SYSTEMIC LUPUS ERYTHEMATOSUS ASSOCIATED WITH CHOLESTATIC HEPATITIS IN A CHILD. A CASE REPORT

Zahrah Hikmah, Ariyanto Harsono

ABSTRACT

Systemic Lupus Erythematosus is an autoimmune disease with the prevalence in children approximately 1 per 100,000. The clinical manifestations are divers, and hepatic involvement is very rare. The patient was a 12 years old girl, admitted to the hospital with the main complaint of prolonged fever and jaundice. Physical and laboratory examinations found 6 criteria of American Rheumatism Association for SLE, justify the diagnosis of SLE. Liver function tests yielded: direct bilirubin 5.36 and total bilirubin 6.82; ALT 565 IU/L and AST 77 IU/L. Viral hepatitis markers were negative. Histopathology examination of liver tissue revealed perportal lymphocytic infiltration, ballooning degeneration, disarray of porta hepatica, and intra-cytoplasmic bilirubin. Prednison induction was given with a dosage 2 mg/kg/day for 30 days. Theoretically combination with azathioprine may give best result, but in this case prednisone alone resulted a good response after 1 week, and consideration of hepatotoxic effect of azathioprine, so azathioprine was cancelled. The results of treatment was good, the patient was discharged from the hospital uneventfully. There is still possibility of relapse.

Keywords: Systemic Lupus Erythematosus, cholestasis, hepatitis

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with many manifestations. (Brogan, 2005; Greenspun, 2004). The etiology of SLE is not known. It can occur at all ages, but is more common in young women. Immune complexes can be deposited in glomeruli, skin, lungs, synovium, mesothelium, and other places. Many SLE patients develop renal complications (Greenspun, 2004; Wallace, 2002). But Liver disease is not one of the common manifestations of SLE. In classical descriptions of SLE, it is stated that clinically important liver disease is infrequent (Hellequa, 2002).

In 1955, Joske first reported the association of the lupus erythematosus (LE) cell phenomenon in active chronic viral hepatitis. This association led to the introduction of the term lupoid hepatitis by Mackay and associates in 1956 (Greenspun, 2004; Hellequa, 2002). The disease may affect as many as 1 in 1000 young women. The prevalence in children and older adults is approximately 1 per 100,000, with a ratio of female to male patients of 3:1 (Greenspun, 2004). Hepatomegaly occurs in 10% to 31% of patients with SLE, jaundice is present in 1% to 4% of patients. Elevated liver enzyme levels are found in 30% to 60% of patients with SLE at sometime. Most are caused by infections, salicylates, or NSAIDs. Hepatic manifestation is uncommon in SLE (Hallequa, 2002; Klein, 2003; Chow, 1997). The purpose of this paper is to report a hepatic manifestation in a child with SLE, focusing on diagnosis and management.

CASE REPORT

I, a 12-year-old girl came to the emergency department of Dr. Soetomo Hospital on December 7th 2004 with the main complaint of fever and icteric skin and eyes. The fever was begun since 2 months ago accompanied with icteric eyes. She suffered from skin rashes, stomatitis, bone and joint pain. She also had nausea, and fallen hair, weak and malaise. She lost her appetite and lost weight 14 kg. No history of chronic bleeding, fullness and enlargement of the abdomen. The urine was tea like color but the stool was normal. No history of liver disease or prolonged medication. No history of family disease. She was hospitalized twice in different hospital with the same complaint before admission.

The physical examination on admission revealed a weak girl with the body weight of 31 kilograms and body height was 146 centimeters. Body temperature was 39.5°C, respiratory rate was 32 times per minute, the pulse rate was 140 beats per minute and blood pressure was 110/30 mmHg. She looked pale and icteric but no dyspneic and cyanotic. There were malar rash, oral ulcers and alopecia. The chest moved symmetrically and retractions were not found. The heart and lung was

Department of Child Health
Airlangga University School of Medicine
Dr Soetomo Teaching Hospital, Surabaya
On 6th day of hospitalization, the body temperature was 40°C, respiratory rate was 32 times per minute, the pulse rate was 138 beats per minute and blood pressure was 90/60 mmHg. The skin rashes were getting worse, and there were four bullous were develop (contain of pus) in the skin of the both of the leg. Hemoglobin level was 8.6 g/dl, Platelets count was sufficient, White cell count was 3,500/cmm, Blood Urea Nitrogen was 10 mg/dl, creatinine was 0.6 mg/dl. Urine examination showed; protein was trace, bilirubin and urobilin was positive, erythrocyte 1-2, leukocyte was 6 -8. The working diagnosis was suspicion of urinary tracts infection. The initial treatment of lupus hepatitis was prednisone 2mg/kg body weight/daily divided into three dosages for 4 weeks.

On 9th day of hospitalization, Hemoglobin level was 7.2 g/dl. Transfusion of washed erythrocyte 300 ml/day for two days was performed.

On 15th day of hospitalization, the patient got dysuria. The body temperature was 38°C, respiratory rate was 32 times per minute, the pulse rate was 120 beats per minute and blood pressure was 100/60 mmHg. The malar rash and skin rashes gradually subsided. The liver got smaller: Hemoglobin level was 13.2 g/dl, Platelets was sufficient, White cell count was 10,500/cmm, Blood Urea Nitrogen was 17 mg/dl, creatinine was 1.0 mg/dl, ALT was 46 IU, AST was 46 IU, Albumin was 3.16mg/dl, total bilirubin was 6.60 mg/dl, direct bilirubin was 5.74 mg/dl. Urine examination showed; protein was trace, bilirubin and urobilin was positive, erythrocyte 1-2, leukocyte was 10 -12.

On 20th day of hospitalization, the urine culture was positive E. Coli pathogen > 10^7/high power field. The result of sensitivity test showed the germ was sensitive to meropenem and amikacin. According to sensitivity test, the patient was treated with Amikacin 225 mg intramuscularly, 2 times daily for 10 days.

On 28th day of hospitalization, the condition of the patient was getting better, the appetite was better, and her weight was increased. The vital sign was normal. No icteric. The malar rash and skin rashes subsided, the liver was just palpable: Hemoglobin level was 11,2 g/dl, Platelets count was sufficient, White cell count was 7,600/cmm, ALT was 64 IU, AST was 38 IU, total bilirubin was 1.81 mg/dl, direct bilirubin was 0.61 mg/dl. Liver biopsy showed disarray and ballooning of hepatocyte with intra cytoplasm bilirubin. Intra canaliculi bilirubin pigmented. Proliferation of kupffer cells. Kiernan triangle with lymphocytes infiltration and periportal fibrosis. Degeneration cells. From this feature the pathologist concluded a cholestasis as a liver involvement of SLE. The treatment was amikacin 2 x 225 mg/day; prednisone 4 – 4 - 4 (18th day), urdafalk 3 x 100 mg daily, thermoregulation. The diagnosis of SLE associated with cholestatic Hepatitis was established.
On 40th day of hospitalization, Hemoglobin level was 11.5 g/dl, Platelets count was sufficient, White cell count was 6,000 cmmm, and erythrocyte sedimentation rate was 18. ALT was 27 IU, AST was 13 IU, Total bilirubin was 1.37 mg/dl, and direct bilirubin was 0.43 mg/dl. The patient was discharged with the good condition.

Figure 1. The figure of the patient before treatment.
DISCUSSION

A 12-year-old girl came with a history of prolonged fever, pain stomatitis, skin rashes, fallen hair, articular pain, and icteric for two months. She lost her appetite and lost her weight ± 14 kgs. The urine was tea like color, but the stool was normal. She was a non-alcoholic and no prolonged medication. No history of the family with the same disease or other genetic disease. She never got liver disease.

From general examination revealed a weak girl, icteric and pale. The body temperature was 39.6°C, malar rash, hepatomegaly, skin rashes, and oral ulcers. Other parts of the examination were within normal limit. At emergency department, laboratory examination revealed: Hemoglobin was 8.7 g/dl, White cell count was 3.500/cmm, ALT was 565 IU, AST was 77 IU, Albumin was 3.1 mg/dl. Prothrombin time was normal. Total bilirubin was 6.82 mg/dl and direct bilirubin was 5.36 mg/dl. Markers for viral hepatitis (anti HAV; HBs Ag; Anti HBs were negative) ANA test 180.9, Anti ds-DNA Antibodies 471.3 units/ml, C3 < 30 and C4 <10, LE cells negative for 3 days. Liver biopsy showed disarray and ballooning of hepatocyte with intra cytoplasm bilirubin Intra canaliculi bilirubin pigmented. Proliferation of kupffer cells. Kiernan triangle with lymphocytes infiltration and periportal fibrosis degeneration cells indicating a cholestatic in this patient. There were six of 11 criteria ARA present in this patient (malar rash; photosensitivity; oral ulcer; hematological disorder; immunologic disorder and anti nuclear antibody). Based on these data, the diagnosis was Systemic Lupus Erythematosus associated with cholestatic Hepatitis.

Hepatitis is a general term that refers to inflammation of the liver. This condition may result from various infectious and noninfectious etiologies. Infectious etiologies include viral, bacterial, fungal, and parasitic organisms. Medications, toxins, and autoimmune disorders may cause noninfectious hepatitis (Buggs, 2005; Lee, 2003).
Five major hepatotropic viruses cause the majority of clinical cases of viral hepatitis. These are hepatitis A virus (HAV), HBV, HCV, hepatitis D virus (HDV), and hepatitis E virus (HEV). HAV, HBV, and HCV cause more than 90% of cases of acute viral hepatitis (Buggs, 2005).

In this case, the viral hepatitis markers were negative (anti HAV, HBs AG and anti HCV). No history of prolonged drug or herbal medication. Systemic Lupus Erythematosus (SLE) is defined by its clinical features and by the almost invariable presence in the blood of antibodies directed against one or more components of cell nuclei. Certain manifestations seem to be associated with the presence of different antinuclear antibodies and genetic markers, which suggests that SLE may be a family of diseases. However, clinical presentations frequently overlap, and there is currently no conclusive evidence that SLE is more than a single disorder with a broad range of manifestations, the expression of which may be influenced by the patient's genetic background (Brogan, 2005; Greenspun, 2004; Lee, 2003).

Evidence from a broad range of basic science studies indicates that the pathogenesis of this disease is equally complex and may vary from patient to patient. The diverse expression of the common lupus syndrome may result from variable abnormalities in intersecting genetic, immunologic, hormonal, and environmental pathways (Greenspun, 2004).

Within the healthy population, a subset of individuals exists who have small amounts of low titer antinuclear antibody (ANA) or other autoantibody. In lupus, much greater production of autoantibodies leads to immune complex formation and tissue damage due to direct binding and/or immune complex deposition in tissues. Whether these antibodies are produced in reaction to exposure of normally no exposed self antigens or as a consequence of a broad spectrum of immune deregulation resulting in excessive production of many antibodies without regard to prior stimulation is unclear (Greenspun, 2004).

Patients with SLE make antibodies against DNA, other nuclear antigens, ribosome, platelets, erythrocytes, leukocytes, and other tissue-specific antigens. Thus, the resulting immune complexes result in widespread tissue damage. Cell-mediated autoimmune responses also play a pathophysiologic role.

The most frequent presenting symptoms of SLE are prolonged fever and malaise with evidence of multisystem involvement. The children often present with a history of fatigue, joint pain, rash, and fever. However, children may present with a variety of acute symptoms, including memory loss, psychosis, transverse myelitis, hemoptysis, edema of the lower extremities, headache, and painful mouth sores. Eleven criteria are used for the classification of lupus in adults. The same criteria can serve as a guideline in children. Any 4 criteria are sufficient and should be sought in the history (Klein, 2003; Greenspun, 2004; Lee, 2003; Kemikii, 2003).

In this case, the patient suffered from prolonged fever, malaise, fatigue, lost of appetite, skin rash, joint pain, headache and painful mouth sores. The presence of autoantibodies can usually be determined by the antinuclear antibody (ANA) test performed on patient serum from blood. The titer, or strength, of the ANA gives a rough indication of the severity of the disease. Not all positive ANA tests indicate autoimmune disease, particularly when the titer is low. After a positive screening ANA test, more specific tests for SLE include detection of autoantibodies to double stranded DNA and to Smith antigen (Klein, 2003; Greenspun, 2004; Lee, 2003; Roger, 2001; Dall’Era, 2001; Kemikii, 2001).

In this case, the ANA test and anti ds-DNA antibody were strong positive. Antibodies to native or double-stranded DNA and to Sm, a ribonucleic protein antigen, are more specific than other antinuclear antibodies for the diagnosis of SLE. Their presence does not predict particular disease manifestations, although nephritis is more common in patients with anti-native DNA. For many of the patients who have antinative DNA, the titer of this antibody is a useful measure of disease activity. Criteria to distinguish SLE from other connective-tissue diseases have been established by the American Rheumatism Association and were last revised in 1982. They are intended to provide a degree of diagnostic certainty primarily for research purposes. It is often possible to be reasonably confident about a diagnosis of SLE on less strict clinical grounds.

Involvement of the liver of the liver in SLE is a frequently misunderstood complication of the disease. The liver can be affected as a result of lupus itself, as well as the medications used to treat inflammation caused by lupus. Enlargement of the liver or hepatomegaly was present in 10% of SLE patients. The liver usually extends 2 to 3 cm below the costal margin, but it occasionally can reach the iliac crest. Tenderness is uncommon unless peritonitis or viral hepatitis is present. Hepatomegaly and tenderness maybe present with normal liver function test. As enlarged liver can be histologically normal. Jaundice was present in 1% to 4% of the patients with SLE. Manifested by high levels of bilirubin, which are responsible for this pigmentation. The most common jaundice in SLE is hemolytic anemia and viral hepatitis, cirrhosis, or bile duct obstruction.
Mild liver enlargement, jaundice, or ascites in severe anorexia. Jaundice is present in fulminant hepatitis with nonspecific symptoms of fatigue, malaise, and liver-kidney microsomal and mitochondrial antibodies are rare, with antibody to smooth muscle, ribosomal P protein is strong marker for lupus hepatitis. Patients with autoimmune hepatitis and primary biliary cirrhosis characterized by antibody to smooth muscle, liver-kidney microsomal and mitochondria rarely fulfill criteria for SLE (Hallequa, 2002; Craja, 2002). Hepatitis resulting from SLE was most likely to be lobular and associated with autoantibodies such as like anti double-stranded DNA anti ribosomal P antibodies (Hallequa, 2002). In contrast, autoimmune hepatitis was more likely portal (chronic active hepatitis) with resetting of liver cells and dense lymphoid infiltrates and often has specific auto antibodies to antiliver-specific protein or have antiliver-kidney-microsomal antibody. Liver enzyme, gamma globulin, alkaline phosphatase, and bilirubin level are elevated, the albumin level is decreased and the prothrombin time maybe prolonged (Hallequa, 2002; Craja, 2002).

In this case, the liver enzyme was elevated 10 times from normal, the value of anti double-stranded DNA was high, and ANA test was positive. Albumin serum was normal. The prothrombin time was normal. Steroids remain the mainstay of treatment, prolonging life and making the patient more comfortable. It can be given alone or combined with azathioprine. In a controlled study comparing prednisolone alone (40 mg daily as initiation of treatment and 15 mg daily maintenance), azathioprine alone (150-200 mg daily), and prednisolone and azathioprine combined (10 mg and 100 mg daily). Mackay reported that the relapse rate was lowest and overall survival longest in the combined-treatment group. All three regiments suppressed the disease, and indices of liver function showed improvement (Hallequa, 2002; Katz, 2005).

In this case, prednisone was given alone without azathioprine (2mg/kg/day) and there were improvement in liver function test. Mistilis and Blackburn recommended a daily dose of 60 mg of prednisone for the first 2-3 weeks, with gradual reduction over several months to a maintenance level of 5 to 20 mg daily. Steroids alone did not improve survival but did reduce early mortality. This group recommended a daily dose of 1.5-mg/kg azathioprine to control the disease activity, but other controlled studies have questioned the efficacy and safety of azathioprine. Cyclophosphamide is an alkylating agent originally used in cancer chemotherapy. It is used in severe organ-threatening lupus. It is usually used as a regular intravenous pulse at a dose of either 10 – 15 mg/kg monthly, or 500 mg, fortnightly for three months. Alternative management strategies for treatment failure have included the administration of cyclosporine, ursodeoxycholic acid, and budesonide. Patients with lupus hepatitis and...
symptoms of nausea and vomiting may require intravenous fluids and even total parenteral nutrition; however, most patients can tolerate a regular diet. A high caloric intake is desirable (Greenspun, 2003).

The prognosis of Lupus hepatitis has improved. In 1968, Mackay reported the 5-year survival rate as being 56%. In 1988, 80% 5-year and 70% 10-year survival rates with prednison and azathioprine therapy. Patient with this disease have a light, but definitively increased, risk of developing hepatoscellular carcinoma.

**SUMMARY**

A rare case of cholestasis manifestation in a child with Systemic Lupus Erythematosus has been reported. The diagnosis of Systemic Lupus Erythematosus was established by the presence of 6 out of 11 criteria from the American College of Rheumatology for classification of SLE. Hepatic manifestation and other manifestations of the disease responded well to steroid therapy.

**REFERENCES**


