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Case Report

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

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1. Abstract

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease with a wide variety of clinical manifestations. However, hepatic dysfunction is not included in the diagnostic criteria for the disease and has not been recognized properly. Abnormal liver tests are common (60%) in some point of 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 rather are mostly drug related. In rare cases, severe cholestasis may invite diagnostic dilemma. 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-years old Bangladeshi woman. The cholestatic hepatitis progressed as part of the lupus activity and responded to steroid therapy.

2. Introduction

SLE is a heterogeneous, multifaceted disorder of autoimmune aetiology with various organ involvement including musculoskeletal, kidney, cardiovascular system, hematological system and central nervous system [1]. It is associated with production of auto antibodies and diverse clinical features. It is most common in female 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 rare as a part of its disease activity. Non immune hepatopathy e.g. hepatotoxic drugs, coincident viral hepatitis and non-alcoholic fatty liver disease are some common possibilities of abnormal liver function test in SLE. But rarely lupus hepatitis or overlap syndrome of autoimmune hepatitis (AIH) may complicate this disease [3]. One study reported 9.3% incidence of lupus hepatitis[1]. However, the prevalence is widely variable 3-23% [4]. On the other hand, AIH is a chronic inflammatory disease of the liver of unknown etiology with female to male ratio 4:1 [5]. Diagnosis based on elevated IgG, specific auto antibodies, characteristic histology in absence of 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 non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and immunosuppressants or immunomodulators.

3. Case Report

A 36 years old pleasant house wife from rural Bangladesh, not known to have hypertension, diabetes mellitus, bronchial asthma presented to us with progressive yellowish coloration of urine, sclera for 1 month and generalized itching for 20 days. On query, she admitted to have polyarthralgia but she denied any fever, abdominal pain, weight loss, abdominal lump, oral ulcer, photosensitivity, rash, any prior abortion, red or dry eye, diarrhoea, proximal muscle pain or weakness, dysphagia or any history suggestive of raynauds phenomenon. Her menstrual history was also noncontributory. She had neither any sexual promiscuity nor had any history of tuberculosis

or any contact with the patient with active tuberculosis. On examination she was ill looking, febrile, (temperature 100^0 F) with 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 were no organomegaly, 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 R/E revealed; proteinuria (++), RBC- 15-20/HPF (non menstruating), granular cast 8-10/HPF. But there were no RBC or tubular cast. 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, Urine C/S all were noncontributory.PT was raised(patient 20.2 sec control 11 secs). On immunological test, ANA was moderately positive in coarse speckled pattern, Anti ds DNA was positive in high titer(171.3 IU/L,normal 0-10 IU/L). RA factor, Anti CCP all came negative.C4 was low 0.15 g/l. CXRP/A, Echocardiography, X-ray of both hands, USG of W/A and MRCP revealed no evidence of biliary obstruction. Serological investigations for HBV and HCV were negative, VDRL non-reactive. AMA, ASMA (Anti smooth muscle antibody), Anti-LKM(liver kidney microsomal antibody), Anti SLA(soluble liver antigen), p-ANCA were negative. As there was still strong clinical suspicion of SLE, ENA profile was done and anti Sm and Po (RPP)60 or anti-ribosomal P antibody came positive. She was 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 unit FFP. After three weeks, on OPD follow up, tapering of systemic steroid was started. She was explained about the course of the disease, treatment options, recognition of flares, and pregnancy outcome. Last but not the least, reassurance was given. During follow up her Hb%-13.1gm/L, Total count 5200/cmm(PMN-68%,L- 30%),ESR- 34mm in 1st 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 3 months steroid was withdrawn, azathioprine was continued. Anti-dS DNA came negative. Now she is on regular OPD follow up and doing well.

4. Discussion

Systemic lupus erythematosus is an immunologically mediated disease characterized by flares and remissions. Liver involvement in SLE is common but the prevalence of lupus hepatitis is rather a wide range. Prevalence of lupus hepatitis is more common in active disease than inactive SLE (11.8 vs 3.2%)[1]. Absence of viral hepatitis, NAFLD and use of hepatotoxic drugs raised the possibility of 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 difficult to elucidate the aetiology. 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 studies of mortality in SLE agree that hepatic affection is not an important cause of morbidity or mortality [15]. Despite all of 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 establish the diagnosis, and neither of the measurement tools include 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]. 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 an 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 it as 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 develop thrombosis as it happens in antiphospholipid syndrome. Portal thrombosis, Budd-Chiari syndrome (obstruction of the suprahepatic veins or inferior vena cava) and hepatic artery thrombosis are some examples. SLE is associated with a higher prevalence of positive antiphospholipid antibodies, causing or not thrombotic disease. They are usually related to SLE activity.

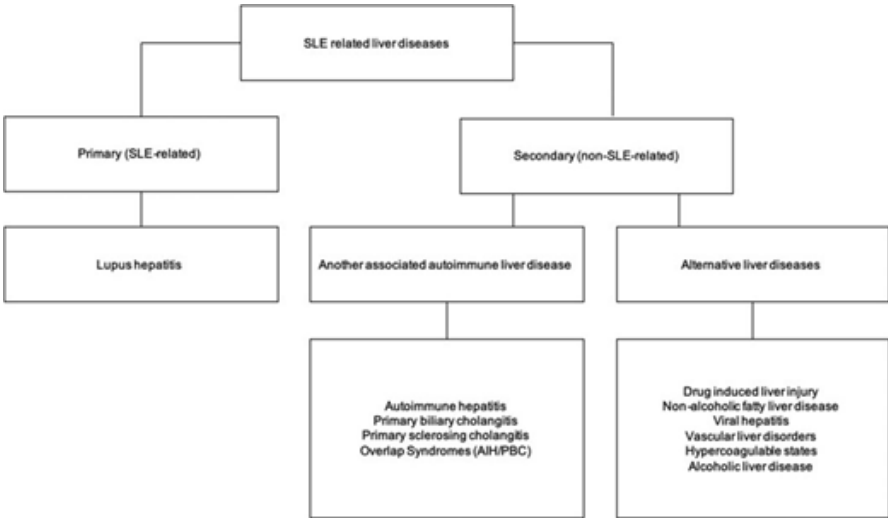

Figure 1: Liver diseases in patients with SLE.

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

5. Lupus Hepatitis

Even though the role of SLE in triggering an asymptomatic hepatopathy is controversial, there are numerous experts who 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. The presence of antiribosomal P antibodies in serum is 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. In that series, almost all patients were treated with corticosteroids and improved their LFTs [25]. It is also important to highlight the difference between lupus hepatitis 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 some other features like anti-ribosomal P antibody positivity [27]. In the histopathology it can be observed 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 and lymphoplasmacytic infiltrates, portal mononuclear infiltrates that invade the limiting plate causing fragmentary periportal necrosis periportal and rosettes formation. If the disease progress, bridging necrosis, panlobular or multilobular necrosis and finally cirrhosis can be observed. Bile ducts may also be affected, causing ductopenia, destructive and non-destructive cholangitis.12 Along with lupus hepatitis, they can both present with arthralgias, hypergammaglobulinemia and aminotransferases increment. Absence of viral hepatitis, NAFLD and use of hepatotoxic drugs raised the possibility of diagnosis of lupus hepatitis in this patient According to Simplified diagnostic criteria for the diagnosis of AIH, score of this patient is only 3 (positive ANA +1 and absence of viral hepatitis +2) . According to serology, AIH is further subdivided into 2 types: type 1 positive for anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (ASMA) or anti-soluble liver antigen (SLA), while 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 both also can 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 outcome with 5 years survival rate is 50% [29]. In this subject, it was not possible to do the most important liver biopsy due to financial constrain. High dose prednisolone (1-2mg/kg daily) and azathioprine is the mainstay of treatment of AIH [30]. About 85% 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 of treatment [32] This patient was responding well with oral prednisolone and azathioprine. Severe cholestasis is rare in the both conditions though well managed here with ursodeoxycholic acid.

6. Conclusion

Altered liver function is very common in patients with SLE. In general, these are mild, transient and asymptomatic and due to other pathologies not related to SLE (NAFLD, DILI, AIH, PBC, PSC, viral hepatitis, vascular liver disorders, hypercoagulable states and alcoholic liver disease) 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 (medical history, blood test, imaging studies and/or liver biopsy) 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. Liver biopsy is in some cases the last resort as a diagnostic method, and should be performed if suspected. Progression to advanced chronic liver disease is unusual and occurs in most cases when another liver disease coexists. We hope that the information in this review will help in the understanding of liver involvement in patients with SLE, as well as providing physicians with a simple tool to facilitate the diagnostic and therapeutic approaches to these diseases.

7. Conflict of Interest

None declared

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