

Lupus-related advanced liver involvement as the initial presentation of systemic lupus erythematosus

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Background and Purpose: Systemic lupus erythematosus (SLE), a prototype of systemic autoimmune disease characterized by multiorgan involvement with diverse clinical and serological manifestations, principally affects women in their child-bearing years. Clinically significant hepatic abnormality as the initial presentation of SLE has rarely been reported.

Methods: Eleven patients with lupus with initial presentation of lupus-related hepatitis were included in this retrospective review. Clinical manifestation, immunological profiles, and risk factors for poor prognosis were analyzed.

Results: The most commonly associated clinical manifestations were found to be thrombocytopenia, leukopenia, advancing age, and presence of anti-SSA/Ro antibody and anti-thyroid antibodies. The diagnosis of SLE was delayed due to dominant hepatic abnormalities. Age greater than 50 years and marked hepatic decompensation in accordance with Child classification B and C might suggest poor prognosis ($p=0.06$). However, the p value was not statistically significant because of the small sample size.

Conclusions: Lupus-related hepatitis, particularly in late-onset lupus, is common. In addition, the presence of anti-SSA, anti-thyroglobulin, and anti-microsomal antibodies is indicative of hepatic involvement in patients with SLE.

Key words: Autoantibodies, hepatitis, prognosis, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an immune-mediated systemic disease associated with diverse abnormalities of the skin, kidneys, and hematological and musculoskeletal systems. Abnormalities of liver function, however, are not included in the diagnostic criteria of SLE, and the liver is generally not regarded as a major target organ for damage in patients with SLE [1]. Nonetheless, patients with SLE have 25% to 50% incidence of developing abnormal findings on liver function tests at some point, but most of these

abnormalities might be precipitated by viral infection or drugs [1,2]. Hepatic disease may be more common in SLE than is usually reported, and in some patients, hepatitis may be the initial presentation of SLE. Therefore, a retrospective analysis was conducted to assess the clinical characteristics of patients with SLE who had lupus-related hepatitis at the time or before SLE was diagnosed.

Methods

Patients

Patients with abnormal liver function tests at the time or before they were first diagnosed with SLE at the National Taiwan University Hospital between 2002 and 2005 were included in the study. Viral hepatitis caused by organisms such as hepatitis B virus (HBV), hepatitis

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C virus (HCV), cytomegalovirus (CMV), and Epstein Barr virus (EBV) was excluded by serology test. Drug-related hepatitis was excluded after a careful review of the medication history. Patients were diagnosed with SLE if at least 4 of the 11 American College of Rheumatology (ACR) criteria were met, and patients were diagnosed with "probable" SLE if 3 of the 11 ACR criteria were met [3].

Data on patients' sex, age, clinical manifestations, and SLE disease activity index (SLE-DAI) were analyzed. Modified Child-Turcotte-Pugh classification was applied for the severity of chronic liver disease. Child A was regarded as compensated status, and Child B and Child C were regarded as decompensated status. Complete blood count, liver function tests, anti-extractable nuclear antigens (anti-SSA, anti-SSB, anti-Scl-70, anti-RNP, and anti-Smith), diluted Russell's viper venom time (dRVVT), and complements C3 and C4 were measured using standard laboratory methods. Antinuclear antibody (ANA) was analyzed by indirect immunofluorescence using HEp-2 cells. Anti-double-stranded (ds) DNA, anti-neutrophil cytoplasmic antibody (ANCA), anti-smooth muscle antibody (ASMA), anti-mitochondria antibody, anti-microsomal antibody, anti-thyroglobulin antibody, and anti-cardiolipin antibody (ACA, immunoglobulin G subtype) were analyzed by commercially available enzyme-linked immunosorbent assay using standard laboratory methods.

Two-tailed Fisher's exact test was employed for categorical variables. A value of $p < 0.05$ was considered as statistically significant.

Results

From 2002 through 2005, a total of 9 definite SLE patients with abnormal liver function as the initial presentation and 2 patients with probable SLE were enrolled in this study. There were 10 female and 1 male patients (10:1). The average age of these patients was 46.5 years. Biochemical tests indicated elevated aspartate aminotransferase/alanine aminotransferase levels for all patients. Four patients had abnormal liver function for several years without definite precipitating factors such as chronic viral hepatitis or history of hepatotoxic drug use.

Clinical characteristics of the patients are summarized in Table 1. There were 4 patients (36%) with prolonged interval (more than 1 year) between the first time of abnormal liver function and the final corrected diagnosis (Table 2). The most common manifestation was hematological abnormalities (10 patients), that included leukopenia and thrombocytopenia. Nephritis defined by active urinary sediment or proteinuria was found in 6 patients and arthritis in 4 patients. Two patients had skin manifestations. No neurological abnormalities were found in these patients.

Immunologic profile of these patients showed 9 patients (82%) with elevated anti-ds DNA and low complement levels. In all, 5 (45%) of the patients were positive for anti-SSA, 3 (27%) for anti-SSB, 2 (18%) for anti-Smith, 1 (9%) for anti-RNP, and 1 (9%) for anti-Scl-70. Two patients were positive for ACA

Table 1. Clinical characteristics of patients and manifestation of systemic lupus erythematosus (SLE)

Patient no.	Age (years)	Gender	Diagnosis	Time to diagnosis	Anti-ds DNA	C3/C4	SLE-DAI	Clinical manifestations				
								Kidney	CNS	Skin	Hematology	Arthritis
1	27	F	SLE	1 month	143.00	↓/↓	15	+	-	-	+	+
2	24	F	SLE	3 weeks	35.43	↓/↓	14	+	-	-	+	-
3	47	F	SLE	1 month	17.54	N ^a /↓	8	+	-	-	+	-
4	58	F	Probable SLE	1 month	-	↓/↓	3	-	-	-	+	-
5	41	F	SLE	4 years	73.90	↓/↓	9	-	-	-	+	+
6	50	F	Probable SLE	2 months	90.20	↓/↓	6	-	-	-	-	+
7	31	F	SLE	2 months	342.00	↓/↓	22	+	-	-	+	+
8	50	F	SLE	7 years	184.00	↓/↓	7	-	-	-	+	-
9	48	F	SLE	14 years	-	N/↓	1	-	-	-	+	-
10	61	M	SLE	2 years	-	↓/↓	10	+	-	+	+	-
11	74	F	SLE	4 months	148.00	N/N	23	+	-	+	+	-

Abbreviations: F = female; M = male; ds = double-stranded; C3 = complement 3; C4 = complement 4; DAI = disease activity index; CNS = central nervous system; ↓ = below normal; N = normal; - = absent; + = present

^aWithin normal limits.

Table 2. Autoantibodies and liver function

Patient no.	Antithyroid ATA/AMA	AMA	Anti-SMA	ANCA MPO/PR3	Anti-ENA	ACA	LA ^a	Bil (T/D) (mg/dL)	AST/ALT (IU/L)	ALP/gamma-GT (IU/L)	Child-Pugh score	Outcome	Other diagnosis
1	-/-	+	-	NA	-	-	-	0.3/0.2	1205/251	685/930	A	Survival	-
2	+/+	-	-	NA	-	+	-	13.1/12.9	1757/366	458/198	C	Survival	-
3	+/+	-	+	NA	SSA	-	-	3.4/2.8	556/288	211/140	A	Survival	Autoimmune thyroiditis
4	-/-	NA	NA	NA	Sm	NA	NA	6.5/3/5	189/175	466/239	C	Death	-
5	+/+	NA	-	NA	SSA, SSB, Scl-70	NA	NA	0.8/0.6	102/79	267/120	A	Survival	Autoimmune thyroiditis
6	-/-	-	-	-/-	-	NA	-	1.6/0.6	180/103	315/82	A	Survival	-
7	-/-	-	-	NA	SSA	-	-	0.5/0.3	940/472	202/480	A	Survival	-
8	NA	NA	NA	-/-	-	-	-	4.3/2.8	672/402	149/32	C	Death	-
9	+/-	+	NA	-/-	SSA, SSB	+	-	0.9/0.5	95/154	562/249	A	Survival	Autoimmune thyroiditis, APS
10	-/-	-	NA	-/-	RNP, Sm	-	-	3.4/2.6	283/245	500/817	B	Survival	Type 2 DM
11	+/+	-	-	-/-	SSA, SSB	-	-	0.9/0.5	54/22	1542/295	B	Morbidity ^b	Graves disease

Abbreviations: ATA = anti-thyroglobulin antibody; AMA = anti-mitochondria antibody; SMA = smooth muscle antibody; ANCA = anti-neutrophil cytoplasmic antibody; MPO = myeloperoxidase; PR3 = proteinase 3; ENA = extractable nuclear antigens (anti-SSA, anti-SSB, anti-Scl-70, anti-RNP, and anti-Sm); ACA = anticardiolipin antibody; LA = lupus anticoagulant; Bil (T/D) = bilirubin (total/direct); AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GT = glutamyl transpeptidase; - = absent; + = present; NA = not available; Sm = Smith; APS = autoimmune polyglandular syndrome; DM = diabetes mellitus

^aDiluted Russell's viper venom time.

^bHypoxic encephalopathy related to pneumonia, ventilator-dependent.

immunoglobulin G, and none of the patients were positive for dRVVT. Only 1 ACA-positive patient had a history of recurrent abortion, and the other patient did not show any evidence of thrombosis or abortion. Anti-thyroid antibodies were detected in 5 of 10 patients. ASMA was detected in 1 of 7 cases, anti-mitochondria in 2 of 8 cases, and 6 cases were negative for ANCA.

There were 2 mortalities — 1 patient died of spontaneous bacterial peritonitis-related sepsis and the other due to intracranial hemorrhage. One patient had major morbidity with hypoxic encephalopathy related to pneumonia. We analyzed the possible variables for the poor prognosis (death or major morbidity) including age, SLE-DAI, anti-ds DNA, total bilirubin level, and liver reserve based on Child classification. Age greater than 50 years and marked hepatic decompensation in accordance with Child classification B and C might suggest poor prognosis ($p=0.06$). However, the p value was not statistically significant because of the small sample size. All patients, except 1, received steroid therapy after diagnosis. Liver function improved within

days after treatment and returned to normal within 2 months.

Discussion

Liver involvement in patients with SLE has been well documented, but clinically significant hepatic disease is generally regarded as unusual. Although hepatomegaly was presented in 23% patients, only 3.8% of patients with SLE developed functional impairment with jaundice [4]. The most common cause of jaundice in SLE is hemolytic anemia, while the second most frequent etiology is hepatitis that is usually due to viral origin or hepatotoxic drug. Moreover, abnormal liver function as the initial presentation of SLE is very rare. A retrospective analysis of 81 patients with SLE revealed 45 patients (55%) with elevated liver enzymes [5]. Of the 45 SLE patients, 19 had abnormal liver function and did not show any precipitating factors except for the disease itself. Another prospective study surveying 260 SLE patients reported 23% patients with elevated

liver enzyme levels and 8% may have been due to SLE itself [6]. No serious hepatic complication was noted during follow up. However, Runyon et al [7] reviewed 238 patients with SLE and found that elevated liver enzyme was not uncommon and severe liver disease such as liver cirrhosis and hepatic failure were often present.

These 11 cases presented with significant hepatic involvement and other systemic manifestations. None of these cases had a history of previous medication use or alcohol abuse, and available viral hepatitis markers including HAV, HBV, HCV, CMV, and EBV were all negative. Therefore, the possible pathogenesis of hepatitis with jaundice is related to an immune-mediated process. According to the International Autoimmune Hepatitis Group revised criteria [8], 9 of 11 cases had a score more than 15. Hence, the diagnosis of probable autoimmune hepatitis (AIH) should be considered. However, clinical and serological evaluations of 9 cases fulfilled the ACR criteria for lupus [3]. Of the remaining 2 patients who met 3 of 11 ACR criteria for SLE, 1 patient had a high titer of anti-ds DNA antibody and the other patient had anti-Smith antibody; both the conditions evolved to be lupus due to these specific autoantibodies. SLE is a systemic autoimmune disease characterized by multiorgan involvement with diverse clinical and serological manifestations. However, AIH is merely an organ-specific disease that is classified as immune mediated-chronic active hepatitis (CAH) in the absence of viral infection, drugs, and alcohol consumption. From the point of systemic autoimmune disease, particularly lupus, which rarely occurs in combination with other organ-specific autoimmune diseases, SLE with liver involvement might be a more appropriate diagnosis than AIH and lupus in these 3 cases.

One of the interesting findings in our reported cases is that anti-mitochondrial and anti-thyroglobulin antibodies were present in half of the cases examined (5/10). In a large general survey, thyroid autoimmune disease developed in 5.9% (25/426) of lupus patients [9]. The incidence of thyroid autoimmune disease in AIH was around 8% to 12% [10,11]. Therefore, thyroid autoimmune disease could be a characteristic manifestation of lupus-related hepatitis.

Mackay et al coined the term "lupoid hepatitis" in 1956 to describe cases of active chronic hepatitis associated with a positive lupus erythematosus cell test and occasionally minor manifestation of lupus [12]. Traditionally, SLE is regarded as a systemic autoimmune

disease with diverse clinical and serological manifestations. Common clinical features included skin manifestation, arthritis, nephritis, hematological manifestation, fever, neuropathy, lymphadenopathy, and lung involvement [13]. Significant liver involvement is regarded as uncommon in lupus and abnormal liver function in patients with lupus is often thought to be related with drug use or viral infection. On the other hand, due to the positive lupus erythematosus cell test, hypergammaglobulinemia, dense intrahepatic infiltration, and clinical response to immunosuppressive drugs observed in some patients with CAH, the term AIH was used instead of lupoid hepatitis [14]. However, patients diagnosed with AIH might also have many extrahepatic manifestations such as arthritis, skin lesions, serositis, and renal or hematological manifestations [15]. Thus, some cases may have been misdiagnosed as AIH and may actually be SLE with liver involvement.

Histopathologically, AIH was characterized by "piecemeal necrosis" and is currently identified as interface hepatitis. Besides lobular hepatitis, rosette formation and plasma cell infiltration were also frequently found [16]. However, the histopathology of lupus-related hepatitis is quite nonspecific and ranges from venous congestion and nonspecific reactive hepatitis to inactive cirrhosis [17]. Moreover, the typical features of CAH can occasionally be found in lupus patients [5,6]. These findings suggest complex immunopathogenesis in lupus with liver involvement, and CAH could be one of the presentations.

Several autoantibodies such as ASMA, anti-LKM (liver-kidney microsomes), and ANCA are characteristic of AIH [18]. However, ASMA is not specific for AIH and the prevalence of ANCA and anti-LKM is quite low. ANAs are important serological markers of both AIH and SLE; however, ANA is not specific and includes a heterogeneous spectrum of autoantibodies that react with various nuclear components. Recently, anti-chromatin or anti-nucleosome antibodies such as anti-histone, anti-SSA, anti-SSB, anti-RNP, and anti-ds DNA antibodies were also found to be present in the early stage of SLE. These antibodies play a central role in the primary autoimmune reaction against nuclear antigens. These autoantibodies are also detected in the serum of some AIH patients [19]. In addition, the well-established criteria for AIH exclude the possibility of viral infection, drug metabolism, and alcohol consumption. Therefore, lupus with liver involvement, anti-phospholipid syndrome with liver involvement, or other systemic autoimmune disease such as myositis, rheumatoid arthritis,

and primary Sjögren's syndrome with liver involvement could also be diagnostic of AIH. Thus, the diagnosis of primary AIH should be considered only after excluding other systemic autoimmune diseases.

A growing body of evidence reveals that hepatic involvement in patients with SLE is more common than before [20]. Although the hepatic involvement is largely limited to biochemical abnormalities without decompensation, the functional impairment even to liver cirrhosis and hepatic failure is noteworthy [7]. However, significant hepatic abnormalities as the initial presentation of SLE are still rarely reported. In addition, SLE with significant hepatic involvement and AIH were believed to differ in terms of complications and treatment therapy, despite considerable difficulty in the differential diagnosis by serologic and histological findings [2,21].

In conclusion, hepatitis with significant functional impairment could be an important manifestation of SLE, even as an initial presentation. Therefore, screening for SLE should be considered for all patients with AIH. The presence of anti-microsomal and anti-thyroglobulin antibodies might be one of the important indicators of SLE-related immune-mediated hepatitis. A prospective study should be conducted to further elucidate and characterize lupus-related hepatitis.

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