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| RESEARCH ARTICLE

Co-existence of Sickle Hepatopathy with Autoimmune Hepatitis: More than a Coincidence – A Case Report

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| ABSTRACT

Sickle Cell Hepatopathy is a multifactorial liver disease that can have an impact on half of patients with Sickle Cell Disease (SCD), with a cryptic and puzzling connection appearing to be associating Sickle Cell Disease (SCD) with Autoimmune Hepatitis (AIH), repeatedly yielding diagnostic neglect and delay, bringing about disastrous consequences. This case introduces to you a 41-year-old single Saudi male known to have Sickle Cell Disease (SCD), who was accidentally diagnosed with advanced liver cirrhosis by pure chance during laparoscopic cholecystectomy. This study will draw attention to the diagnostic challenges concerning the overlap between sickle hepatopathy and Autoimmune Hepatitis (AIH), while sharing intriguing histopathological findings. Suggested theories that point out the unique relationship between the two entities are offered for a greater understanding of the complex pathophysiological process. Literature gaps are also discussed, owing to the absence of an agreed-upon recommended and safe therapeutic option for Autoimmune Hepatitis (AIH) in the context of Sickle Cell Disease (SCD) specifically, which forced starting the patient on the second line of treatment – Mycophenolate Mofetil (MMF). We learn from this case the value of early screening for liver disease in patients with Sickle Cell Disease (SCD) as well as the essential need for tailoring the therapeutic plan according to the type of patients when Autoimmune Hepatitis (AIH) is present.

| KEYWORDS

Sickle cell disease, sickle cell hepatopathy, autoimmune hepatitis, liver cirrhosis

| ARTICLE INFORMATION

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Introduction

Sickle Cell Disease (SCD) is regarded to be one of the most prevalent hemoglobinopathies, stemming from an autosomal recessive mutation in the beta-globin chain gene, a substitution of amino acid Valine for Glutamate, leading to prompting the red blood cells to adopt an abnormal sickle-shaped form, with a lessened lifespan and lowered oxygen-carrying capacity. The onset of symptoms in Sickle Cell Disease (SCD) typically takes place 6 months after birth, as the adult type of hemoglobin known as HbA1 will start predominating while the synthesis of the fetal type of hemoglobin known as HbF will be switched off [1]. Since HbF is composed of two alpha-globin and two gamma-globin chains, while on the other hand, HbA1 is composed of two alpha-globin and two beta-globin chains, instead of forming normal HbA1, people affected by Sickle Cell Disease (SCD) will have an abnormal HbS secondary to the use of defective beta chains during the process of synthesizing adult hemoglobin [1]. This hemoglobinopathy will eventually contribute to long-term pain and reduced median life expectancy [1]. As with many hemoglobinopathoies, the gold standard diagnostic modality for these cases will remain hemoglobin electrophoresis, demonstrating HbS as a major form of hemoglobin and a higher amount of HbF than usual. The probability and severity of

variable symptoms and even organ involvement are both found to be dependent on the haplotype. A haplotype is defined as the set of specific genetic variations for a disease [2]. Sickle Cell Disease (SCD) evolved as a natural protective mechanism against Malaria. It started initially in endemic regions for Malaria [2]. Although it is chiefly found in Africa and the Middle East region, it became widespread due to continuous ethnic migration. While originating as a disease, people acquired different types of mutations, which gave rise to several well-recognized haplotypes [2]. For instance, the Arab-Indian haplotype, which is often encountered in the Middle East, is characterized by several striking features; one of them is being a softer clinical form with higher levels of HbF and less painful crises [2]. In comparison, kidney involvement in the form of glomerulopathy and tubulopathy inducing Chronic Kidney Disease (CKD) is more frequently observed in the Bantu Haplotype in Central and Southern Africa [2]. Many organs could get involved as the disease progresses, and one of these organs is the liver. In spite of the fact that half of Sickle Cell Disease (SCD) patients have elevated liver enzymes, sickle cell-related hepatopathy is regarded and perceived as an uncommon complication, owing to the previous shortage of standard diagnostic criteria for such entities in the literature. Sickle hepatopathy seems to be multifactorial in origin, as a result of complex pathophysiological processes in most cases. It is also suggested to classify it into a group of different disorders, but the main triggers remain transfusion-related iron overload, viral liver cell injury, ischemic injury, and extrahepatic and intrahepatic cholestasis [1]. 80% of patients usually present with hepatomegaly, and many of them already have severe hyperbilirubinemia, reaching levels exceeding 100mg\dl [1]. Some recent definitions have already been suggested for sickle hepatopathy; one of these is a total serum bilirubin of 13mg\dl in the absence of acute hemolysis, viral hepatitis, hepatic sequestration, and finally, extra-hepatic obstruction [3]. Even though it is more frequent in children, it tends to behave more severely in adults, most likely on account of the natural progression of the pathophysiological process [3]. When comparing patients affected by Sickle Cell Disease (SCD) to the normal population, Autoimmune Hepatitis (AIH) can be found to be more prevalent; these unique cases of dual liver pathology strongly suggest a conceivable link and relationship between the two diseases [4]. This, unfortunately contributes to the delay in recognition of Autoimmune Hepatitis (AIH) in patients with Sickle Cell Disease (SCD) thanks to the presence of a dual pathology manifesting with the same manifestations, including jaundice, fatigue, and abnormal Liver Function Tests (LFTs). This also provides a treatment dilemma since some potential treatment options, such as Corticosteroids and Azathioprine could play a role in potentiating the occurrence of vaso-occlusive crises in patients with Sickle Cell Disease [4]. Not to mention the required caution when prescribing bone morrow suppressant medications like Azathioprine in a patient that might need another bone marrow suppressant such as Hydroxyurea one day, increasing the risks of thrombocytopenia and neutropenia. This study reports to you a challenging case in terms of diagnosis and treatment, in an attempt to offer a chance of enhancing the understanding of such pathology, highlighting all the potential challenges and literature gaps.

Case Presentation

Patient's history

This case report presents to you a 41-year-old single Saudi male, not known to be a smoker. He has Sickle Cell Disease (SCD) but is medically free from hypertension and diabetes. He was not on Hydroxyurea or any other regular medication. Also, the patient confidently denied any substance abuse, alcohol intake and unprotected sex. A history of herbal use was also explored with the patient, which turned out to be unremarkable. His family history did not reveal any instance of liver disease or transplantation; the same goes for lung disease and emphysema. Though the patient received blood transfusions on some occasions, he never tested positive for viral hepatitis or received antiviral treatment for Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV). About his hematological disease, he usually experiences 2-3 severe vaso-occlusive crises per year, which eventually lead to hospitalization. Even so, he was never admitted to the Intensive care unit (ICU) nor received exchange transfusions. Additionally, he has no history of Acute Chest Syndrome (ACS), Avascular Necrosis (AVN) or stroke. Our patient was undergoing laparoscopic cholecystectomy for acute cholecystitis, which went uncomplicated and was done smoothly, but the operating team discovered by pure accident a grossly cirrhosed liver with clear nodular and shrunken gross morphology, which led to his referral to us. Upon referral to our facility, a thorough history excluded any persistent fatigue, weight loss, bleeding, sleeping disturbance, irritability, gynecomastia, peripheral edema, or other complications of liver cirrhosis such as abdominal distention and hematemesis. It is worth addressing that the patient was not in pain during the assessment and confirmed the complaint of mild jaundice described as increasing above his usual baseline. The jaundice was associated with dark urine but there was no notable change in stool color. Otherwise, no fever, right upper quadrant pain, or pruritus.

Physical examination

By examination, he was afebrile and normotensive with stable vitals. He appeared pale and jaundiced but had no signs of muscle wasting. The patient was of average build and Body Mass Index (BMI). His hands showed neither palmar erythema nor clubbing. Spider nevi and flapping tremors were also absent. His abdomen and periumbilical veins did not appear distended. By Palpation, the liver was not palpable, nor was the spleen. Other systemic findings such as Kayser-Fleischer rings, static tremors, gynecomastia, and peripheral edema were not there as well.

Laboratory results

In search of cause, comprehensive lab work had to be done, as shown below (Table 1).

Laboratory test	Result	Normal Range
WBCs	9.47 x 10^9\L	4-10 x 10^9\L
Platelets	262 x 10^3\L	150-430 x 10^3\L
Hemoglobin	10.3 g\dL	13-17 g\dL
Reticulocytes	7.33%	0.5-3%
LDH	617 U\L	80-230 U\L
Na	136 mmol\L	135-153 mmol\L
K	4.12 mmol\L	3.5-5.3 mmol\L
Creatinine	50 umol\L	53-106 umol\L
Total bilirubin	99 umol\L	0-20 umol\L
Conjugated bilirubin	44 umol\L	0-5 umol\L
Alkaline phosphatase	145 U\L	50-135 U\L
GGT	155 U\L	5-85 U\L
AST	77 U\L	15-35 U\L
ALT	50 U\L	7-55 U\L
Albumin	33 g\L	35-52 g\L
PT	16.6 s	11-15 s
PTT	32.5 s	26-36 s
Alpha Fetoprotein	4.2 ng\ml	0-7 ng\ml
HIV 1 and 2 ELISA	Negative	Negative
Anti HBc IgM	Negative	Negative
HBsAg	Negative	Negative
AntiHCV	Negative	Negative
Alpha 1 antitrypsin	QNS	88-174 mg\dL
Ceruloplasmin	42.40 mg\dL	22-58 mg\dL
Ferritin	217.5 ug\L	22-322 ug\L
LKM 1	Negative	Negative
ASMA	Negative	Negative
Anti SLA	Not Available	Negative
ANA	Positive: 1\160	Less than 1:40 is negative
Total IgG	3310 mg\dL	700-1600 mg\dL
Total IgE	10.40 mg\dL	0-165 mg\dL
Total IgA	748 mg\dL	70-400 mg\dLL
ESR	10 mm\h	0-15 mm\h
C3	84.8 mg\dL	80-150 mg\dL
C4	8.43 mg\dL	10-40 mg\dL
RF	Less than 20	Less than 20
Anti DNA	Negative	Negative
Anti Smith	Negative	Negative
Anti RNP	Negative	Negative
Anti RO (Anti SSA)	Negative	Negative
Anti LA (Anti SSB)	Negative	Negative
Anti Mitochondrial Antibody	Negative	Negative

Liver Biopsy

An abdominal ultrasound was conducted, and it verified the existence of findings that strongly suggest liver cirrhosis. Laboratory work also hinted at the possibility of autoimmune hepatitis, which indicated the pressing need for a liver biopsy to affirm the diagnosis and evaluate the underlying pathology. Three needle-core biopsies were obtained without any complications. As shown in the image (Figure 1, 2, 3 and 4), Liver architecture was distorted by fibrotic bands and nodules highlighted by trichome stain. Hepatocyte atrophy and perisinusoidal fibrosis were also noted in Zone 3. Moreover, sinusoidal dilation, congestion,

Kupffer cells, erythrophagocytosis, intrasinusoidal sickled Red Blood Cells (RBCs) are seen with evidence of interface hepatitis/ Mild patchy cholestasis and hepatic ballooning are also identified. The iron special stain was negative for iron overload. These microscopic features strongly suggest sickle cell hepatopathy, but some portal areas demonstrate evidence of lymphocyte and plasma cell infiltration. When combined as evidence with the raised serological markers, according to the simplified criteria proposed by the International Autoimmune Hepatitis Group for diagnosis of Autoimmune Hepatitis (AIH), the presence of autoimmune hepatitis is highly likely due to a total score of 7 points. These 7 points reflect the absence of viral hepatitis, compatible liver histopathological findings, the patient's ANA titer and elevated total IgG.

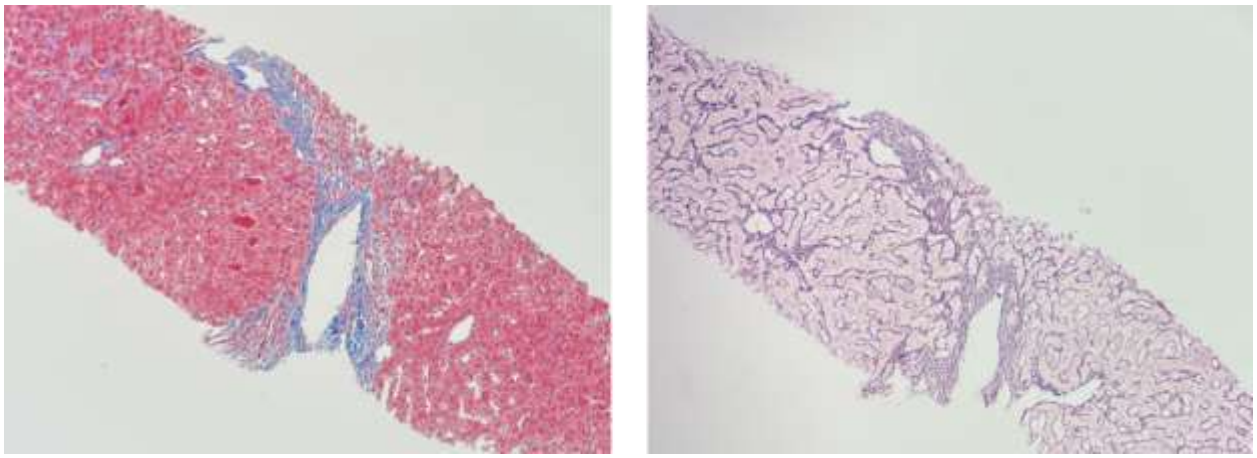

Figure 1: intermediate-power view of trichome stain and reticulum stains highlighting delicate Zone 3 perisinusoidal fibrosis.

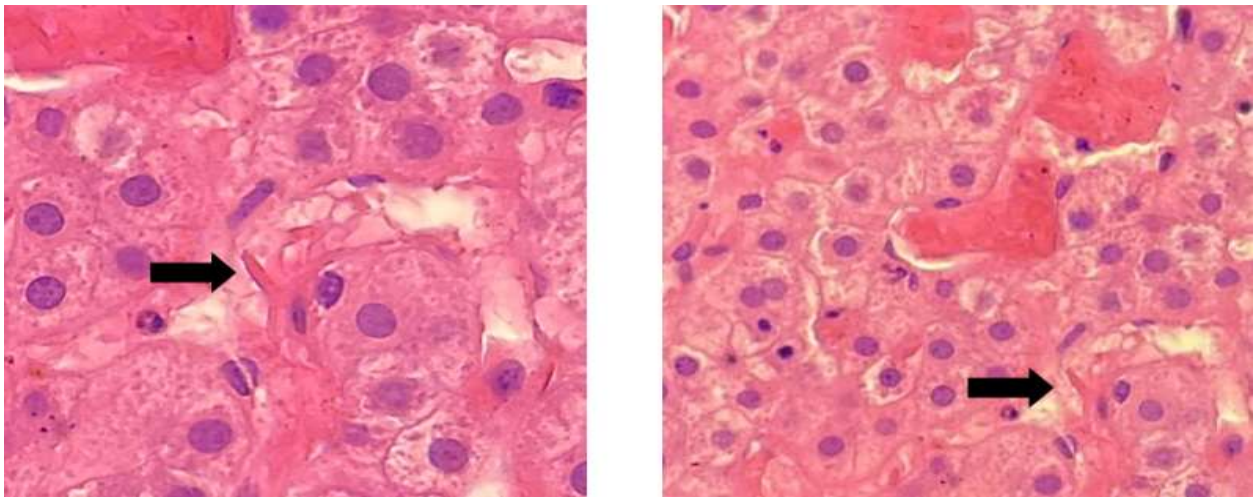

Figure 2: high power view showing examples of intrasinusoidal sickled red cells.

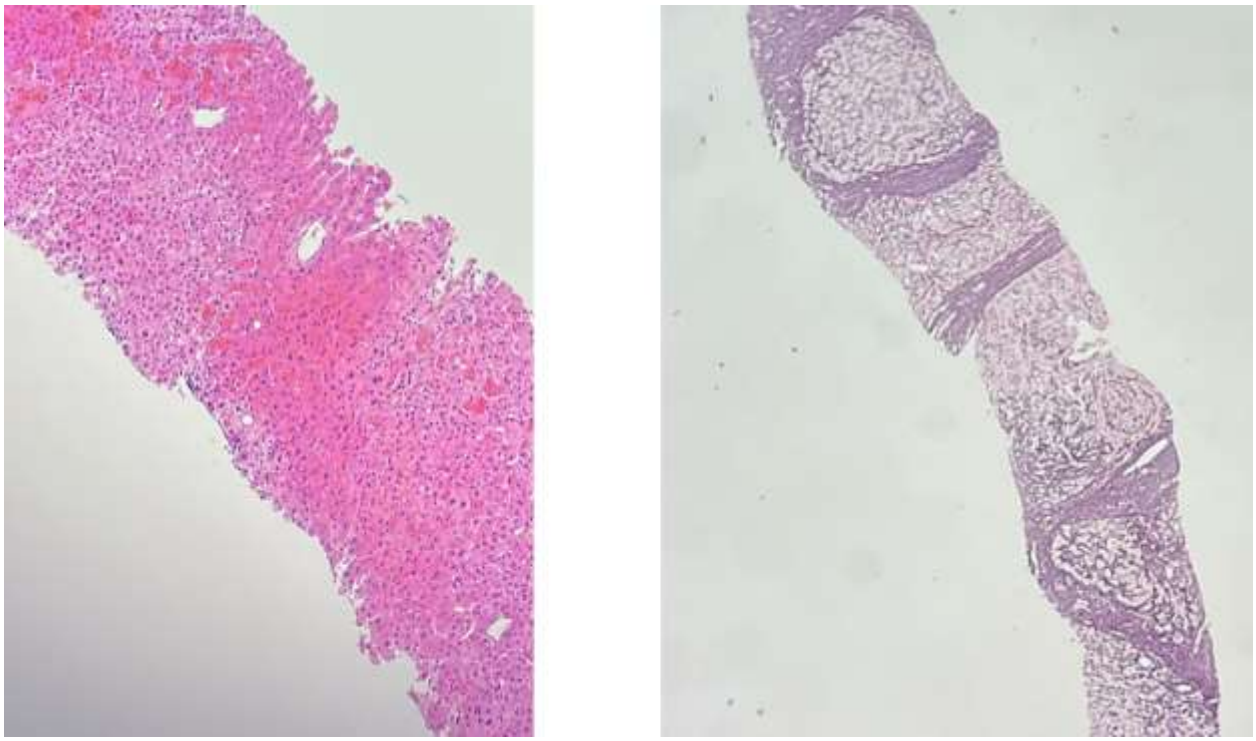

Figure 3: left picture showing intermediate power view of intrasinusoidal congestion and right picture of low power view showing 4 fibrosis.

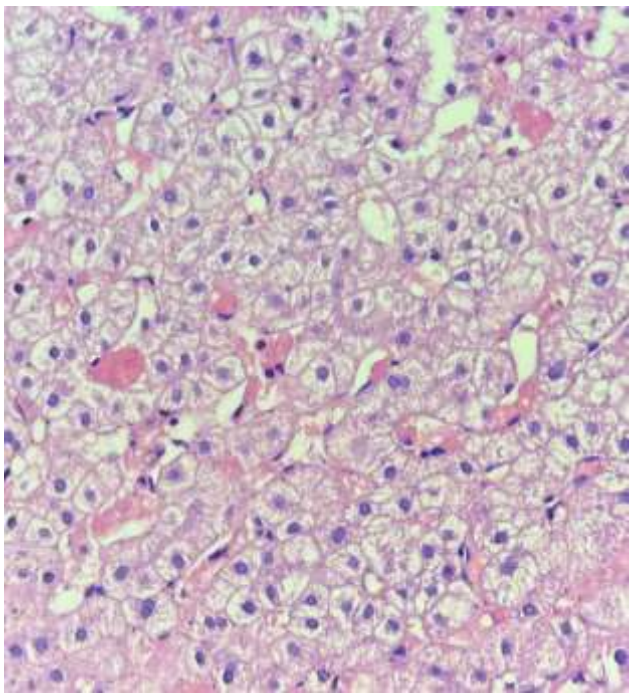

Figure 4: high power view showing multiple Kupffer cell erythrophagocytosis.

Management and follow up

The patient was started on Mycophenolate Mofetil (MMF) with a plan of monitoring clinical jaundice, Liver Function Tests (LFTs) and total IgG.

Discussion

Autoimmune Hepatitis (AIH) could affect any age and ethnic group, especially females with a noteworthy bimodal age peak, affecting people aged 10–30 and 40–60 [1]. This bimodal pattern was recently acknowledged and led to the identification of more of the late-onset cases. As known, there is no pathognomonic diagnostic tool or definitive test for Autoimmune Hepatitis (AIH). Diagnosis of Autoimmune Hepatitis (AIH) could only be confirmed based on a combination of biochemical testing, autoantibodies and histopathological evaluation. As in this case, the absence of viral hepatitis will support the diagnosis, as well as positive ANA and high total IgG [4]. Even though Autoimmune Hepatitis (AIH) generally responds well, or at least in an acceptable way, to immunosuppressive therapies even among patients with Sickle Cell Disease (SCD), it is still challenging to diagnose as the existence of a dual pathology could lead to diagnostic neglect and delay. Autoimmune Hepatitis (AIH) is an accelerator of liver disease in the setting of Sickle Cell Disease (SCD), and missing the chance to obtain a diagnostic biopsy could contribute to bad outcomes, including rapid acute decompensation [4]. Many hypotheses have been suggested to explain this mysterious link between the two entities, including the heme inflammatory hypothesis, which implies that the release of heme from hemolyzed cells can enhance auto-inflammatory processes; the transfusion-associated alloimmunization hypothesis, which demonstrates that receiving blood transfusions in certain susceptible individuals could trigger forming cross-reacting antibodies in response; and finally, the complement generation hypothesis proposes that serial release of mediators like C3a and C5a on account of the altered shape of sickle cells and their tendency to deform enhances the autoimmune responses in any injured organ [4]. This even raises the question about whether Sickle Cell Disease (SCD) could be a risk factor for other autoimmune conditions, but data are lacking enough evidence to judge this aspect. On the other hand, the presence of intrahepatic cholestasis, sinusoidal congestion, intrasinusoidal sickle cells and erythrophagocytes serve as solid evidence supporting the presence of elements related to sickle hepatopathy in this case. Unfortunately, the diagnosis was established in a late stage of the disease after accidental discovery, pointing to the compelling need for early recognition and screening for liver disease among patients with Sickle Cell Disease (SCD). Though multifactorial, Autoimmune Hepatitis (AIH) shouldn't be ignored as a potential cause, especially since some of the other similar case reports displayed fulminant course and signs of decompensation. The clinical spectrum of Autoimmune Hepatitis (AIH) is also wide and heterogenous, with 25–34% presenting without any clinical manifestations [5]. The clinical manifestations are not only diverse but also have poor correlation with prognosis, as even asymptomatic individuals are at risk of a 10-year decrease in survival if left untreated [5]. Nonetheless, Easy fatigue-ability is consistently the most prominent symptom, and it was found in 85% of cases [5]. However, absence of easy fatigue-ability should also be expected, as seen in this case, which should also bring our attention to other frequently encountered chronic symptoms such as jaundice, arthralgia and amenorrhea in females [5]. When treating any case of Autoimmune Hepatitis (AIH), Corticosteroids are deemed the cornerstone of treatment but still generate controversy and debate when treating specific patients as those with Sickle Cell Disease (SCD) because Corticosteroids are regarded as culprit for the increase in the incidence of vascular-occlusive crises in Sickle Cell Patients (SCD) [6]. Even if standard treatment of Autoimmune Hepatitis (AIH) is mainly based on Corticosteroids and Azathiprine, sometimes the management should be personalized. If we come to Azathioprine as a therapeutic option in this case, we'll find that it is a bone morrow suppressant, and the patient might need another bone morrow suppressant in the future, which is Hydroxyurea. Prescribing Azathipro, in this case might put the patient at high risk of thrombocytopenia and neutropenia if Hydroxyurea was to be considered in the future [7]. Consequently, the second preferred line of treatment was started, which is the drug with the highest amount of available date on efficacy, Mycophenolate Mofetil (MMF) [7]. It is also crucial to expect that the patient might not respond; therefore, in refractory cases, we should be considering biological therapies such as Rituximab and Infliximab as additional agents. Any delay in introducing these biological therapies could affect the patient's prognosis [7]. Another therapeutic challenge is the non-presence and unavailability of an agreed-upon definition of complete response during treatment of Autoimmune Hepatitis (AIH). Variable guidelines offered different criteria for complete and partial response, including normalization of liver function tests, histopathological remission, fall in total IgG and improvement of clinical symptoms such as fatigue and jaundice [8]. Some studies doubted the efficacy of Mycophenolate Mefotil (MMF) and assumed that it is beneficial in patients with Azathioprine intolerance rather than refractoriness or actual treatment failure; however, it is used here as an initial monotherapy, and remission is forecasted in 60-80% of cases with tolerable gastrointestinal side effects [8]. Yet, when discontinued or tapered, a possible relapse should be monitored, as it is expected in 30-40% of patients, typically after 12–24 months [8]. Finally, Hydroxyurea is an agent that is widely recognized to be capable of decreasong life-threatening complications of Sickle Cell Disease (SCD), and theoretically, it could also serve as reasonable additional treatment for this patient since it will decrease iron overload, chronic hemolysis-related liver injury, and hepatic vaso-occlusion but data supporting its benefits in sickle cell-related hepatopathy specifically is finite and insufficient [9]. While Hydroxyurea could be considered as part of the overall management plan for its indirect and secondary benefits, it is not

specifically recommended by any guidelines, and there are some concerns about its hepatotoxicity in patients with severely impaired liver functions since it is metabolized and excreted by the liver [9]. A detailed treatment approach for Autoimmune Hepatitis (AIH) in the setting of Sickle Cell Disease (SCD) specifically could be a helpful future advancement.

Conclusion

Establishing the diagnosis of Autoimmune Hepatitis (AIH) requires clinical, biochemical, serological, and histopathological evidence. People with Sickle Cell Disease (SCD) appear to be susceptible to developing Autoimmune Hepatitis (AIH), which presses the need for early recognition and screening when appropriate. Sickle hepatopathy is multifactorial in origin and could be accelerated by underlying Autoimmune Hepatitis (AIH), leading to poor prognosis and bad outcomes. The standard treatment of Autoimmune Hepatitis (AIH), including Corticosteroids and Azathioprine is questionable in the setting of Sickle Cell Disease (SCD) and raises the question about possible literature gaps in this regard.

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