Hepatic Manifestations in Systemic Lupus Erythematosus (SLE) and Cholestatic Hepatitis as Rare Initial Presentation: A Diagnostic Challenge

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Abstract: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease with various clinical manifestations. However, hepatic dysfunction is not included in the diagnostic criteria for the disease and has not been appropriately recognized. Abnormal liver tests are common (60%) at some point in Systemic Lupus Erythematosus (SLE) illness. The spectrum of hepatic involvement described in these patients ranges from abnormalities in liver function tests (LFTs) to fulminant hepatic failure. Usually, abnormalities in LFTs are only mild and transient, have a hepatocellular pattern, and are not related to SLE but instead are primarily drug-related. In rare cases, severe cholestasis may invite diagnostic dilemmas. The most frequent finding on liver biopsy is steatosis (non-alcoholic fatty liver disease). Patients do not frequently progress to advanced chronic liver disease, and their outcome is favorable. Those who develop cirrhosis have traditional risk factors, such as other non-SLE-related conditions. We report a case of systemic lupus erythematosus presenting as cholestatic hepatitis in a 36-year-old Bangladeshi woman. The cholestatic hepatitis progressed as part of the lupus activity and responded to steroid therapy.

Key Words: *Systemic lupus erythematosus, autoimmune disease, cholestasis, cirrhosis, steroid*

Introduction: SLE is a heterogeneous, multifaceted disorder of autoimmune etiology with various organ involvement, including musculoskeletal, kidney, cardiovascular system, hematological system, and central nervous system [1]. It is associated with the production of autoantibodies and diverse clinical features. It is most common in females, and the female-to-male ratio is 9:1 [2]. It usually affects women younger than 50 years of age. Gastrointestinal manifestations occur in 20–50% of patients with SLE, and up to 25–60% will present hepatic involvement at some point during the course but are rare as a part of its disease activity. Nonimmune hepatopathy, e.g., hepatotoxic drugs, coincident viral hepatitis, and non-alcoholic fatty liver disease, are some common possibilities of abnormal liver function tests in SLE. But rarely, lupus hepatitis or overlap syndrome of autoimmune hepatitis (AIH) may complicate this disease [3]. One study reported a 9.3% incidence of lupus hepatitis[1]. However, the prevalence is variable, 3-23% [4]. On the other hand, AIH is a chronic inflammatory disease of the liver of unknown etiology with a female-to-male ratio of 4:1 [5]. Diagnosis is based on elevated IgG, specific autoantibodies, and characteristic histology without viral hepatitis. Patients may present with nausea, anorexia, abdominal discomfort, and jaundice and sometimes with acute fulminant hepatic failure [6]. Arthralgia is a common feature in both SLE and AIH. Treatment consists of the administration of corticosteroids and immunosuppressants or immunomodulators.

Case report: A 36-year-old pleasant housewife from rural Bangladesh, not known to have hypertension, diabetes mellitus, and bronchial asthma, presented to us with progressive yellowish coloration of urine, sclera for one month, and generalized itching for 20 days. On query, she admitted to having polyarthralgia. Still, she denied any fever, abdominal pain, weight loss, abdominal lump, oral ulcer, photosensitivity, rash, any prior abortion, red or dry eye, diarrhea, proximal muscle pain or weakness, dysphagia, or any history suggestive of Raynaud's phenomenon. Her menstrual history was also non-contributory. She had neither any sexual promiscuity nor any history of tuberculosis or any contact with the patient with active tuberculosis. On examination, she was ill-looking, febrile (temperature 100^0 F), and had stable vitals. She was icteric but not anemic. There were scratch marks all over her body. There were no enlarged cervical nodes. On abdominal examination, there was no organomegaly, and GB was not palpable. There was no evidence of ascites. Other systemic examinations were non-contributory. On investigation hemoglobin was normal with 13.2 gm%, ESR 90 mm in 1st hour, TC-2100/cmm (N38%, L-54%), TPC-90000/cmm, CRP. 18.5mg/dl, PBF- leucopenia and thrombocytopenia. Urine routine examination revealed proteinuria (++), RBC- 15-20/HPF (non-menstruating), granular cast 8-10/HPF. But there were no RBC or tubular casts: s albumin 31gm/L, UTP- 1.01 gm/day, s. bilirubin 10.68 mg/dl, ALT- 104 U/L, ALP- 768 IU/L (normal 45-170 IU/L), S. ferritin 4035 ng/L. RFT, RBS, CPK, IgG, DCT, Blood C/S, and Urine C/S all were noncontributory.PT was raised (patient 20.2 sec control 11 secs). On immunological test, ANA was moderately positive in a coarse speckled pattern; Anti ds DNA was positive in high titer (171.3 IU/L, normal 0-10 IU/L). RA factor and Anti CCP all came negative.C4 was low at 0.15 g/l. CXRP/A, Echocardiography, X-ray of both hands, USG of the whole abdomen, and MRCP revealed no evidence of biliary obstruction. Serological investigations for HBV and HCV were negative, and VDRL was non-reactive. AMA, ASMA (Anti smooth muscle antibody), anti-LKM (liver kidney microsomal antibody), Anti SLA (soluble liver antigen), and p-ANCA were negative. As there was still strong clinical suspicion of SLE, an ENA profile was done, and anti-Sm and Po (RPP)60 or anti-ribosomal P antibody came positive. She started treatment with prednisolone 1mg/kg/day along with azathioprine (initially 50 mg od later 50 mg bd) along with ursodeoxycholic acid and transfusion of 6 units FFP. After three weeks, on OPD follow-up, tapering of systemic steroids was started. She was explained about the course of the disease, treatment options, recognition of flares, and pregnancy outcomes. Finally, reassurance was given. During follow-up, her Hb%-13.1gm/L, Total count was 5200/cmm (PMN-68%, L- 30%), ESR- 34mm in 1^{st} hr, TPC -192000/cmm, CRP-4.92 mg/dl, Urine R/E- no protein, no casts, no RBC, no WBC, S. Ferritin-243 ng/ml. Serum bilirubin was 2.36 gm/dl, ALP 216 IU/L, ALT 32 U/L. After three months, the steroid was withdrawn, and azathioprine was continued. Anti-dS DNA came back negative. Now, she is on regular OPD follow-up and doing well.

Discussion: Systemic lupus erythematosus is an immunologically mediated disease characterized by flares and remissions. Liver involvement in SLE is expected, but the prevalence of lupus hepatitis is instead a wide range. Prevalence of lupus hepatitis is more common in active disease than inactive SLE (11.8 vs

3.2%) [1]. The absence of viral hepatitis, NAFLD, and the use of hepatotoxic drugs raised the possibility of a diagnosis of lupus hepatitis in this patient[3]. In SLE patients' abnormalities in liver function tests are found in almost 60% of patients, in contrast with the findings in the general population (1–4%) [7].

On physical examination, the most common findings are hepatomegaly in 12–55%, splenomegaly in 20–30%, ascites in 5–10%, and jaundice in 1–4% of patients [8,9]. In general, LFT abnormalities are mild and transient. Significant elevations are uncommon (<10%), and these usually tend to improve after effective therapy for SLE is initiated [10]. These LFT abnormalities can have three different patterns – hepatocellular, cholestatic, or mixed – which can guide the cause of liver injury. The 'R formula' (R = (ALT value/ALT upper limit of normal (ULN))/ (Alk Phos value/Alk Phos ULN)) can be calculated and allows the cause of liver injury to be orientated, with a R of <2 for cholestatic injury, a R >5 for hepatocellular pattern and a R between 2 and 5 for a mixed pattern. The most common pattern of abnormal LFTs in patients with SLE is the hepatocellular pattern, although cholestatic and mixed patterns also could be present. Ascites is rarely related to liver involvement or portal hypertension, and sometimes, it is challenging to elucidate the etiology. Lastly, the most feared and extraordinary complication is hepatic rupture, generally a consequence of arteritis, with very few reported cases. [11,12].

It is of utmost importance to consider that chronic liver disease (active chronic hepatitis and cirrhosis) is rare and only present in about 4–5% of SLE patients and is usually related to secondary causes of hepatic involvement [10,13,14]. There are also only a few case reports of fulminant hepatic failure due to secondary causes. Multiple SLE studies suggest that hepatic affection is not a significant cause of morbidity or mortality [15]. Despite the above, the latest SLE classification criteria published in 2019 by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) do not consider hepatic involvement relevant to establishing the diagnosis. Neither of the measurement tools includes any liver criteria to evaluate disease activity, probably due to the rarity of primary hepatic involvement and the benign, transient course of these abnormalities [16,17].

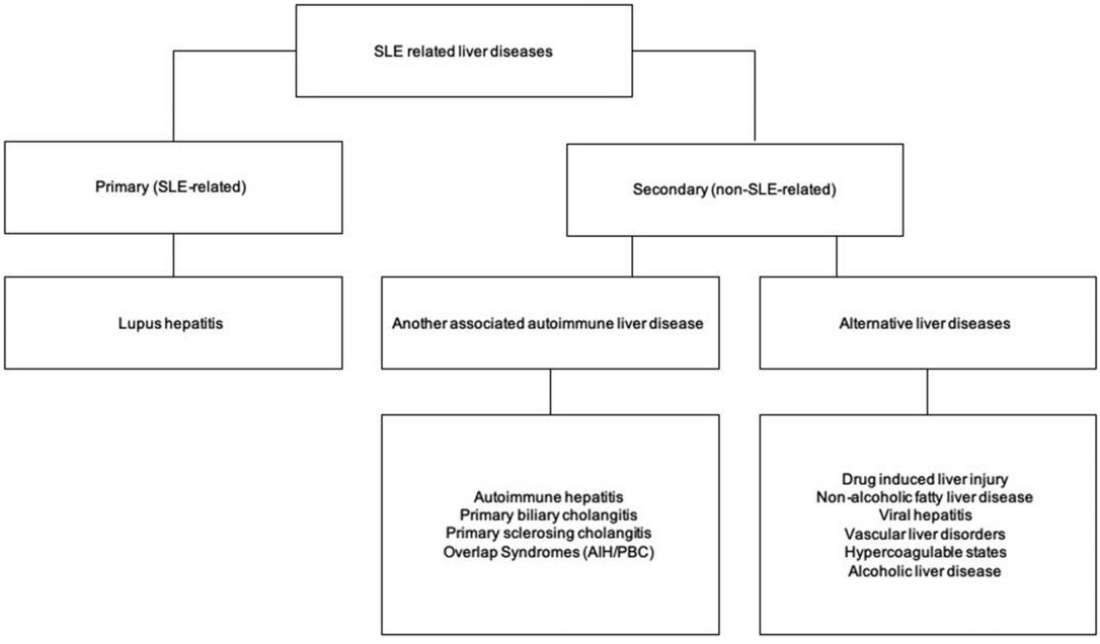

Fig 1. Liver diseases in patients with SLE.

SLE: systemic lupus erythematosus; AIH: autoimmune hepatitis; PBC: primary biliary cholangitis.

However, hepatic dysfunction frequently affects patients with SLE as a primary component of their disease known as 'lupus hepatitis,' another AILD (lupoid hepatitis or autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC)) or alternative liver disease (drug-induced liver injury (DILI), NAFLD, viral hepatitis, alcoholic liver disease, and vascular disorders). Thus, hepatic involvement in SLE can be classified as primary (SLE-related) and secondary (non-SLE-related). SLE-related hepatic abnormalities are usually synchronous with disease activity. Therefore, it is always necessary to rule out secondary causes before considering them primary. Figure 1 shows the most frequent liver diseases related to patients with SLE.

Finally, patients with SLE may have vascular diseases of the liver as they may be susceptible to developing thrombosis, as happens in antiphospholipid syndrome. Some examples include portal thrombosis, Budd-Chiari syndrome (obstruction of the suprahepatic veins or inferior vena cava), and hepatic artery thrombosis. SLE is associated with a higher prevalence of positive antiphospholipid antibodies, causing or not a thrombotic disease. They are usually related to SLE activity.

Lupus hepatitis: Even though the role of SLE in triggering an asymptomatic hepatopathy is controversial, numerous experts have recognized an often-subclinical liver dysfunction caused by SLE, which is called lupus hepatitis [18]. Lupus hepatitis is a non-specific reactive liver disease, mainly due to organic damage caused by complement deposition and the presence of vasculitis in the liver. [19,20,21] Studies have described vasculitis in liver samples. However, histological findings of the liver in patients with lupus vary, and the exact damage mechanisms remain unclear [22,23]. Lupus hepatitis is characterized by asymptomatic hypertransaminasaemia, frequently associated with SLE flares or clinical activity. Anti-ribosomal P antibodies in serum are frequent, and histopathological findings are usually lobular or periportal [24] inflammation with few lymphoid infiltrates. It can only be diagnosed by ruling out secondary causes of liver involvement and differentiating it from AIH can be difficult. A liver biopsy may be required. In a recent study, lupus hepatitis was the second most important cause of LFT abnormalities, proven by biopsy in patients with lupus. Almost all patients were treated with corticosteroids in that series, and their LFTs improved [25].

It is also essential to highlight the difference between lupus and lupoid hepatitis. The former refers to liver dysfunction associated with SLE, and the latter is a term used in the 1950s to define what is now known as AIH [24,26]. These are two immune-mediated conditions that have similar clinical manifestations and laboratory findings, leading to difficulties in diagnosis. Lupus hepatitis is commonly associated with SLE flare, usually asymptomatic or related to mild symptoms. The laboratory can show hypertransaminasemia, bilirubin increment, and other features like anti-ribosomal P antibody positivity [27]. In histopathology, mild portal infiltration with lymphocytes, neutrophils, and plasma cells, hydropic degeneration, steatosis, mild cholestasis, focal necrosis, and nodular cirrhosis [18]. It is an exclusion diagnosis that forces to rule out other primary causes and secondary hepatic disorders [16,17]. AIH is a challenging differential diagnosis, requiring liver biopsy in most cases. This entity presents some typical features in the histopathology, evidencing lobular or periportal infiltrates, interface hepatitis, lymphoplasmacytic infiltrates, and portal mononuclear infiltrates that invade the limiting plate, causing fragmentary periportal necrosis periportal and rosettes formation. Suppose the disease progresses, bridging necrosis, panlobular or multilobular necrosis, and finally, cirrhosis can be observed. Bile ducts may also be affected, causing ductopenia and destructive and non-destructive cholangitis [12]. Along with lupus hepatitis, they can both present with arthralgias, hypergammaglobulinemia, and aminotransferases increment. The absence of viral hepatitis, NAFLD, and the use of hepatotoxic drugs raised the possibility of a diagnosis of lupus hepatitis in this patient. According to Simplified diagnostic criteria for the diagnosis of AIH, the score of this patient is only 3 (positive ANA +1 and the absence of viral hepatitis +2). According to serology, AIH is further subdivided into two types: type 1 is positive for anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (ASMA) or anti-soluble liver antigen (SLA). At the same time, AIH-type 2 is positive for anti-liver kidney microsomal antibody type 1 (anti-LKM1) and/or anti-liver cytosol type 1 (anti-LC1) [28]. ANA and ASMA can also be positive in SLE

[3]. The more specific anti-LKM-1 for AIH was negative, and anti-URNP, which is more specific for SLE, was positive here. The similar clinical and biochemical features of lupus hepatitis and AIH make these conditions difficult to differentiate; however, their treatment and prognosis differ(3). AIH has more aggressive histological features and a poor prognosis than lupus hepatitis. Untreated AIH has poor outcomes, with a 5-year survival rate of 50% [29].

In this subject, doing the most essential liver biopsy was impossible due to financial constraints. High-dose prednisolone (1-2mg/kg daily) and azathioprine are the mainstay of treatment of AIH [30]. About 85% of patients required azathioprine as a steroid-sparing agent [31]. The treatment of SLE is individualized and depends on organ involvement, disease activity, disease severity, and previous response to treatment [32]. This patient responded well to oral prednisolone and azathioprine. Severe cholestasis is rare in both conditions, though well managed here with ursodeoxycholic acid.

Conclusion: Altered liver function is widespread in patients with SLE. In general, these are mild, transient, and asymptomatic, and due to other pathologies not related to SLE but cholestatic lupus hepatitis itself as an initial manifestation of the underlying disease is considered rare and can sometimes evolve into a more aggressive form, presenting itself as a diagnostic challenge for the treating physicians. It generally responds to treatment with glucocorticoids. Regarding the diverse clinical manifestations of liver disease in SLE, clinicians should be aware of assessing these patients with a complete clinical evaluation to be able to differentiate lupus hepatitis from secondary causes since a differential diagnosis is sometimes difficult, and this will allow them to provide the appropriate treatment. A liver biopsy is sometimes the last resort as a diagnostic method and should be performed if suspected. We hope the information in this review will help understand liver involvement in patients with SLE and provide physicians with a simple tool to facilitate the diagnostic and therapeutic approaches to these diseases.

Footnotes.

Ahmed Agrodey (professor of gastroenterology, hepatology, and infectious diseases) and Sara Salem (lecturer of internal medicine) were the peer reviewers.

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Ethical approval: All procedures involving human participants followed the institutional and national research committee's moral standards, the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards. All authors declare that consent was obtained from the patient (or other approved parties) to publish this study.

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Authors' contributions

Richmond R Gomes and Rebeka Razzaque formulated the research concept, while Richmond R Gomes and Rebeka Razzaque conducted the clinical examinations and monitored the patients. Richmond R Gomes and Rebeka Razzaque collaborated to gather the necessary laboratory data. All authors actively participated in analyzing and interpreting the patient information and composing the manuscript. All authors thoroughly reviewed and approved the final version of the manuscript.

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