [3,4], ranging from minimal hepatocytes injury to severe liver failure associated with multiple organ failure on the one hand, and from cholelithiasis to sclerosing cholangitis on the other hand. In addition, advanced liver injury is involved in a substantial proportion of deaths in SCD patients, ranging from 3 to 11 % [5–7], indicating that liver, when severely injured, significantly impacts SCD outcome.

In general, SCD doctors, especially pediatricians are more familiar with SCD-related cholelithiasis than with SCD hepatopathy or other rarer liver manifestations of SCD. This concise review will therefore focus on SCD hepatopathies, except for gallstone-related injury. It will also consider some emerging issues as those associated with auto-immune liver diseases, liver transplantation, and hematopoietic

Abbreviations: ACLF, acute-on-chronic-liver failure; ALF, acute liver failure; BET, Blood exchange transfusions; HAV, hepatitis A virus; HBV, hepatitis B virus; HCST, hematopoietic stem cells transplantation; HCV, hepatitis C virus; HEV, hepatitis E virus; FNH, Focal nodular hyperplasia; GVHD, graft versus host disease; MRI, magnetic resonance imaging; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SCD, sickle cell disease; SOS, sinusoidal obstruction syndrome; UDCA, ursodeoxycholic acid; VOC, vaso-occlusive crisis

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stem cells transplantation (HCST). This review will be outlined as follows: SCD-hepatopathy, SCD-cholangiopathy, emerging issues. A section summarizing diagnosis and management of SCD liver diseases will conclude the manuscript.

2. SCD hepatopathy

Among the pleomorphic manifestations of SCD, SCD hepatopathy although well described [1,2,4,7], can be considered as an orphan disease because early forms are often neglected, and severe forms are rare and not well known. In a recent study of 247 SCD patients, advanced liver fibrosis and significant portal hypertension were found in 4.5 and 5 %, respectively [8]. Severe forms of SCD hepatopathy are exceedingly rare, affecting around <2 % of the 3000 SCD patients routinely followed at Henri Mondor Hospital SCD referral center. In this review, the seminal description of liver injury in SCD as reported by Banerjee et al. [4] will be balanced by the experience accumulated over 2 decades at Henri Mondor Hospital to propose a new and simpler vision of a so far poorly known organ injury. Indeed, the Henri Mondor SCD national referral center backed with a liver transplantation (LT) unit made possible to analyze in depth the pathology of SCD explanted livers, and to better understand mechanisms and natural history of SCD hepatopathies.

2.1. Pathophysiology

As shown in the left panel of Fig. 1, hepatic sinusoids are unique blood vessel-structures, 10–15 μm in diameter, of the liver microcirculation. Sinusoidal blood stream aways from the portal space to centrilobular veins in the hepatic lobules. During this short streaming, most of the important liver functions, including gas-exchanges, nutrients absorption, scavenging and detoxification as well as others, are accomplished.

The right panel of Fig. 1 shows that during liver vaso-occlusive crisis (VOC), sickling red cells accumulate in the sinusoids, leading to sinusoid dilatation and congestion. One can reasonably assume that intra-hepatic vaso-occlusion induces a specific form of sinusoidal obstruction syndrome (SOS) of various intensity. This SOS alters gas exchanges, induces hepatocytes hypoxia, impairment in the above-mentioned critical liver functions, with hepatocytes injury ranging from hepatocytes ballooning with intra canalicular cholestasis to ischemic necrosis as seen in acute, severe forms of SCD-liver hepatopathies. Also, sickling-related SOS activates macrophages as Küpffer cells, and related intra sinusoidal hemophagocytosis, triggering an inflammatory response that impaired bile secretion [9]. On the long term, it can also promote liver fibrosis of various magnitude [10,11]. Indeed, hepatic sinusoid hosts non parenchymal cells, including sinusoidal fenestrated endothelial cells but also macrophages and hepatic stellates cells (Fig 1 left panel), the latter serving as myofibroblasts during hepatic injury and repair, promoting liver fibrogenesis by producing extracellular matrix and collagens. This means that on the long term, chronic intra-hepatic sickling can result in chronic hepatopathy, which in general combines features of porto-sinuosidal disease, as sinusoidal dilatation and nodular regenerative hyperplasia, with liver fibrosis of various intensity, often heterogeneous, that mimics cardiac cirrhosis. Vascular obstruction may also cause red cell and platelet trapping, called “sequestration,” in the liver or the spleen. Eventually, ischemic injury of intra and extra-hepatic bile ducts may result from sickling in small peri-ductal vessels, resulting in SDC-related ischemic cholangiopathy.

2.2. Clinical patterns of SCD hepatopathy

2.2.1. Acute liver injury

In the seminal Banerjee et al. [4] description of severe SCD-liver injury, 3 patterns of acute injury were individualized: acute sickle hepatic crisis, hepatic sequestration crisis/reverse sequestration, and sickle cell intrahepatic cholestasis.

Acute sickle cell crisis was characterized by liver pain, jaundice and tender hepatomegaly with mild increase in ASL/ALT levels usually below 300–500 IU/L and total bilirubin < 15 mg/dL. Hepatic sequestration crisis clinically mimicked hepatic crisis but was associated with a marked decrease in the hematocrit and milder liver tests abnormalities; sickle cell intra hepatic cholestasis was described as a

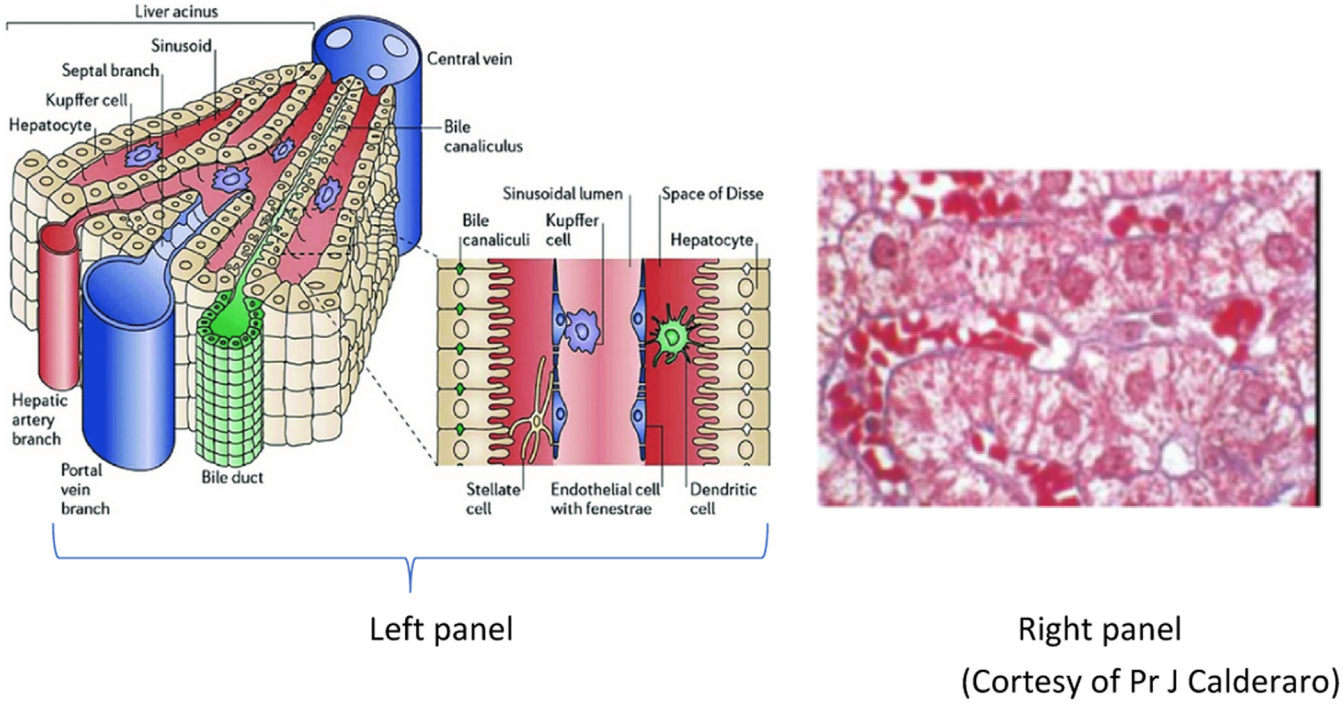

Fig. 1. Anatomy of the hepatic sinusoid (left panel) and SCD-related intra sinusoidal sickling and vaso-occlusion (right panel).

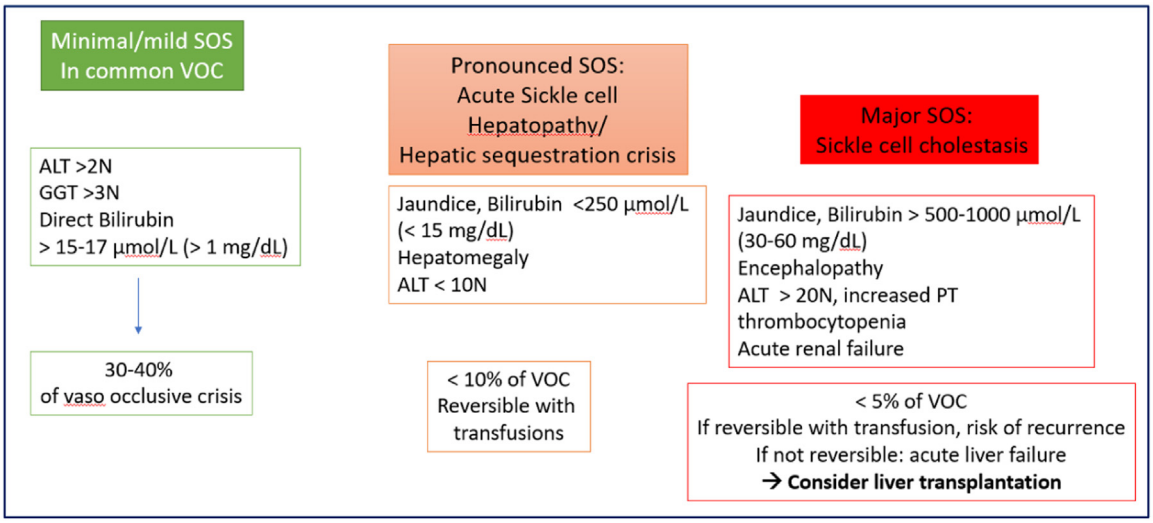

Fig. 2. Acute liver injury in SCD: a sinusoidal obstruction syndrome (SOS) of increasing severity.ALT: alanine aminotransferase; GGT; gamma glutamyl transpeptidase, PT: prothrombin time; SOS: sinusoidal obstruction syndrome; VOC: vaso-occlusive crisis.

disastrous, often fatal condition initially presenting as an acute sickle cell crisis but rapidly evolving toward acute liver failure with marked increase in AST/ALT > 3000 IU/L, associated elevation of alkalin phosphatases and strikingly high bilirubin up to 270 mg/dL, accompanied by increased prothrombin time, bleeding, encephalopathy and renal impairment. Interestingly, pathological descriptions of the liver were pretty similar across these 3 conditions, with widespread sickling in sinusoids, hepatocytes ballooning and intra canalicular cholestasis. We therefore propose to consider these entities as the consequence of a SCD-induced sinusoidal obstruction syndrome (SOS) of increasing severity. The sinusoidal obstruction syndrome expression may range from mild and transient increase in transaminases, in the setting of a VOC, to a reversible condition after blood exchange transfusions (BET), and even to an irreversible condition resisting to BET because of massive sequestration associated with acute liver failure (ALF) and multiple organ failures (MOF). Fig. 2 shows the correspondences between the classical patterns of SCD liver injury and the simplified Henri Mondor Hospital classification.

Of note, mild elevation of ALT > 2 N and direct bilirubin > 1 mg/dL are observed in 30–40 % of common vaso-occlusive crisis(1) reflecting minimal intrahepatic sickling and a minor form of SOS. In this scenario, significance of aminotransferases elevation should be interpreted with caution, because of concomitant increase in AST and bilirubin levels from red cell origin, as usually reflected by an AST: ALT ratio > 1 [12]; liver involvement can be reasonably considered when ALT > 2–3 ULN, with AST/ALT ratio < 1, and direct bilirubin > 1 mg/dL (17 μmol/L) (P Bartolucci, C Duvoux, expert opinion).

The usual work up includes physical examination, looking for a tense hepatomegaly and hepatic encephalopathy, and in case of severe liver dysfunction, emergency Doppler ultrasound examination of the liver, CT scan and ideally MRI, to rule out portal vein and hepatic vein thrombosis, cholelithiasis and to look for silent pre-existing chronic liver injury. In areas of high incidence of Hepatitis B, A and E, acute viral hepatitis may also be responsible for severe acute liver injury in SCD patients and can also promote VOC [13]. We therefore recommend to systematically test SCD patients presenting with acute liver dysfunction for HAV, HEV, HBV, and in HBs antigen positive patients, for HDV. Also, in our experience, associated type 1 auto immune hepatitis mimicking VOC has been occasionally observed, which calls for testing ANA and SMA in this setting [14]

Importantly, since percutaneous liver biopsy in acute liver VOC has been reported as associated with increased risks of bleeding and mortality [15], it should be contra indicated in this setting. In case of uncertain diagnosis requiring pathological confirmation, transjugular liver biopsy can be considered. Also, identification of innovative MRI sequences to better characterized intrahepatic VOCs are eagerly waited to make non invasive diagnosis easier. With this respect, ongoing developments are carried out using multi parametric liver MRI including R2* and BOLD measurements for assessment of oxygen level in acute liver injury [16].

In summary, acute liver injury in SCD ranges from asymptomatic minimal elevation of ALT and direct bilirubin to severe but reversible liver dysfunction and to dramatic, irreversible, acute liver failure (ALF) leading to death, unless liver transplantation is considered. However, severe liver VOC occur quite rarely and the mechanism specifically triggering severe liver VOC remains unknown.

Fig. 3 shows the explanted liver of a SCD patient transplanted for ALF due to massive sequestration of sickling cells in the liver, with corresponding CT scan.

2.2.2. Chronic liver injury in SCD hepatopathy

Several mechanisms can chronically injure the liver in SCD.

Explant-based studies of SCD patients transplanted for advanced chronic liver diseases [14,17] have shown that aside acute VOC, silent chronic sinusoidal vaso-occlusion can induce considerable anatomical changes in liver morphology (Fig. 4). The spectrum ranges from sinusoidal dilatation to nodular regenerative hyperplasia (NRH) favored by chronic ischemia and to a pattern of liver vascular disease very specific to SCD, mixing sinusoidal dilatation, NRH and septal fibrosis, and even pure “vascular” cirrhosis (Fig. 5). These latter patterns, which can be considered as specific forms of SCD porto-sinusoidal diseases, can be observed without any additional cause of liver injury and clearly indicate that chronic vaso-occlusion can promote fibrosis by its own in a SCD liver.

Chronic SCD-related vascular injury is frequently asymptomatic, and its actual prevalence is unknown. It should be considered in case of persisting LFT abnormalities, as a sustained increase in ALT, GGT and alkaline phosphatases > 2–3 ULN. Physical examination should systematically look for a firm hepatomegaly, a feature that patients can spontaneously mentioned. Morphological examination of the liver should be completed by systematic ultrasound /Doppler examination of the liver and cross-sectional imaging. Liver MRI is the ideal imaging technique to perform because investigating morphology of both liver parenchyma and bile ducts but also liver iron content. However, if not available, liver CT scan also brings up substantial information as shown in Fig. 4.

The risk benefit ratio of liver biopsy in investigating chronic liver SCD-related lesions should be again cautiously considered.

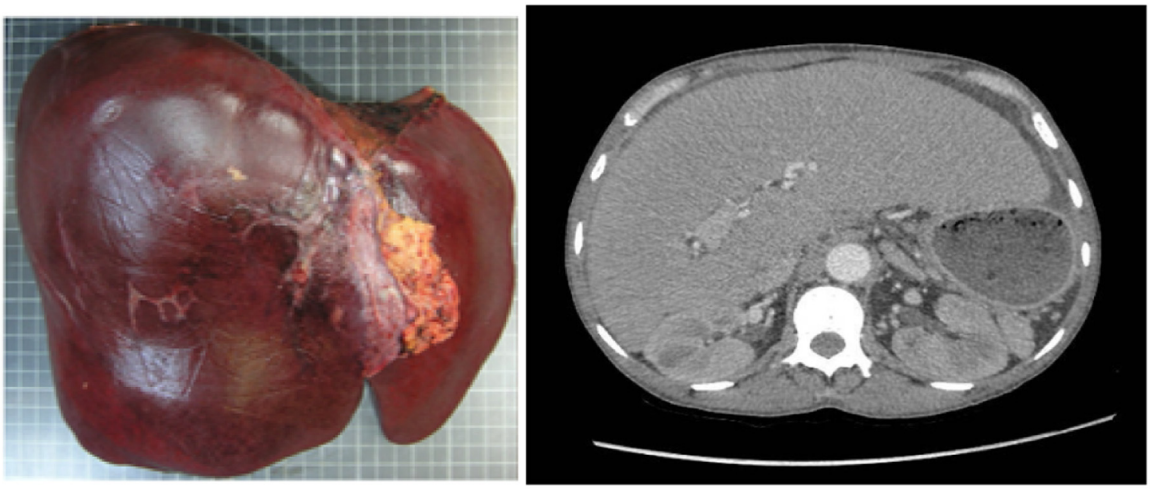

Fig. 3. Congestive explanted liver due to massive liver vaso-occlusion leading to acute liver failure (left panel), with corresponding pre LT CT scan (right panel) showing a homogeneous hepatomegaly with no major changes suggestive of chronic liver injury apart from a limited atrophy of the right lobe.The liver explant weighed 2.1 kg, against 0.8 kg on average after liver transplantation for ALF from other origin, reflecting major sequestration.

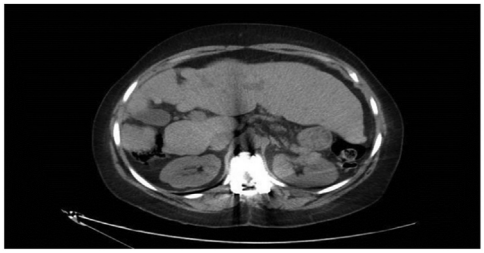

Fig. 4. Highly dysmorphic liver in a SCD patient presenting with mild elevation of liver function tests. CT scan shows a major atrophy of the right lobe with a typical pronounced hypertrophy of the left and caudate lobes.

Transcutaneous liver biopsy is contra indicated in case of acute liver VOC, when performed in close proximity of a crisis, because congestion of the liver considerably increases morbidity and mortality of the procedure [15]. However, in a stable patient with no VOC nor hemostasis impairment, confirmation and staging of liver SCD-related chronic injury with careful description of liver lesions is relevant since it can drive changes in the management of SCD, and guide the decision of hematopoietic stem cell transplantation (HSCT) at early stages. We therefore propose to consider echo-guided transcutaneous liver biopsy in stable patients with persisting LFT changes and imaging suggesting chronic liver injury at distance of liver VOC.

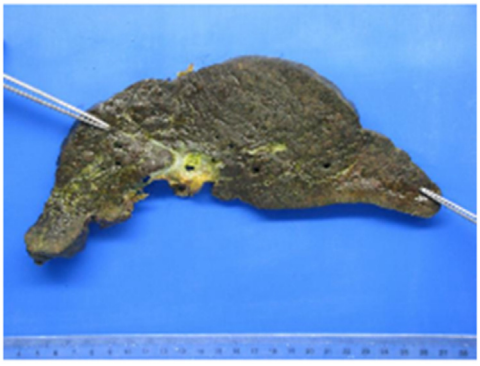

Fig. 5. shows the liver of a patient transplanted for end-stage chronic liver disease related to SCD.Histological lesions combined incomplete fibrotic septae surrounding in some area subcapsular nodules, perisinusoidal and perivivenular fibrosis, marked sinudoidal dilatation with nodular regenerative aspects in peri portal areas.

A minimal 14 day-interval post VOC has been proposed [18]. Some authors consider transfusion before liver biopsy for increased safety. Transcutaneous liver biopsy should also be contra indicated in case of bile ducts dilatation and coagulation disorders. In this last scenario, and in case of advanced dysmorphic liver suggesting cirrhosis or portal hypertension, transjugular liver biopsy with hepatic venous portal gradient (HVPG) measurement is advised, since associated with reasonable safety [18].

Work-up can be completed by noninvasive assessment of liver stiffness (Transient elastography, Fibroscan R) which is validated to evaluate liver fibrosis in a number of liver diseases [19]. Preliminary experience in SCD patients [20] have shown an encouraging positive correlation between liver stiffness and liver fibrosis as assessed histologically. In this study, the median liver stiffness values for patients with Ishak fibrosis score 0–2 vs 3–6 were 4·8 kilopascals (kPa) and 17·6 kPa, respectively. However, high liver stiffness values may not be as specific as in other liver diseases to detect advanced fibrosis because confounding factors as SCD-related liver congestion or right ventricular dysfunction/pulmonary hypertension. We therefore propose to consider transient elastography as a follow –up tool after a 1rst histological assessment of liver fibrosis performed in a stable patient at distance of a liver VOC and with normal cardiac function. Further studies are obviously needed to refine the correlation between SDC liver injury and liver stiffness.

Several additional factors can further drive chronic liver injury and fibrosis progression, notably a-superimposed HCV and/or HBV infections, b- iron overload, and c- associated auto-immune liver diseases, as type 1 auto-immune hepatitis. Sporadically, excessive alcohol consumption can be observed and cardiac dysfunction as well as SCD associated pulmonary hypertension can participate.

a- The prevalence of chronic viral hepatitis has been consistently reported higher than in the general population in SCD patients.

The prevalence of HCV infection in SCD patients varies according to countries. In France, the prevalence of HCV infection was evaluated 7.5 % in a cohort of 267 SCD patient followed in Paris area. Patients were mainly from sub-Saharan origin, and prevalence peaked at 11 % in SCD patients with the SS genotype [21]. Similar figures, with a HCV prevalence of 9 %, have been reported more recently in Ghana [22], a figure that was significantly higher than the 3 %-prevalence of HCV in general population. Surprisingly, in Mali the prevalence in SCD patients was found 1 % [23]. Similarly, the prevalence of HBV infection in SCD patients depends on the country of origin, on the

availability of a nationwide program of vaccination in newborns, having in mind that most SCD patients followed in Western Europe originate from countries with a high prevalence, > 8 %, of chronic HBs Ag carriage. As for HCV, multiples transfusions may also increase prevalence because of a residual risk associated with transfusions [23], notably in case of blood transfusions >10 packs) [24]. By contrast, prevalence of HBV infection in SCD patients have been decreasing markedly in the USA over time, and reported 0.9 % between 2004 and 2009 [25]. HBV reactivation responsible for jaundice has been occasionally reported, underlying the need for systematic screening for HBV both in case of acute or chronic liver dysfunction. However, in the series of Henri Mondor Hospital most adult patients with end-stage SCD-liver disease and HBV infection had undetectable HBV DNA on admission. Similarly, in the Arlet et al. [21] study, 65/153 patients (42.5 %) had anti-HBc anti-bodies, but only 2/65 (3 %) patients had a profile of active HBV infection.

The high prevalence of Hep C and Hep B in SCD patients affected with liver diseases deserve a systematic testing for HCV and HBV. Data are lacking about the actual impact of HBV and HCV infections on liver fibrosis in SCD patients. However in case of active viral replication, a specific oral antiviral treatment, whatever the extension of liver fibrosis or transaminases elevation, can reasonably be considered. Indeed, to ensure an optimal protection of the SCD liver, usually injured by multiple co factors, and to prevent further decompensation, we propose to consider antiviral treatment in a more liberal way than in non SCD patients (expert opinion). Data on efficacy of new direct anti HCV agents (DAA) in SCD are scarce. In a US series [26] of 10 SCD patients treated for 3 months (6 months if cirrhosis in 1 case) with sofosbuvir + ledispasvir with no ribavirin, a 90 %-sustained virological response rate was achieved with good tolerability. In a series of 27 patients with inherited blood disorders, including 25 SCD patients treated at Henri Mondor Hospital [27] with various combinations of DAA, sustained virological response was achieved in 93 %. It can therefore be expected that last generation antiviral combination as sofosbuvir and velpatasvir (S+V) for 12 weeks could achieve virological cure > 95 % as in general population. Of note, ribavirin-free DAA combinations prevent ribavirin-induced haemolytic anemia in SCD, a major achievement compared to historical IFN/ribavirin based regimen. Glecaprevir + pibrentasvir (G+P) for 8 weeks could also be considered in absence of advanced liver insufficiency [27]. However, it should be noted that elevation in indirect bilirubin > 3ULN was occasionally reported in clinical trials and was more frequent on G+P than on S+V. We therefore suggest considering sofosbuvir + velpatasvir as 1rst choice in SCD patients. Treatment should be managed according to international guidelines [28] after checking carefully for drug-to-drug interactions. Of note, ribavirin in cirrhotics, as proposed in the general population, notably genotype 3, can reasonably be avoided to increase tolerability, and a combination of sofusbuvir + velpatasvir for 24 weeks can be considered in this scenario. Similarly, treatment of chronic HBV infection should be based on 3rd generation nucleotidic analogs as entecavir or tenofovir.

As state above, superimposed acute viral hepatitis, either related to HAV HBV or HEV infection, in SCD patients with chronic SCD hepatopathy, may be deleterious, notably in pediatrics [13]. Vaccination against HAV and HBV is therefore strongly advised in SCD patients naïve from HAV and HBV.

b- Iron overload in SCD patients

Three key points should be considered: Iron overload a-promotes liver fibrosis; b- is directly related to frequency and volume of blood transfusions in SCD patients; c- uncontrolled iron overload hampers SCD outcome and survival.

Previous histological studies have shown that the liver intra hepatic content (LIC) is higher in SCD patients with liver fibrosis than in patients without fibrosis (28 vs 17 mg/g dry liver weight) [29]. Sequential liver biopsies in patients transfused without chelation also showed that significant liver fibrosis was found in 1/3 of patients with LIC values > 9 mg/g and was directly proportional to LIC [30]. When transfusions are given without chelation, portal fibrosis can develop as early as 2 years after transfusions and can lead to cirrhosis. Although the exact prevalence of iron overload-induced cirrhosis is unknown, cirrhosis was reported postmortem in around half of patients with severe liver siderosis [5]. It is therefore crucial to early detect liver iron overload to prevent its consequences. Sequential serum ferritin is a convenient tool to estimate iron overload, but it should be interpreted with caution: a- ferritin overestimates iron content when assayed after VOC; b- the correlation between serum ferritin and LIC exists up to ferritin value of 2000 ng/mL or 20 transfusions, or up to 10 mg/g dry liver weight [31] but decreases beyond these thresholds, with lower predictability beyond these values. There is therefore a strong medical need calling for sequential assessment of LIC. This can be done non-invasively by the standardized and validated MRI technique named Ferriscan [32], which has demonstrated a reproducible relationship with LIC assessed histologically. Screening for liver iron content every 1 to 2 years is recommended [33]. MRI intra hepatic iron concentrations > 200 μmol/g were proved as having a negative prognostic value. Iron chelation is therefore advised as far as iron overload is evidenced. Chelation is recommended when serum ferritin is > 1000 μmol/L, or LIC > 7 mg/g dry weight [31]. Yet, in daily practice adherence to iron chelators is relatively poor, which makes the control of iron overload difficult. Therapeutic phlebotomy is effective and should be considered if the venous access allows and Hb is greater than 8 g/dL. Prevention is therefore crucial. With this respect, in patients requiring transfusion exchanges, it has been established that mechanical exchanges were associated with reduced iron overload, compared to manual exchanges. Mechanical exchanges should be preferred, whenever possible [33–35].

c- An increasing interest has recently been drawn to auto-immune liver diseases in SCD liver patients, notably in pediatrics [36–38]. In the Jitraruch et al. study [38], 13/77 children with SCD and hepatic dysfunction were diagnosed with auto-immune liver diseases, notably type 1 auto-immune hepatitis and auto-immune sclerosing cholangitis. Two patients presented with acute liver failure. Auto-immune liver diseases occurred more frequently in females and SS phenotype. We observed a similar experience at Henri Mondor hospital in an adult population. Autoimmune liver diseases were observed in 20 % of adults with advanced SCD-related liver diseases, including type 1 autoimmune chronic hepatitis, auto-immune cholangitis (PBC) and primary sclerosing cholangitis (PSC). In 1 case, auto-immune hepatitis also presented as acute liver failure, mimicking severe VOC. Since liver auto immune diseases can benefit from a specific management, it is crucial to systematically look for specific auto antibodies at 1rst work-up, and also to test for auto-antibodies in case of LFT abnormalities persisting despite optimal management of VOC. Screening for auto antibodies including ANA, SMA, AMA, and PR3 ANCA is advised.

When facing autoantibodies with persisting unspecific LFT abnormalities, a clinical challenge is to differentiate between auto-antibodies associated with concomitant auto immune liver injury vs clinically irrelevant auto-antibodies. In this scenario, liver biopsy can be proposed to distinguish between sickling-related liver injury and auto-immune disease, having in mind that these 2 entities can also co-exist in a same patient and may require a dual management.

d- Occasionally, either pre- or post capillary SCD-related pulmonary hypertension can alter liver outflow and contribute to chronic liver injury. This cofactor can be detected by transthoracic

echocardiography and BNP assay, and confirmed by right heart catheterization and pressures measurement when appropriate. Transvenous liver biopsy may be useful to rule out intrahepatic sickling, showing pure sinusoidal dilatation.

2.2.3. SCD-related predictive factors associated with SCD hepatopathy

The predisposing factors associated with the occurrence SCD hepatopathy have been poorly studied. In one Italian study, including 68 SCD patients free of HBV/HCV infection and alcohol consumption, male sex, SS genotype, lower HbF and frequent transfusions were identified as potentially early markers. In particular, structural (liver stiffness) and biochemical abnormalities were significantly more frequent in SS (and S/ β thal) than in SC genotype patients [39].

2.2.4. The issue of acute-on-chronic liver disease in SCD patients

Recently, a new syndrome named acute-on-chronic-liver failure (ACLF) has been described [40], which is defined as multiple organ failure in patients with pre-existing chronic liver disease, most often cirrhosis. The prognosis is extremely poor with a one-month mortality > 80 %. A triggering factor, usually initiating a strong inflammatory response, is identified in more than 80 % of the cases, as sepsis, alcoholic hepatitis, or HBV reactivation.

The retrospective review of a series of SCD patients transplanted for end-stage liver failure at Henri Mondor Hospital [17] showed that in SCD patients, liver failure was associated in 80 % of the cases with ACFL. This means that liver failure most often occurs in patients with pre-existing, often undiagnosed, chronic SCD liver disease, pure VOC-induced ALF in a previously healthy liver being possible although much rarer. Typically, ACLF in SCD patients combines deep jaundice, hepatic encephalopathy requiring mechanical ventilation, acute renal failure requiring extra renal support, coagulopathy and hemodynamic instability [17]. It is essentially triggered by massive intra hepatic VOC [17]. Pre-existing chronic SCD liver disease is therefore a major risk factor for accelerated liver failure in case of liver VOC and is probably the key driver of the so-called Sickle cell Intrahepatic Cholestasis. This dramatic scenario suggests that SCD management and prevention of further VOC should be reinforced in any patient with early chronic SCD liver disease to anticipate further liver failure. Outcomes after liver transplantation (LT) will be considered in the LT section.

3. SCD cholangiopathy

Aside liver parenchymal cells injury, SCD can also affect biliary tract, resulting in SCD cholangiopathy that can mimic sclerosing cholangitis. SCD cholangiopathy in early stages is usually pauci-symptomatic, diagnosed because of persisting cholestasis with sustained increased in alkalin phosphates and GGT > 3 ULN, and increase in direct bilirubin > 15 mg/dL. Transaminases are usually normal or modestly increased and prothrombin time in the normal range. The liver can be enlarged but not necessarily dysmorphic. In later stages, pruritus, liver pains and cholangitis episodes can be observed.

The diagnosis is based on cholangio MRI that shows bile ducts dilatation and stenosis spread in the liver and a scarcity of bile ducts in distal area (Fig. 6). Cholelithiasis can also develop in the biliary tract.

Three different mechanisms can result in SCD cholangiopathies:

a- SCD-induced ischemic cholangiopathy: in this scenario, vasoocclusion in periductular capillaries and end arteries surrounding bile ducts is supposed to induce progressive bile duct ischemia and ischemic cholangitis resulting in intra hepatic bile ducts dilatations. Such bile duct dilatations can happen in the absence of any biliary obstruction at early stages [41], predominating on extra hepatic and 1rst order intrahepatic bile ducts. They ultimately evolved toward associated stenosis that can mimic sclerosing cholangitis, with or without intrahepatic cholelithiasis. This pattern may be observed in up to 20 % of SCD patients with cholestatic jaundice [41]. Ischemic SCD cholangiopathy should be considered in patients having no associated inflammatory bowel disease and no PCS-associated biomarkers as PR3 ANCA (see below) and unusual bile ducts dilatation with no obvious biliary tract obstruction.

b- Hepatolithiasis-related cholangiopathy (Fig. 7).

In this setting, the primary injury is related to disseminated chronic, hemolysis-related, intrahepatic gallstones associated with persisting bile ducts obstruction, recurrent pyogenic cholangitis and subacute inflammation, resulting in secondary sclerosing cholangitis [42]. Of note, ischemic cholangiopathy and hepatolithiasis can coexist in a same patient. Hepatolithiasis may accelerate progression of ischemic cholangitis and ischemic cholangiopathy may facilitate hepatolithiasis. Of note, two factors can accelerate hepatolithiasis in SCD patients, a-the Gilbert syndrome on the one hand, which requires evidence of UGTA1 gene rearrangement for diagnosis, because of hemolytic related elevation of unconjugated bilirubin in SCD; and b, the so-called hyperhemolytic phenotype [43] on the other hand.

c- Primary sclerosing cholangitis (PSC) (Fig. 8): as stated above, PSC has been increasingly diagnosed in SCD patients, notably in pediatrics [36,38]. The diagnosis of PSC should be considered when a SCD patient also presents with associated inflammatory bowel disease. PR 3 ANCA may be helpful for diagnosis. At Henri Mondor Hospital, PSC accounted for 10 % of liver transplantation indications in SCD patients.

Of note, severe acute liver VOC can simultaneously occur in SCD patients with cholangiopathy. It can be triggered by a septic episode. This scenario should be considered in SCD patients with known cholangiopathy, in case of rapid increase in total and direct bilirubin. It should be managed accordingly by blood transfusions first. Transjugular liver biopsy can occasionally be performed when bile ducts are not dilated, to ascertain concomitant liver VOC and to drive management.

4. Special aspects

4.1. Liver transplantation

Despite well-described severe forms of SCD liver failure, reported cases of liver transplantation in SCD patients are exceedingly rare. So far less than 100 LT in SCD patients have been published [44–47]. The reasons for that are a- the rarity of end-stage liver failure in SCD patients; b- unavailability of LT resources in countries at high prevalence of SCD; c –perceived mitigate outcomes after LT in SCD patients compared to LT outcome in other indications. In a series of 21 SCD patients transplanted at Henri Mondor Hospital [44], overall 5-year survival rate was 57.1 %., and tended to be lower in patients transplanted in an urgent setting, compared to those transplanted electively (41.7% vs 77.8 %). We also observed later on [17] that 5-year survival was > 90 % in patients transplanted with stable cholestatic liver diseases as PCS, and 45 % in patients transplanted for VOC-induced ACLF. These results suggest that multiple organ failure associated with ACLF or ALF drives post LT outcome [17]. Interestingly, analysis of 28 SCD LT patients identified in the US Scientific registry of Transplant [46] confirmed that compared to a reference population of African American LT recipients, SCD patients were more likely to be status 1 at listing (26.1% vs 12.1 %), admitted in ICU (43.5% vs 19.1 %), on preoperative dialysis (17.4% vs 4.9 %), with a higher MELD score (33 vs 21). Overall 5-year patient survival rate was 64.4 %. In 18 SCD recipients 2:1 propensity-matched with the reference population, 5-year survival was 58.8% vs 64.3 % (p = 0.2). Again, these results

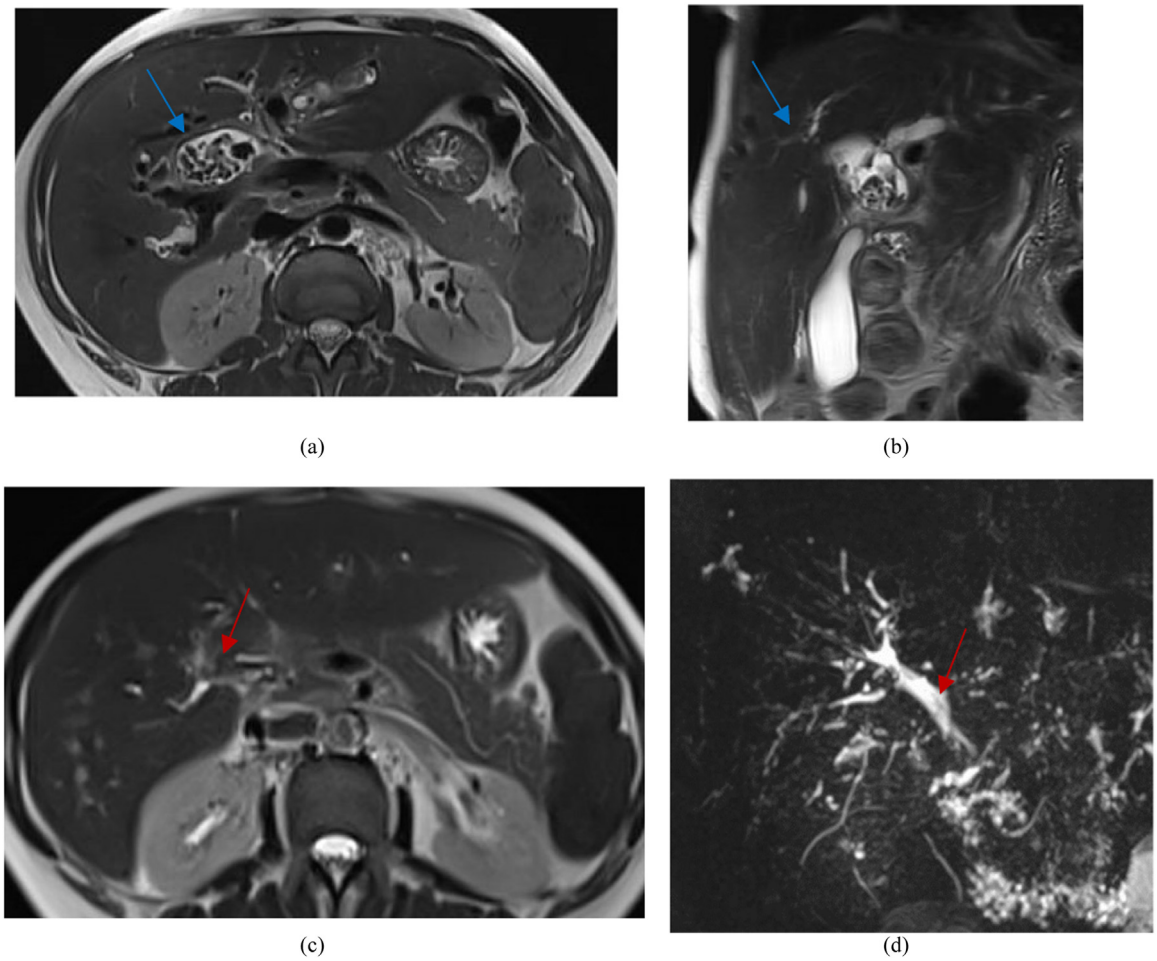

Fig. 6. SCD-ischemic cholangiopathy. Note the extremely enlarged biliary tract containing numerous gallstones (panel a and b, blue arrows) and the reduction in bile ducts diameter after latero duodenal bilio-digestive anastomosis and gallstones extraction (panel c and d, red arrows).

suggest that SCD per se is not a risk factor, but that pre LT status of SCD patients when admitted in ICU because of frequent associated organ failures drives outcomes and makes this indication particularly challenging [44]. Listing criteria for transplantation at Henri Mondor Hospital are based on MELD and Child Pugh scores in patients with stable decompensation and cholestatic diseases. In patients in ALF or ACLF, listing criteria are those of Clichy [48] and/or those of the King's College Hospital [49]. Although such criteria have been defined for patients presenting with ALF, we also apply them for patients in ACLF. In ALF and ACLF patients, the key issue is to determine among SCD patients those who might be too sick to be transplanted, making LT futile because of multiple organ failures. This debate is not specific to SCD and refers to the larger controversy of LT in ACLF patients [50,51]. As experience is still limited, there is no consensus so far to define this point of no return, but recently proposed prognostic models in ACLF patients [52,53] can be used to help decision in SCD patients. The final decision of LT should always be considered by a full staff meeting including intensivists, surgeons, hepatologist and SCD experts.

Three other key issues should be pointed-out when considering LT in SCD patients:

- Pre-LT HLA sensitization is not uncommon in SCD patients because of history of blood transfusion. Anti HLA antibodies should therefore be screened before LT to assess the risk of antibody-mediated rejection and drive post LT immunosuppressive strategy.
- We observed several cases of severe tacrolimus-related neurotoxicity post LT, including seizures and 3 cases of PRESS syndrome, including a fatal one. Following this experience, we opted for an induction immunosuppressive protocol based on either anti IL2 antibodies or anti-lymphocyte antibodies, depending on the magnitude of sensitization preLT, combined with a delayed introduction of tacrolimus by D3-5 post LT and MMF.
- We also observed occasionally, as others [54], intra liver graft sickling post LT. Graft involvement was suspected because of LFT abnormalities occurring in the setting of VOC. It clinically mimicked acute rejection (prominent cholestatic pattern with mild elevation of transaminases). This calls for a- systematic histological confirmation to rule out rejection and cautious and multidisciplinary management of SCD after LT, keeping S Hb < 30 % to prevent sickling, and going on with blood transfusions and/or hydroxyurea as appropriate.

4.2. Hematopoietic stem cell transplantation (HSCT) in SCD: liver aspects

Hematopoietic stem cell transplantation has emerged as a major therapeutic option in SCD patients [55,56]. In SCD candidate to HSCT, mild liver tests abnormalities are not unusual and require careful

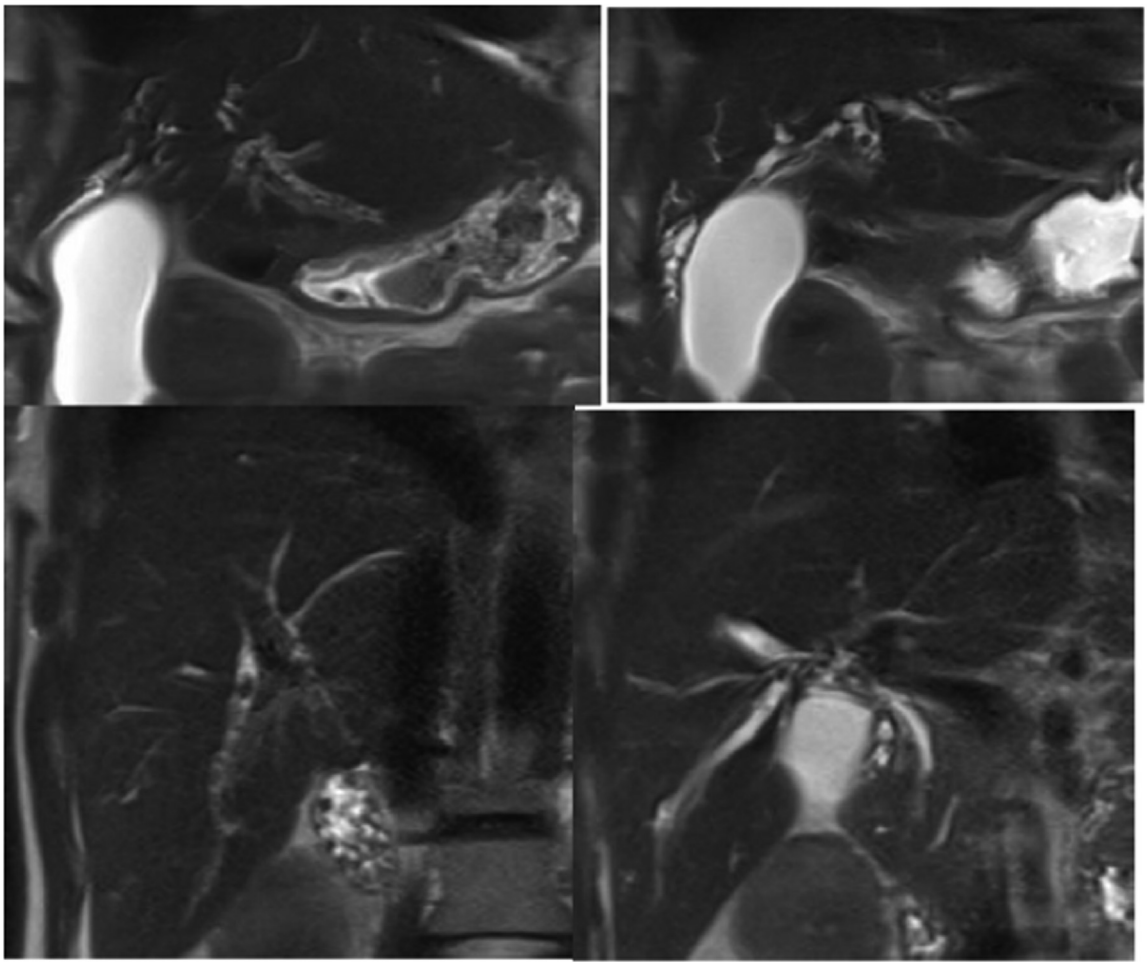

Fig. 7. diffuse right and left intra hepatic gallstones with associated secondary sclerosing cholangitis in a SCD patient. Biliary tract was normal at initial work up 10 years ago. Note the absence of gallstones in the gallbladder.

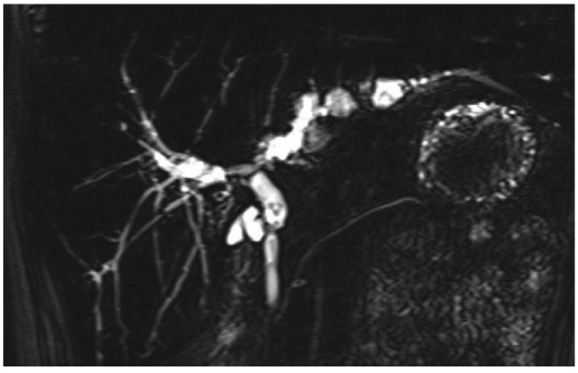

Fig. 8. Primary sclerosing cholangitis in a SCD patient affected with ulcerative colitis.

assessment of liver status a- because pre HCST conditioning can be toxic to the liver and also promote Hep B virus reactivation, b- because advanced chronic SCD-related chronic injury can contra-indicate HSCT whereas, on the contrary, mild SCD related liver injury can further indicate HSCT.

In case of LFT abnormalities, we therefore advocate for liver assessment in an experienced liver unit before HSCT. Work up should include transient elastography and US examination of the liver, screening for HBV and HCV in the recipient but also in the donor, testing for autoantibodies and liver biopsy if necessary. In addition, information on pre HSCT conditioning and its potential toxicity to the liver should be specified. With this respect, busulfan/cyclophosphamide-based myeloablative regimen have been linked to a substantial risk of sinusoidal obstruction syndrome and a 50 % fatality rate in non SCD patients. Reduced-intensity conditioning regimen including fludarabine and busulfan are less hepatotoxic but still associated with a high risk of HBV reactivation. In non myeloablative conditioning regimens, alemtuzumab has also been associated with a high risk of HBV reactivation. In addition, alemtuzumab can induce auto-immune hepatitis [57], a point of concern in SCD patients already diagnosed with such a disease.

Results of the liver work up should therefore be discussed multi-disciplinary with the team proceeding with HSCT, balancing the risks associated with liver toxicity /decompensation/auto-immunity with the benefit of curing/stabilizing SCD-related early liver diseases. With this respect, the HSCT Comorbidity Index [58] which predicts relapse and overall mortality after HSCT might not be discriminant enough in SCD patients because a- affecting 3 points to total bilirubin > 1.5ULN, a threshold which does not take into account hemolysis-related hyperbilirubinemia and b- not considering SCD-related chronic vascular changes in the liver.

As stated above, because of high prevalence of HBV in the SCD population, special attention should be taken to prevent reactivation in HS Ag +ve patients, but also in those with past HBV infection (HBs Ag −ve, antiHBc +ve). In patients undergoing allo-HSCT, HBs Ag reactivation rate of up to 45 % has been reported without antiviral prophylaxis [59].

EASL and AASLD guidelines [60,61]recommend systematic prophylaxis with nucleos(t)ide analogues (NA) in both scenarii. Last generation NA with high genetic resistance as tenofovir or entecavir, can reasonably be advised. There is no consensus about the duration of antiviral prophylaxis which depends on the immune reconstitution of the recipient, and HBV status of both recipient and donor. EASL guidelines propose prophylaxis for at least 18 months post HSCT. In HBs Ag +ve recipients, lifelong prophylaxis might be reasonable.

The HBV status of the donor should also be carefully considered. Although data are still lacking in SCD HSCT candidates, a high prevalence of HBV infection or past infection in matched related donors can be anticipated, both associated with a risk of HBV transmission [62]. On the opposite, HBV immunity can be transferred from an immune donor to the recipient, minimizing the risk of HBV reactivation in the recipient [63], provided a vigorous HBV immunity has been obtained in the donor.

After HSCT in a SCD candidate with active or past HBV infection, or in a naïve patient transplanted from an HBV positive donor, a close, quarterly follow-up of HBV serological status and HBV DNA should be undertaken while on antiviral prophylaxis.

In case of recipients and donors naïve of HBV infection, vaccination with a reinforced vaccine scheme should be proposed. Adoptive transfer of HBV immunity from donors vaccinated against HBV to recipients have been reported.

As far as HCV infection is concerned, testing for HCV RNA should be systematic in HSCT candidates and donors with HCV+ antibodies. In case of serum HCV RNA detection, treatment of HCV infection with last generation direct antiviral agents should be undertaken before HSCT to prevent transmission of HCV and cholestatic fibrosing hepatitis post transplantation in the recipient.

After HSCT, the liver may also be injured by both acute and chronic graft versus host disease (GVHD). Persisting cholestasis in the recipient should prompt liver biopsy to differentiate GVHD from past SCD related liver injury or recurrent sickling in case of graft failure. Of note, current conditioning regimen in SCD patients have been reported to be associated with a low risk of GVHD [64].

4.3. Focal intrahepatic lesions in the SCD liver

Diagnosis of focal liver lesions in SCD patients is an emerging field which has been poorly investigated so far. The prevalence of focal liver lesions in this population is unknown but at our referral center, SCD patients are explored on a regular basis for this purpose. Several types of liver focal lesions can be considered. In theory, hepatocellular carcinoma is expected to be observed because of high prevalence of HBV in this population. However, among 3000 patients followed on a routine basis at our referral center, HCC has only been sporadically diagnosed. This unexpected low incidence could be due to young age, low prevalence of active viral replication and low prevalence of cirrhosis. Similarly, cholangiocarcinoma, the incidence of which is rising worldwide [65], and which could be potentiated by iron overload, chronic bile duct injury and HCV carriage in SCD patients, was only occasionally observed.

Other types of liver focal lesions observed in SCD patients include extra-medullar hematopoiesis foci (EMF) [66], and, in our experience, benign tumors as adenoma or adenomatosis, focal nodular hyperplasia (FNH) or FNH-like lesions, as in other liver vascular diseases (unpublished data, cortesy of Dr E Reizine).

Liver nodules in SCD patients are most often asymptomatic and discovered on liver imaging requested for another reason. Liver MRI is the best imaging technique to characterize these lesions. However, data are still lacking to correlate histological aspects with imaging features. Imaging should therefore be discussed multidisciplinary and echoguided liver biopsy considered in case of uncertainty. Of note, the risk of bleeding related to guided biopsy should be evaluated as well as the risk benefit ratio of such a procedure. Large observational cohorts are necessary to clarify the risk of both HCC and cholangiocarcinoma as well as the incidence of various types of benign liver lesions in SCD patients.

5. Management of sickle cell liver injury

The management of liver injury in SCD patients should be multidisciplinary, driven in close cooperation with hematologists or internists, expert in SCD and hepatologists. It should follow a strict 5-step process, which are summarized in Fig. 9.

5.1. Step 1: assessing severity of liver involvement

This step is crucial to drive further management. The severity of liver involvement is based on clinical assessment, including intensity of jaundice, clinical signs of hepatic decompensation including encephalopathy, liver function tests (LFT), prothrombin time and estimation of renal function.

Mild, asymptomatic increase of LFT in the setting of usual sickle cell vaso-occlusive crisis does not need a specific management. Clinically relevant involvement of the liver requiring further investigations and treatment should be considered when AST/ALT > 5 fold UNL, serum conjugated bilirubin > 50 μmol/L and increase in prothrombin time.

In severe hepatic vaso occlusive crisis, transaminases can increase above 20 fold UNL, conjugated bilirubin above 200 μmol/L and prothrombin time > 20 s. Encephalopathy is present and renal function deteriorates. In this setting, blood transfusions should be set in emergency.

5.2. Step 2: looking for manifestations of underlying chronic liver disease

This step is crucial because severe vaso-occlusive crisis occurring on a chronically injured liver can precipitate liver as well as multiple organ- failures, resulting in a pattern of ACLF. This should be at best anticipate, and management adjusted accordingly. Clinical examination looks for hepatomegaly or ascites. US Doppler examination of the liver followed by abdominal CT scan should be performed systematically, looking for a dysmorphic liver, focal liver lesions and radiological signs of portal hypertension. When available, liver MRI is the best imaging technique as stressed above, since it can also explore the morphology of biliary tract. Evidencing associated chronic liver disease should also prompt additional investigations to clarify the cause of chronic injury.

5.3. Step 3: looking for additional factors of liver injury

As discussed previously, several factors should considered, whether the liver being acutely or chronically injured. This includes past or recent history of infection with hepatitis B (D), C, A and E. Genomic diagnosis of viral hepatitis is helpful to distinguish between LFT abnormalities due to vaso-occlusion or viral injury. Biomarkers of associated auto-immune liver diseases (Ig G, Ig M, auto antibodies including ANA, SMA, AMA, ANCA) should be systematically investigated to rule out other treatable factors of liver injury. Iron overload deserves careful estimation but ferritin levels do not accurately reflect iron exposure in case of marked/acute cytolysis. Associated intra hepatic cholelithiasis should also looked for by the mean of imaging, ideally cholangio MRI, which is also helpful to analyze morphology of bile ducts.

5.4. Step 4: identifying the final pattern of liver injury

Five patterns of liver injury can be identified in SCD patients:

- *1-Acute, SCD-related liver injury/failure:* in this setting, there is no past story nor clinical or radiological signs of chronic liver/bile duct injury, and the full etiological work up is negative. Acute liver

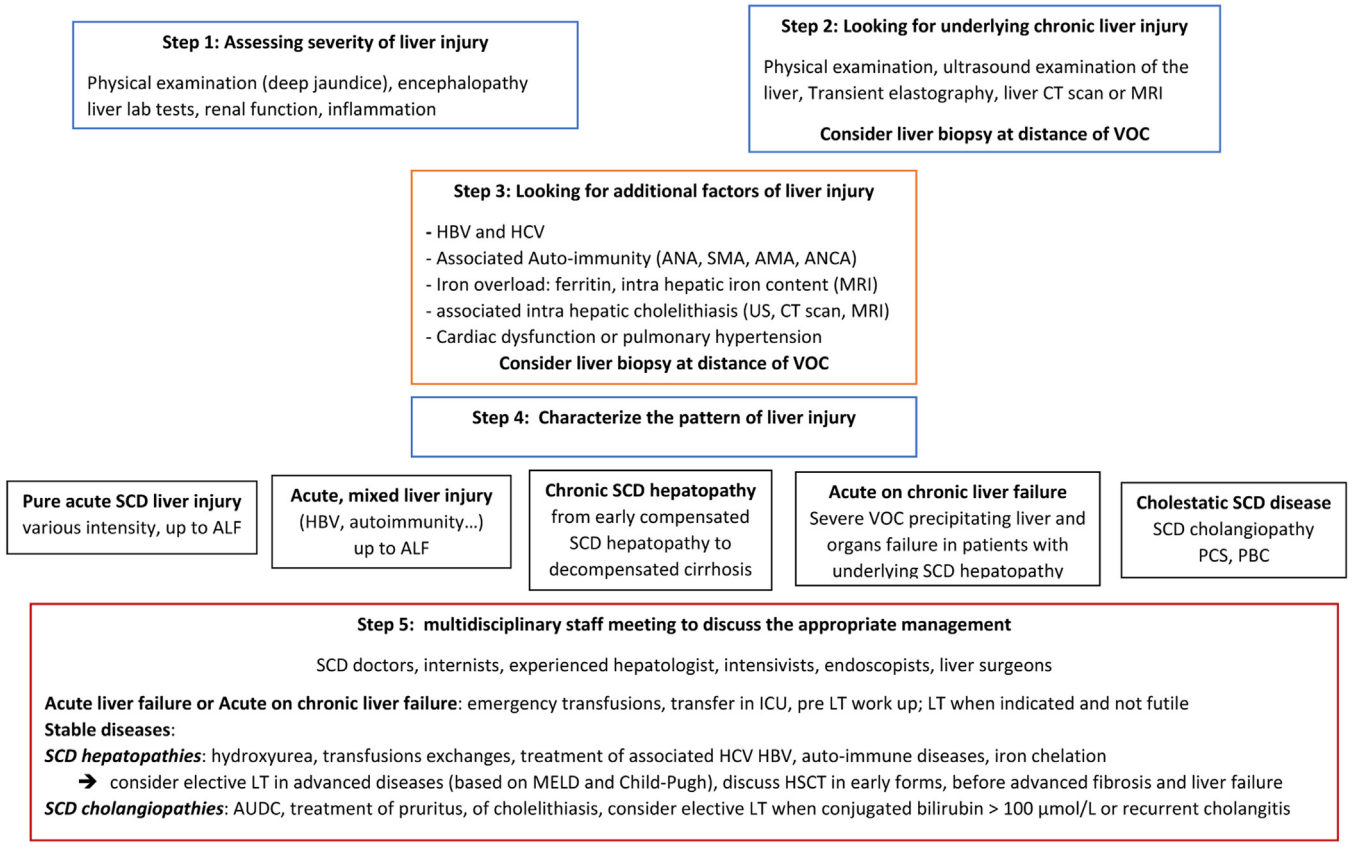

Fig. 9. simplified management algorithm for SCD patients with liver injury.

dysfunction is purely due to liver vaso-occlusion of various magnitude.

- *2-Acute, mixed pattern of liver injury/failure:* in this setting, cofactors, as viral infection, iron overload or auto-immunity, participate to liver deterioration.
- *3-Acute on chronic liver injury /failure:* this pattern is characterized by a combination of severe liver dysfunction with clinical decompensation, combined with coagulopathy and other organ failures, notably renal, pulmonary, and in some instances, haemodynamic instability. These organ dysfunctions occur in a patient with past history of chronic liver injury, either due to chronic sickling or other factors, as described above. The prognosis is spontaneously dismal.
- *4-Chronic liver disease in a SCD patient:* in this pattern, the liver is investigated because mild mixed liver tests abnormalities or asymptomatic hepatomegaly. Clinical presentation can mimic early stage cirrhosis. Initial work up should differentiate between pure chronic vaso-occlusive injury and participating cofactors as viral and iron injury. A key issue is to evaluate the morphology of the liver using CT scan or MRI, and the extension of liver fibrosis by the mean of liver biopsy and transient elastography. Oeso-gastroscopy is necessary to look for esophageal varices. end-stage chronic liver diseases present as decompensated cirrhosis.
- *5-Cholestatic pattern:* in this setting, the most prominent feature is an increase in alkalin phosphatases and GGT, associated, in most severe forms, with a marked increase in total and conjugated bilirubin and deep jaundice. Cholestasis can be due in rare instances to PBC. More frequently, it is related to underlying cholangiopathy. In this scenario, three factors which are not mutually exclusive, can coexist: a-chronic bile duct injury, because of underlying sclerosing cholangitis, whatever the cause, b-obstructive jaundice due to intra hepatic cholelithiasis, and c- associated intra hepatic vaso occlusion. MRI is the best imaging technique to explore this pattern. In case of elevation of AST > ALT, associated liver VOC should be considered.

5.5. Step 5: define the appropriate management

Given the frequent complexity of SCD liver injuries, multidisciplinary discussion in dedicated staff meetings is encouraged.

5.6. Acute, SCD-related liver injury/failure and ACLF

In these 2 patterns, the key first intervention is blood exchange transfusion, targeting HbS levels <30 %. Transfusions protocol should be defined in close cooperation with SCD experts and adjusted to severity of liver failure. Transfusions can sometime reverse liver failure by rapidly counterbalancing the deleterious effects of liver hypoxia. However, in some instances, the beneficial effect of transfusions is insufficient or only transient. Persisting liver failure should prompt to consider liver transplantation and the patient referred to a LT unit (see LT section). Of note, in some instances, ACLF may be precipitated by a delayed hemolytic transfusion reaction [67], secondary to alloimmunization to red blood cells antigens. In this scenario, further transfusions may be contra-indicated and the management of this concerning presentation should be undertaken in cooperation with SCD experts, discussing the role of rituximab, IV immunoglobulins, plasma exchanges, and even anti C5 therapy as eculizumab [68,69]. When a relevant cofactor of liver injury is identified, specific therapeutic intervention should be concomitantly initiated. This is particularly true for type 1 associated autoimmune liver injury, that can

benefit from steroid therapy, and acute or chronic active B or C hepatitis that should be treated with specific antiviral drugs.

5.7. Chronic SCD liver disease

In this setting, the key objective is to stabilize the remnant liver function to prevent further decompensation. Diagnosing asymptomatic chronic SCD hepatopathy should prompt a multidisciplinary discussion to optimize the management of SCD, and consider introduction of hydroxyurea or initiation of transfusion exchanges. HbS levels below 30 % should be targeted. Management of any other cofactors of liver injury should also be discussed with the hepatologist, including indication for antiviral treatment and specific treatment of associated auto-immune diseases. Since corticosteroids can promote VOCs [70], including intrahepatic VOCs, BET before starting steroid therapy is advisable. Liberal antiviral treatment is advised in case of Hep B or Hep C, even in case of minimal fibrosis (see above). Also, a frequent situation is to distinguish between asymptomatic auto-antibodies associated with SCD, and auto-antibodies associated with actual auto-immune liver diseases, as auto-immune hepatitis or BPC. In this scenario, liver biopsy should be proposed. When a prominent component of vaso-occlusion with no or minimal inflammation on liver histology is observed, steroid therapy can be avoided. In case of major iron overload, ideally assessed on MRI, chelation should be initiated by the SCD team. Caution is yet advised because based on routine experience, adherence of SCD patients to iron chelation if often very poor. Also, iron chelators can result in liver drug injury.

In case of liver decompensation, liver transplantation should be considered. LT indication criteria are based on MELD and Child-Pugh scores, and the patient should be referred to a LT center for assessment. Excellent outcomes can be expected in case of elective transplantation.

5.8. Cholestatic liver diseases

In patients with anicteric cholestasis, i.e. marked increase in GGT and alkaline phosphatases with no jaundice, related to PBC or PSC, treatment with ursodeoxycholic acid (UDCA) and fenofibrate, in case of poor response to UDCA, should be initiated, as is non SCD patients. In some instances, pure vascular liver injury is also associated with marked anicteric cholestasis. As small bile ducts injury is difficult to be ruled out, UDCA can also be proposed but data are lacking to assess efficacy in this scenario.

In case of jaundice, the key issue is to look for additional co-factors as intra hepatic cholelithiasis or associated liver vaso-occlusion. If intra hepatic cholelithiasis is evidenced, management can be complex and should be discussed with a multidisciplinary team including endoscopists, radiologists and surgeons. The risk benefit ratio of a conservative approach vs LT should be cautiously evaluated.

In the absence of cholelithiasis, a marked increase in total and conjugated bilirubin in a patient with a previously known biliary disease should prompt to look for superimposed intra hepatic vaso occlusion. Diagnosis is often difficult because intra hepatic vaso-occlusive crisis can induce liver pains and mimic cholelithiasis. Liver biopsy is advised when bile ducts are not dilated to ascertain vaso-occlusion and guide transfusion policy. In case of persisting jaundice with conjugated bilirubin over 100 μmol/L, LT should be considered. As in decompensated SCD chronic hepatopathy, excellent outcomes can be expected when no organ failure is associated.

6. Conclusion

Liver involvement in SCD patients is frequent but often misdiagnosed or underestimated, except in case of advanced liver diseases. Because of so far poorly recognized forms of chronic SCD-related vascular injury that can silently evolved towards end stages or facilitate ACLF, any persisting liver function tests abnormalities should be carefully investigated, following the above proposed algorithm. Work up and management must be considered multidisciplinary in relationship with a Hepatologist. Early SCD hepatopathy should prompt revision of SCD management to prevent further liver injury and decompensation, discussing transfusion exchanges and hydro urea when not yet initiated, and control for any cofactor of liver injury. The role of HSCT in early SCD hepatopathies also deserves evaluation. In advanced SCD hepatopathies, liver transplantation, which has been rarely performed so far, is the only therapeutic option associated with improved survival. It should definitely be discussed- either electively in case of decompensation in SCD cirrhosis or jaundice/recurrent cholangitis in cholestatic diseases, with excellent outcome, - or emergently in case of ALF or ACLF with more mitigate results.

To improve knowledge and management of SCD liver diseases, creation of national and international registries, as well as longitudinal observational cohorts are encouraged.

Disclosure of Interest

The authors declare that they have no competing interest.

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