Analysis of 15 patients with abnormal liver function as the first systemic lupus erythematosus symptom

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Abstract

Objective : **To understand the clinical characteristics of patients with abnormal liver function as the first symptom of systemic lupus erythematosus (SLE).**

Methods : **Here, 15 patients admitted to a hospital from January 2010 to December 2013 with initial presentation of lupus-related hepatitis or cirrhosis were included. Their SLE-DAI scores and clinical and laboratory data were collected. All cases received liver protection therapy and active SLE controlling treatment with methylprednisolone combined with rapamycin.**

Results : **When hepatic abnormalities were the most prominent feature during the first visit, the patient was more likely to receive an incorrect diagnosis or be diagnosed with SLE late. Of the 15 cases, only 7 (46.7%) were identified as SLE within a week of presentation of abnormal liver function ; meanwhile, the 7 remaining patients (46.7%) were not correctly diagnosed until more than 2 weeks later and as late as 4 months ; in addition, 1 patient was not diagnosed with SLE until 8 years after the initial presentation of abnormal liver function. In the 3-month follow-up after active treatment, liver function was completely restored in 10 cases with no cirrhosis and significantly improved in 3 patients who still had cirrhosis. Another case showed no improvement in liver function and was self-discharged, and another died from chronic liver failure.**

Conclusion : **Liver injury caused by SLE is not uncommon, and it is easy to tentatively diagnose it as hepatitis, delaying the correct diagnosis of SLE. In such patients, physicians should perform a thorough differential diagnosis as soon as possible and administer proper treatment. Corticosteroid conjugated with immunosuppressants with no or little liver toxicity would be suitable for patients with SLE-induced liver injury.** (Acta gastroenterol. belg., **2016**, 79, **441-446**).

Key words : systemic lupus erythematosus ; hepatic abnormality ; clinical characteristics ; glucocorticoid treatment.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease caused by genetic and environmental factors ; it causes a dysfunction of the acquired immune response and often demonstrates multiple organ involvement [1]. In the past, a few reports have indicated that the liver is the target organ involved in SLE, while some recent studies have reported liver injury in a few patients with SLE, and even liver cirrhosis during the course of the disease [2]. In SLE, damage to the liver is far rarer than damage to the kidney, brain, or other organs. However, a patient with SLE presenting abnormal liver function as the predominant symptom is likely to be incorrectly diagnosed upon the first hospital visit. He or she may instead be diagnosed with other liver diseases such as viral hepatitis, toxic hepatopathy, or autoimmune liver disease, among others. In the present study, the clinical characteristics of 15 patients with SLE presenting with liver damage as the main manifestation were retrospectively analyzed. These findings should help prevent erroneous diagnoses in individuals with SLE and liver diseases.

Subjects and methods

Subjects

A total of 15 patients with SLE, first admitted for abnormal liver function from January 2010 to December 2013 in Beijing You'an Hospital, were included in present study. The diagnosis of SLE met the criteria proposed by the Chinese Medical Association of Rheumatology [3]. Cases positive for hepatotropic virus biomarkers, drug-induced liver injury, alcoholic liver disease, non-alcoholic fatty liver disease, and Wilson's Disease were excluded, as were those with hemolytic anemia, myonitis, and neoplastic disease, etc.

Among the tests used to rule out the non-recruited patients, Electrochemiluminescent enzyme immunoassay kits (Roche Diagnostics (Shanghai, China) Ltd) were used to detect and rule out viral (HAV, HBV, HCV, HEV) etiologies, instant CHEKTM-HIV l+2 kits (BBI Life Science Corporation, HK, China) were used to screen and rule out the patients infecte with HIV. Genetic(iron, alpha 1 anti-trypsin, etc.) and metabolic etiologies were detected with the combined methods including genetic detection in Beijing Genomics Institute (BGI), MRI or CT, related enzyme and protein detection. Toxic etiology was ruled out through history – taking and detection of toxic substances in the toxicology detection center in Beijing. Indirect immunofluorescence kits (Euroimmun medical diagnosis (China) Co., Ltd) were used to detect autoimmune etiologies.

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Patients' records were examined retrospectively. They included demographic characteristics (age and sex), clinical parameters (signs and symptoms), laboratory values (hematologic, biochemical, and microbiological findings), radiologic data, status at discharge (recovered or died), admission and discharge dates, and length of hospital stay (LOS).

Criteria for liver injury

Liver injury was determined by abnormal function or jaundice during the course, by iconographic abnormalities, or both. Parameters of abnormal liver function included serum alanine aminotransferase (ALT) >40 IU/L, aspartate aminotransferase (AST) >40 IU/L, gamma glutamyl transpeptidase (γ-GT) >50 IU/L, total bilirubin (TBIL) >20 μmol/L, conjugated bilirubin (CBIL) >8 μmol/L. Ultrasonography abnormalities of liver-included increment or reduction in liver size, non-uniform intrahepatic resonance, rough surface, disproportionality between the two lobes.

Criteria for active SLE

Impairment of organ systems was evaluated by referring to the systemic lupus international collaborating clinics (SLICC) [4], and the diagnosis of SLE in this group patients was made by consultation of the specialist physicians of rheumatic immunology . Patients were considered to have active SLE if they had integral scores greater than 4 ; otherwise they were considered to have stable SLE.

Treatment measures

All cases were first given liver protection therapy such, as magnesium isoglycyrrhizinate (150–200 mg/d) and ademetionine (1000 mg/d). Once SLE diagnosis was reached, all patients except for No. 2 were also treated with methylprednisolone (1 mg/kg/d). Case No 2 had liver cirrhosis complicated with esophageal variceal bleeding and received rapamycin (3 mg/d). Three cases (No. 7, 13, and 14) received plasmapheresis 1–2 times due to hyperbilirubinemia. As liver function improved, methylprednisolone was gradually reduced and adjusted to maintain the lower degree of immunosuppressive therapy with 10–20 mg/d of prednisolone acetate.

Laboratory data

Parameters of liver function and autoimmune antibodies, such as concentrations of antinuclear antibody, anti-ds-DNA antibody, anti Sm antibody, anti-ribosomal antibody, anti SSA antibody, SSB antibody, IgA, IgG, IgM, and complements C3 and C4, were collected from patients' medical records archived in the medical record library and the medical computerized database at Beijing You'an Hospital, Capital Medical University.

This study was approved by the Beijing You'an Hospital Ethics Committee. All participants provided written informed consent for their information to be stored and used for research. Human experimentation guidelines of People Republic of China were followed in conducting this clinical research.

Results

Clinical characteristics

Of the 15 cases, 3 (20%) were male, and 12 (80%) were female, a male to female ratio of 1:4. Their ages ranged from 22 to 82 years, averaging 51.5 ± 18.3 years. Here, 7 cases (46.7%) were definitively diagnosed with SLE within a week of emergence of abnormal liver function, and 7 others (46.7%) admitted for liver function abnormality received a definitive SLE diagnosis from 2 weeks to 4 months later. One of the 15 cases had liver function abnormality lasting 8 years, was not definitively diagnosed with SLE until she was admitted to the hospital ; she was only 22 years old (Table 1).

Liver function of patients was not improved during only received the liver protection therapy until immunosuppressive therapy was prescribed. In the 3 months of follow-up after active treatment, liver function showed marked recovery in 10 cases with no cirrhosis, and showed significant improvement in 3 patients but with cirrhosis. Meanwhile, case No. 2 did not show any improvement in liver function and was self-discharged, and case No. 3 died of chronic liver failure (Table 1).

Liver function at admission

Upon admission, 13 (86.7%), 11 (73.3%), 13 (86.7%), 9 (60%), and 7 (46.7%) cases showed elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (γ-GT), alkaline phosphatase (ALP), and total bilirubin/conjugated bilirubin (TBil/Dbil), respectively (Table 2).

Autoantibody spectrum

Only anti-nuclear antibody (ANA) was detected in all 15 cases. Other autoantibodies were detected in 11–14 patients, except No. 1, 3, 4, and/or 5 (Table 3). A total of 6 of 13 (46.2%) cases showed positive anti-Sjögren's syndromes antigen type A (anti-SSA) ; 2 of 13 (15.4%) cases were positive for ribonucleoprotein (anti-RNP antibodies) ; 7 of 13 (53.8%) patients had positive anti-double stranded DNA antibodies (anti-Ds-DNA antibodies) ; 2 of 11 (18.2%) cases had positive anti-neutrophil cytoplasmic antibodies (ANCA) ; 2 of 13 (15.4%) cases had positive anti-ribosome antibodies (ARA) ; and 1 of 13 (7.7%) showed positive anti-mitochondrial antibody-M2 (AMA-M2) (Table 3).

Table 1. — **Clinical characteristics of the 15 cases**

Number of cases	Age	Sex	Diagnosis of liver disease(s)	Time of definitive diagnosis	Clinical manifestation						Prognosis
					SLE-DAI	Kidney	Central nervous system	Dermal	Anemia	arthritis	
1	22	F	LC, ascites	Eight years	17	+	-	+	+	-	Improvement
2	43	F	LC, EGVB	Within one week	5	+	-	-	+	-	No improvement
3	56	F	LC, chronic liver failure	Within one week	25	+	+	-	+	-	Death
4	21	F	Chronic hepatitis	Within one week	9	+	-	+	-	-	Improvement
5	82	F	Chronic hepatitis	Within one week	7	-	-	+	+	+	Improvement
6	53	M	Chronic hepatitis	One month	6	-	-	-	-	+	Improvement
7	56	F	Subacute liver failure	Two months	2	-	-	+	-	-	Improvement
8	67	F	Chronic hepatitis	Three months	2	-	-	+	-	-	Improvement
9	68	F	LC, ascites	Within one week	7	-	-	+	-	-	Improvement
10	76	M	Chronic hepatitis	One month	16	+	-	+	+	-	Improvement
11	48	F	Chronic hepatitis	Three weeks	15	+	-	+	-	+	Improvement
12	37	F	LC	Two weeks	9	-	-	-	+	+	Improvement
13	43	F	Chronic hepatitis	Within one week	6	-	-	-	+	-	Improvement
14	48	F	Chronic hepatitis	Four months	5	+	-	-	-	-	Improvement
15	23	M	Chronic hepatitis	Within one week	5	-	-	+	-	-	Improvement

F, female; M, male; SLE-DAI, systemic lupus erythematosus disease activity index; LC, liver cirrhosis; EGVB, esophageal variceal bleeding

Table 2. — **Indices of liver function**

Case No		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
ALT(IU/L)	Pre-T	45.4	15.5	183.0	123.0	112.0	437.0	77.0	59.0	24.5	24.2	260.0	19.9	63.0	817.0	127.0
	Aft-T	30.6	76.3	213.6	40.2	32.6	59.4	35.1	36.2	21.5	23.5	50.6	19.6	35.4	45.7	39.5
AST(IU/L)	Pre-T	57.2	17.8	417.0	122.0	92.0	652.0	150.0	205.0	45.0	51.5	856.0	29.5	135.0	500.0	57.0
	Aft-T	36.4	124.6	432.9	45.3	30.1	70.6	49.8	51.3	39.4	32.6	78.3	25.7	53.1	30.4	27.3
TB(μmol/L)	Pre-T	9.7	15.0	22.9	7.1	20.0	276.0	371.0	144.0	12.6	4.6	89.2	4.6	322.0	342.0	9.6
	Aft-T	10.2	95.2	265.4	8.0	18.2	56.2	68.2	32.4	10.3	4.5	26.5	5.2	32.7	24.6	8.9
CB(μmol/L)	Pre-T	2.5	4.5	14.0	1.2	4.9	129.0	154.0	54.0	4.5	0.3	55.2	0.5	193.0	193.0	1.3
	Aft-T	2.6	60.7	146.2	1.3	4.2	21.3	30.4	11.8	3.7	0.5	12.9	0.7	17.5	16.6	1.2
GGT(IU/L)	Pre-T	13.2	183.4	69.0	110.0	725.0	120.0	92.0	635.0	914.0	190.0	1951.0	31.0	58.0	415.0	97.0
	Aft-T	21.1	320.4	278.5	70.5	118.3	46.3	41.7	102.5	119.2	45.1	213.8	32.5	49.3	105.0	41.0
ALP(IU/L)	Pre-T	51.5	148.2	66.0	156.0	560.0	143.0	17.0	261.0	167.0	122.0	474.0	16.0	73.0	101.0	65.5
	Aft-T	50.4	253.7	128.3	51.7	80.7	48.2	16.5	60.2	52.2	42.3	114.5	18.8	42.9	51.3	39.4
ALB(g/L)	Pre-T	24.0	28.0	14.4	35.4	37.7	34.4	31.3	36.6	32.4	18.9	29.0	28.5	26.4	32.9	41.4
	Aft-T	35.5	15.0	12.7	36.2	36.5	36.4	32.8	37.5	33.7	31.3	34.3	32.6	35.4	35.2	40.6

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; CB, conjugated bilirubin; GGT, gamma-glutamyl transpeptidase;ALP, alkaline phosphatase; ALB, albumin; C-P score, Child-Pugh score; Pre-T, pre-treatment with immunosuppressive therapy; Aft-T, after treatment with immunosuppressive therapy

Discussion

SLE is a chronic autoimmune inflammatory disease with a variety of clinical manifestations and positive autoantibody spectra. Common manifestations of SLE include fever, erythra, arthritis, renal injury, abnormal hematopoietic function, encephalopathy, lymphadenectasis, and myocardial involvement [1,4]. Lupus has only rarely been reported to cause hepatic injury. However, in recent years, lupus-induced hepatic injury has been increasingly observed [5,6]. In 1956, Cowling first reported a case of liver injury caused by lupus, and multiple studies followed reporting lupus-related liver injury [7]. For instance, Gibson found that 55% of patients with SLE had secondary liver injuries [8]. In addition, Vaiphei's study showed elevated levels of ALT in 81% of SLE patients [9]. A meta-analysis by Runyon covering 238 patients with SLE indicated that 43 cases had secondary liver injuries, with 6 patients dying from liver failure [10]. Liver biopsies of 33 cases with

Table 3. — **Autoantibody spectrum and C_3/C_4**

No	**ANA**	**AMA**	**SMA**	**SSA**	**SSB**	**RNP**	**Ds-DNA**	**NA**	**Scl-70**	**ANCA**	**AMA-M2**	**RA**	C3/C4
1	1:1000	n	n	n	n	n	2+	n	n	\	n	4+	↓/↓
2	1:1000	n	n	4+	n	4+	n	n	n	n	n	n	↓/n
3	1:320	n	n	\	\	\	\	\	\	\	\	\	\
4	1:1000	\	\	\	\	\	\	\	\	\	\	\	↓/↓
5	1:320	n	n	4+	2+	n	n	n	n	\	1+	n	n/n
6	1:3200	n	n	n	n	n	3+	n	n	n	n	n	\
7	1:1000	n	n	n	n	n	2+	n	n	n	n	n	↓/n
8	1:1000	n	n	n	n	n	1+	n	n	n	n	n	n/n
9	1:320	n	n	1+	n	n	n	1+	n	n	n	n	↓/n
10	1:3200	n	n	n	n	n	n	n	n	1:32	n	n	↓/n
11	1:1000	n	n	n	n	n	1+	2+	n	n	n	n	↓/↓
12	1:3200	n	n	1+	n	n	2+	1+	1+	n	n	n	↓/↓
13	1:100	n	n	3+	n	n	n	n	n	n	n	n	↓/↓
14	1:1000	n	n	n	n	n	2+	n	n	1:32	n	n	↓/↓
15	1:1000	n	n	3+	n	1+	n	n	n	n	n	3+	N/N

ANA, anti-nuclear antibodies; AMA, anti-mitochondrial antibodies; SMA, smooth muscle antibodies; SSA, Sjögren's syndrome antigen type A; SSB, Sjögren's syndrome antigen type B; RNP, ribonucleoprotein; Ds-DNA, Double-stranded-DNA; NA, nucleosome antibodies; Scl-70, Scleroderma 70 antigen; ANCA, anti-neutrophil cytoplasmic antibodies; AMA-M2, anti-mitochondrial antibodies type M2; RA, ribosomal antibody; C3/C4, compliment 3/4; \, none detected; n, normal.

liver injuries showed the histopathological presentations of liver tissue damage, including active inflammatory changes, cirrhosis, allergic granulomatosis, vasculitis, and steatosis. Lu reported that the proportion of SLE patients with liver disease as the first manifestation can account for 6.3–37.1% of all lupus cases, and those patients who find themselves treated by someone other than an immune specialist are easily misdiagnosed, at a rate of 62.5–81% [11].

A total of 15 SLE patients who had been hospitalized in the department of liver diseases in the same hospital with abnormal liver function as the chief complaint were retrospectively analyzed in this study. Among these, 8 cases (53.3%) were not definitively diagnosed with SLE-induced liver injury upon the first visit. The shortest time to diagnose SLE-induced liver injury was 2 weeks after disease onset, and the longest more than 8 years. This indicates that the rate of misdiagnosis of SLE in patients with liver disease is relatively high in the liver department of our hospital. The remaining 7 cases (46.7%) were treated for liver disease symptoms after definitive diagnosis with SLE. The interval between the first presentation of liver damage to diagnosis of SLE ranged from 1 to 15 years. One of the 15 cases developed ascites with cirrhosis ; another presented with bleeding of the esophageal varices with cirrhosis, and still another died of chronic liver failure due to the cirrhotic condition. Autoimmune hepatitis, drug-induced liver damage, and unexplained cirrhosis were the most common first diagnoses for this group of patients. For the 8 cases described above, it was later clear that liver damage was caused by SLE.

Multiple organ damage is the main clinical characteristic of SLE. It is caused by autoimmune abnormality with a variety of clinical symptoms and serological presentations [1,3–4]. SLE in patients with liver injury can be accompanied by abnormal function of any other organ or system, including skin, joints, kidneys, and blood system, as observed in the patients of this study. Due to the abnormal autoantibody screening results, it is easy to diagnose autoimmune hepatitis (AIH) in patients with SLE-induced liver injury in the department of liver diseases. AIH, which is a specific autoimmune disease mainly limited to the liver and prone to develop chronic and active hepatitis, is very distinct from SLE-induced liver injury [12]. It manifests primarily as abnormal liver function, elevation of liver enzymes such as ALT, AST, GGT, and ALP, and is more common and salient than SLE-induced liver injury. Other autoimmune diseases, including Sjögren's syndrome, rheumatoid arthritis, and thyroiditis, may co-occur in 17–48% of patients with AIH, but they only rarely co-occur with the injury of the skin, kidney, or hematological system. In addition, SMA (in AIH type I), anti-LKM (in AIH type II), and anti-SLA/LP (in AIH type III) are often heavily expressed autoantibodies in patients with AIH [12,13]. ANA has a very high positivity (> 98%) in SLE, but it is also often positive in other autoimmune diseases. Anti-dsDNA and anti-Sm have high specificity but relatively lower sensitivity in SLE[5]. It is often helpful for clinic diagnosing SLE and differentiate it from other autoimmune diseases by joint detection of ANA, anti-dsDNA and anti-Sm combined with multiple organ damage and SLICC

scoring criteria. But histology is the most important method to definitively diagnose SLE and differentiate it from the other autoimmune diseases [4].

SLE complicated with liver injury can be misdiagnosed as drug-induced liver injury. This is due to the potential liver toxicity of some drugs used to treat SLE, such as CTX (cyclophosphamide) and azathioprine [14,15]. Although the curative effect of CTX is documented in SLE patients with kidney, central nervous system, and vascular injury, it has been reported that liver function can be recovered by patients with SLE-induced liver injury after treatment with CTX combined with glucocorticosteroids [16]. However, the use of CTX in patients with SLE-induced liver injury remains controversial due to its potential liver toxicity. Because liver injury occurs during the treatment (including CTX and/or azathioprine) of SLE patients, it is difficult to determine whether liver injury is caused by an insufficient course of original treatments to control the SLE-induced liver injury or is caused by liver toxicity of the drugs. For this reason, liver histology should be performed as early as possible to identify the cause of liver injury. To avoid secondary drug-induced liver injury, rapamycin rather than CTX or azathioprine was selected and combined with methylprednisolone to control active SLE, and the therapeutic results were observed in this group of patients.

A total of 5 cases were initially diagnosed with cirrhosis due the abdominal cavity effusion observed by B ultrasound. Further examination revealed only 2 cases to have any evidence of cirrhosis with portal hypertension, such as esophageal varices under gastroscopy. Cirrhosis was ruled out in the remaining 3 cases through ultrasonographic inspection, computed tomography (CT), and gastroscopy, with further examination revealing bilateral pleural effusion and pericardial effusion. Multiple serous cavity effusion is also very common in patients with SLE, but it comes from the exudate with elevated levels of protein and lactate dehydrogenase (LDH) in the fluid, and it is not solely located in the serous cavity. After SLE targeted treatment, serous cavity effusion can be quickly absorbed, and administration of corticosteroids and rapamycin in combination was found to eliminate the serous cavity effusion within one month in the 3 patients with SLE described above.

From the results obtained here, the overall prognosis of the cases after treatment with corticosteroids and rapamycin in combination was found to quite satisfactory. This was mainly due to the synergic inhibitory effects of these drugs on non-bacterial inflammation, which is closely related to consequent liver injury with oxidative stress [17].

This paper was only the retrospective study based on the medical record database, it was regretful to found that none of this group patients underwent liver biopsy. The diagnosis of SLE in this group patients was made by consultation of the specialist physicians of rheumatic immunology , although they had ever left the suggestion of liver or kidney biopsy in consultation sheets, none of this group of patients was willing to accept biopsy.

In conclusion, SLE is an autoimmune disease that can induce multiple organ injury, and SLE-related liver injury is not rare. When a SLE patient visits a health service center with the major complaint of abnormal liver function with no damage to the kidneys, skin, or other organs, a tentative diagnosis of hepatitis can be made readily, which may delaying the correct diagnosis of SLE. For such patients, physicians should provide a correct differential diagnosis as soon as possible and administer proper treatment to prevent adverse consequences. Corticosteroids combined with immunosuppressants with no or little liver toxicity should be considered suitable for patients with SLE-induced liver injury.

Conflict of interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

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