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# Liver Involvement During Flare-ups in Pediatric SLE: Lupus Hepatitis vs. Other Causes

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**Abstract**

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by production of autoantibodies that can affect multiorgan of the body, including the liver. Liver dysfunction is not part of the SLE classification criteria and rarely found compared to other organs. In patient with SLE with liver involvement signed by abnormal liver enzyme should consider whether it is SLE-associated hepatitis, known as lupus hepatitis, or cause by other entities such as drug-induced hepatitis, or a primary liver disease such as viral hepatitis and autoimmune hepatitis condition that coexisting with SLE. We are reporting a 13-year-old boy that has been diagnosed with SLE who had flare since he discontinued his medication by himself. He presented with jaundice, alopecia, oral ulcers, pale and malaise. Laboratory examination showed anemia, thrombocytopenia, elevated transaminases and bilirubin level. It is important to differentiate the cause of deranged liver function test in patient with SLE, because other entities may present similar to lupus hepatitis, but they have a different management and prognosis.



## 1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that involves many organs marked by circulating autoantibodies directed against self-antigens. It has a wide range of clinical manifestations and often mimics other diseases [1, 2]. It can be affect any organ of the body, including the liver. Liver involvement as one of the organs affected in SLE is not part of the American College of Rheumatology (ACR), Systemic Lupus International Collaborating Clinics (SLICC) or European League Against Rheumatism/ European League Against Rheumatism (EULAR/ACR) classification criteria and is a relatively rare case [1].

Childhood-onset SLE (cSLE) is a rare disease that represents approximately 20% of all SLE cases. It is often reported with higher disease severity, morbidity and mortality than adult-onset disease. Childhood-onset SLE has an incidence rate of 0.3-0.9 per 100,000 children and a prevalence rate of 1-6 per 100,000 population [2, 3].

SLE-associated hepatitis, or commonly known as lupus hepatitis, is a rare manifestation of SLE that involve liver dysfunction which is well documented, but considering rare that occurs in approximately 3-8% of SLE patients and is generally marked by mild elevated liver enzymes, but it can also occur in more severe degrees [1, 4]. A retrospective study by Zhang et al. in China at 2013 showed that from 504 SLE patients, approximately 47 patients (9.3%) had lupus hepatitis and the prevalence of

lupus hepatitis events with active phases SLE was higher than those with inactive phases SLE (11.8% vs 3.2%, p<0.05) [5]. Around 50% of patients with SLE report having liver dysfunction at some point in their life, which may be correlated to SLE disease itself and its treatment, or it may be a primary liver disease such as viral hepatitis and autoimmune hepatitis (AIH) condition that coexists with SLE [1, 4].

Although there is some severity of liver involvement in SLE, few cases of SLE and AIH have been reported concurrently. There has been some debate previously about whether lupus hepatitis is a separate entity from liver dysfunction in AIH, however, increasing evidence suggests that these two diagnoses are two conditions that actually have distinct etiologies and has a very different potentials results if proper treatment is not carried out, especially in the case of AIH. Lupus hepatitis and AIH are two immunological conditions that cause hepatic dysfunction that can have similar clinical manifestations, laboratory studies and systemic features that may leads difficulty to differ in diagnosis [5, 6]. Doctors need to be cautious of these two entities of liver disease because proper diagnosis and treatment need to be done early in the course of the disease to prevent the development of advanced liver disease. In this case report, we will present the case of children with SLE who discontinued maintenance medication by themselves and develop into flare with liver involvement.

## 2. Cases

A 13-year-old Asian boy from non-consanguineously married couple presented to the outpatient clinic with 14 days history of his whites of his eyes turn yellow, pale, malaise, hair loss and oral ulcer (Figure 1). He had neither arthralgias, chest pain, shortness of breath nor skin rashes. He has been diagnosed as SLE 1 year prior by American College of Rheumatology (ACR) criteria included arthritis, oral ulcer, hematological disorder, high ANA titer, and abnormal anti-double-stranded DNA. Liver enzyme at the time of initial SLE diagnosis showed in normal limit. He had been on multiple medications before, including hydroxychloroquine, and methylprednisolone, but as of 6 months prior to this acute presentation, he discontinued his medication by himselves. He also had no medication at all for the past 6 months. No significant past history and family history. He is developmentally appropriate for age and had been fully immunized according to national immunization schedule. On physical examination, he was noted to have alopecia, painless oral ulcer at hard palate, pale conjunctiva, scleral icterus, and mild hepatomegaly (3 cm below the costal margin). Mental status examination was normal. There was no ascites, joint redness, asterixis, or Kayser-Fleischer rings.

Laboratory examination was done included complete blood count with differential and chemistries, included liver function tests. Complete blood count showed normocytic normochromic anemia 8.1 g/dl, normal white blood cell 9340/mm, thrombocytopenia 76000/mm, and elevation in the number of reticulocytes. Peripheral smear showed normocytic normochromic anemia with spherocytes. Coombs's test showed positive. Liver function test showed elevated bilirubin level (total/direct bilirubin=6.16/4.70 mg/dl), transaminases (AST/ALT=246/331 IU/dl), alkaline phosphatase 195 IU/l and gamma GT 1742 IU/l. Albumin was 3.1 g/dl and normal coagulation profile. Anti-HAV, anti-HCV and HbsAg was negative. Urine routine showed hematuria 10-15 RBC/hpf, no proteinuria and normal renal function test. Immunological laboratory examination showed decreased level of complement (C3/C4=34/8 mg/dl) and increased anti dsDNA 701 IU/l. Laboratory examination can be seen in Table 1. SLEDAI score was 13 (high disease activity) and provisionally diagnosed to have SLE with severe flare. Abdominal ultrasound revealed non-specific hepatomegaly (Figure 1). Unfortunately, we cannot perform the liver biopsy in our hospital. We used 2008 International Autoimmune Hepatitis Group (IAIHG) diagnostic criteria of 1999 IAIHG, we only get a total score 4 (ANA > 1/80 and absence of viral hepatitis) without liver biopsy and IgG examination due to limitation in our hospital facilities.

We started on high dose intravenous methylprednisolone 10-30 mg/kg/daily for 3 consecutive days. At the fourth day, we started oral prednisone 1 mg/kg/day for 6 weeks (given on the day the patient does not get the high dose intravenous methylprednisolone) and planned for tapering it down until the lowest doses (≤7.5 mg/day) that sufficient to obtain good disease control. The patient was also started on hydroxychloroquine and an adjunctive mycophenolic acid for its steroid sparing effect. Hydroxychloroquine is given at dose 5 mg/kg/day orally for the duration of their lives in the absence of retinal toxicity. Follow up after given high dose intravenous methylprednisolone 3 consecutive days for 3 series with interval 1 months for each series and 3 months after starting oral prednisone, hydroxychloroquine and mycophenolic acid, the SLE flare symptom such as icteric sclera, pale and oral ulcer was revolved. His laboratory studies for complete blood count, liver enzymes and urine routine had normalized. The patient was doing well with SLEDAI score down to 2.

**Table 1.** Laboratory examination results

| Laboratory examination | |
|---|---|
| Hemoglobin | 8,1 g/dl |
| Hematocrit | 36 % |
| Erythrocyte | 4.05 million/mm |
| Leukocyte | 9.3 K/mm$^3$ |
| Platelets | 76 K/mm$^3$ |
| Reticulocyte | 6.2 % |
| AST/ALT | 246/331 IU/dl |
| Total bilirubin | 6.16 mg/dl |
| Bilirubin direct | 4.70 mg/dl |
| Bilirubin indirect | 1.46 mg/dl |
| BUN | 12 mg/dl |
| Creatinine | 0.43 mg/dl |
| Alkaline phosphatase | 195 IU/l |
| GGTP | 1742 IU/l |
| Albumin | 3.1 g/dl |
| HbsAg | Negative |
| Anti HAV IgM | Negative |
| Anti HCV IgM | Negative |
| C3 | 34 mg/dl |
| C4 | 8 mg/dl |
| ANA | 1:640 |
| Anti ds DNA | 701IU/l |
| Coombs test | 3+ |
| Urinalysis | 10-15 RBC/hpf<br>Leukocyte negative<br>Protein negative<br>Ketones negative |

ANA, antinuclear antibody; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; dsDNA, double-stranded DNA; GGTP, gamma-glutamyl transpeptidase; HbsAg, Hepatitis B surface antigen; Anti HAV IgM, Anti Hepatitis A Virus IgM; Anti HCV IgM, Anti Hepatitis C Virus IgM.

## 3. Discussions

Systemic lupus erythematosus is an autoimmune disease with production of autoantibodies reactive with nuclear, cytoplasm and cell membrane, characterized by damage of multiorgan including the liver [5]. Liver involvement in SLE or lupus hepatitis frequently found in active SLE than in inactive SLE. It often manifests as abnormal liver enzymes and may appear in mild to severe degrees [1, 4, 7]. Liver involvement in lupus can be due to lupus disease itself (lupus hepatitis), secondary to SLE drug toxicity or it can be overlap with primary liver disease such as viral hepatitis and autoimmune hepatitis [7, 8]. All of the possibility etiologies above that can cause manifestations of liver dysfunction have a different management and prognosis, so it is necessary to differentiate it [4].

Studies of liver involvement etiology in adult SLE patients are numerous, but studies in children are still limited. Study by Chowdhary et al. at 2008 showed that from 40 adult patient SLE with liver dysfunction, 10% caused by drug-induced hepatitis, 20% caused by viral hepatitis and 15% due to autoimmune hepatitis [8].

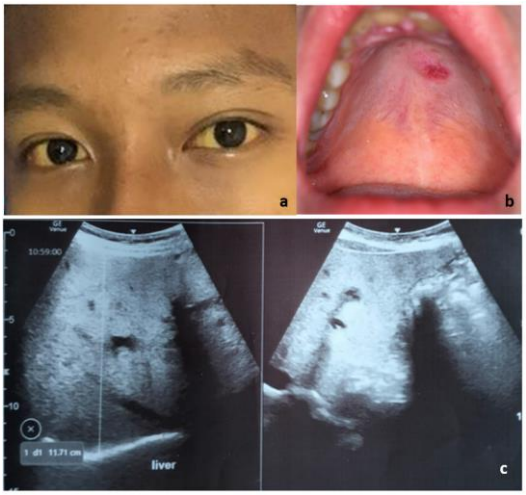


**Figure 1.** SLE-flare manifestation in this case: a) icteric sclera; b) oral ulcer; c) hepatobiliary ultrasound showed non-specific hepatomegaly.

In a retrospective Korean study by Lacroix et al. showed that 46 (32.6%) out of 141 SLE patients had liver enzyme dysfunction caused by drug-induced hepatitis. Most cases are caused by nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, or steroids [1]. Millian et al. studied 46 patients with autoimmune hepatitis; 16 patients (34.8%) were diagnosed concurrently with autoimmune connective tissue disease, including 6 patients with SLE [9]. Lupus hepatitis itself has a wide varies of prevalence in adult SLE patient, from 3 to 23%. In one study of lupus hepatitis by Miller et al. showed that 8% of the 260 patients were diagnosed as cases of lupus hepatitis, while a retrospective analysis study by Arnett et al. showed that 4 from 131 patients (3%) had lupus hepatitis [7]. Little is known about the cause of liver dysfunction in children with SLE. Study by Mariniello et al. showed that liver involvement was noted in 6 from 32 patients (18.75%) in children with SLE [10]. While in larger study evaluated the prevalence and type of liver involvement in 138 children with SLE patients in Iran, there were 48.5% of the patients had an increase of liver enzymes [11]. In one study by Irving et al. showed that the prevalence of autoimmune hepatitis was 9.8% (9 of 92 patients) in the children with SLE. All of the patients in that study developed autoimmune hepatitis prior to SLE [12]. One case report by Sarda et al. showed that their patient had been diagnosed of SLE around 1 year prior to their current diagnosis of autoimmune hepatitis [4].

Clinically, children SLE with liver involvement may show a clinical symptom such as fatigue, nausea, malaise, and anorexia. Icteric, hepatomegaly, and splenomegaly may be present in physical examination. These manifestations appear in almost all etiologies that cause liver involvement in children with SLE [1]. Laboratory examination may show elevated liver enzymes such as

alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and bilirubin. In most cases, lupus hepatitis had only mild elevation liver enzyme (<10 times) [7]. Study by Tahernia et al. showed that 48.5% from 138 children with SLE had an increase of AST 8.7%, ALT 5% and 34.7% abnormal both AST and ALT. It categorized on the base of their levels <100 U/mL (23.1%), 100-1000 U/mL (23.1%), and >1000 U/mL (2.1%) [11]. In this case report, our patient showed mild elevation liver enzymes less than 10 times upper limit of normal. Study by Chowdhary et al. reveal that there were no differences in mean bilirubin, AST, ALT, and ALP levels in SLE patient with liver involvement due to drug-induce hepatitis, autoimmune hepatitis, viral hepatitis and other miscellaneous causes [8]. These results indicate that liver enzyme examination cannot be used as an indicator to determine the etiology of liver abnormalities in SLE patients.

Drug-induced hepatitis is reported around 2.3% of SLE patients according to study by Huang et al. in 2012 [13]. The most common drug that cause drug-induced hepatitis in patient with SLE are NSAID, azathioprine and methotrexate. Patients with SLE are more likely to experience NSAID-induced hepatitis than healthy people due to elevated levels of oxidative stress [6]. Since our patient in this case had been discontinued all of his SLE medication for the last 6 months and he did not consume any other drug, so we can rule out drug-induced hepatitis in this case. Also, the liver involvement cause by viral hepatitis could also be ruled out in this case due to the results of the viral hepatitis serological examination were showed negative.

On the other hand, autoimmune hepatitis is generally marked by hypergammaglobulinemia with elevated IgG, positive antinuclear antibody (ANA) with anti-smooth muscle antibody (ASMA), anti-liver–kidney microsomal antibody-1 (anti-LKM-1) and histological features being the most specific finding [1]. The diagnostic criteria for autoimmune hepatitis were made by IAIHG in 1993 and were revised in 2010, uses scoring system based on biochemical, serologic, and histological findings. However, patients with lupus can also have a high score using the IAIHG diagnostic criteria, but the histological features may not support the diagnosis. Accordingly, the assessment of AIH using these criteria may be inaccurate in patient with SLE. It is indicating that liver biopsy is very important in differentiating liver involvement due to lupus hepatitis or autoimmune hepatitis. Histological feature in lupus hepatitis commonly shows lobular or periportal infiltrates with few lymphoid cells. While in AIH often showed portal mononuclear infiltrates that invade the limiting plate, into the surrounding lobule that may cause periportal piecemeal necrosis, and form rosettes of hepatocytes [6]. Generally, treatment in SLE and autoimmune hepatitis is much alike, but AIH has more aggressive histology findings than lupus hepatitis, and it leads to more severe liver dysfunction to end stage liver disease while SLE more often leads to end stage renal disease. Lupus hepatitis and autoimmune hepatitis may have overlap response rapidly to corticosteroid therapy, but generally liver dysfunction improves in parallel with other systemic manifestations of SLE in patients with SLE, as seen in this case [6]. Unfortunately, our patient in this case cannot undergo a liver biopsy and other immunological examination due to lack of facilities in our hospital to determined autoimmune hepatitis diagnosis. We are more inclined to the diagnosis of lupus hepatitis because the improvement in liver function parallels with the clinical improvement of other forms of SLE after treatment.

Management of SLE patients generally consists of administration of corticosteroids and immunosuppressive depending on the degree of disease activity. Glucocorticoids can be given as oral or intravenous high-dose methylprednisolone. Hydroxychloroquine is an antimalarial agent that can inhibit Toll-like receptor pathways to minimizes flares and reduces the rate of autoantibody production which is given to almost all patients with adult or pediatric SLE. Other immunosuppressive such as mycophenolate mofetil, cyclophosphamide, azathioprine, and rituximab generally given to severe activity SLE disease such as lupus nephritis, neuropsychiatric SLE or in conditions when steroid-sparing agent are needed to help minimize side effects of steroid long-term used (such as weight gain, osteoporosis, infection risk, cataract, glaucoma, increased blood sugar and blood pressure), to controlled the disease [14].

## 4. Conclusions

Liver dysfunction in patient with SLE may present a complicated and difficult differential diagnosis since it has a resemble clinical, laboratory, and systemic manifestation that causing difficulty in establishing the diagnosis. Physicians need to be careful and aware of other entities causes of liver involvement in patient with SLE because it has a different management and prognosis. In this case, the liver involvement may be cause by lupus hepatitis since liver dysfunction improves in parallel with other systemic manifestations of SLE after given corticosteroid, hydroxychloroquine and mycophenolic acid.

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