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ABSTRACT

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Case Report: Herein, we report a case of a 17-year-old female with a two-year history of multiple joint pain, six-month history of swelling, rash, mouth ulcers and a 15-day history of jaundice. An investigation revealed positive antinuclear antibody, positive anti-DsDNA, low serum C3, C4, very high serum bilirubin, high SGOT/SGPT and nephrotic range proteinuria. Antibody tests for autoimmune hepatitis were negative. Renal biopsy showed focal proliferative lupus nephritis. Liver biopsy was suggestive of lupus-hepatitis. Jaundice responded to steroid therapy dramatically.

Conclusion: Lupus associated hepatic disease must be differentiated from hepatitis caused by drugs, toxins, viral and other autoimmune diseases. Liver histology may be necessary to confirm a diagnosis.

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CASE REPORT

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Keywords: Lupus nephritis, Lupus associated hepatitis, Autoimmune hepatitis

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INTRODUCTION

Systemic lupus erythematosus (SLE) and autoimmune hepatitis (AIH) both are autoimmune disease causing inflammation of the liver. Prior treatment with potentially hepatotoxic drugs or viral hepatitis is usually responsible for the main cause of liver disease in SLE patients. If we exclude all the possible causes of liver disease in a patient of active SLE, primary liver disease may have autoimmune association or may be presentation of active SLE itself. It is necessary to know whether the autoimmune hepatitis and lupus hepatitis are the spectrum of same disease or both are different entities. In this case report, we present lupus associated hepatitis in active lupus nephritis patient.

CASE REPORT

A 17-year-old unmarried female presented with a two-year history of multiple joint pain, six-month history of on and off swelling of whole body, mouth ulcers and characteristic butterfly rash over face and a 15-day history of jaundice. She had been treated on and off with tramadol hydrochloride for joint pain since last six months. No other new medications were reported. She denied any sick contacts, recent travels, or new diet. Her laboratory profile is given in Table 1. Wilson's disease

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Table 1: Laboratory profile of the patient.

Hemoglobin	7.8 g/dL
TLC	9700/mm ³
Platelet count	2.3x10 ⁵ /mm ³
Serum creatinine	1.5 mg/dL
Blood urea	64 mg/dL
Serum albumin	1.7g/dL
AST (SGOT) and ALT (SGPT)	830 and 698 U/L
Serum bilirubin(Total / Direct / Indirect)	11.21 / 7.45 / 3.76 mg/dL
Gamma-glutamyltranspeptidase	727 U/L(increased)
alkaline phosphatase	505 U/L(increased)
ESR	115 mm
Serum CRP	54 mg/L
Serum RA factor	Negative
ASO/anti U1 RNP/Anti Jo1 antibody	Negative
Antinuclear antibody	Positive
Anti-DsDNA	Positive
Serum C3 and C4	41.1 mg/dL (low) and 4.5 mg/dL (low)
Anti-ribosomal P antibody	Positive
Serum HIV, HBsAg, antiHCV	Non reactive
Hepatitis C virus RNA (by PCR)	Negative
IgM anti HAV, Ig M antiHEV	Negative
Cytomegalovirus DNA (by PCR)	Negative
Epstein-Barr Virus DNA (by PCR)	Negative
Antibodies against smooth muscle (SMA) and liver/kidney microsomes (LKM)	Negative
Urine routine & microscopy	Protein: 3+, RBCs: 10-15/hpf, WBCs:2-3/hpf
24-hour urine protein	6.3 g/day

Figure 2: Capillary and mesangial deposits of IgG in a glomerulus, (Immunofluorescence, x400).

Figure 3: Liver biopsy specimen showing mild chronic hepatitis with predominantly lobular inflammation, with mild chronic inflammatory infiltrate in portal tracts and mild cholestasis with maintained lobular architecture.

Figure 1: Kidney biopsy specimen showing a glomerulus with focal endocapillary proliferation and mesangial expansion (H&E stain, x400).

was excluded because of normal serum ceruloplasmin, normal 24-hour urinary copper levels and negative Kayser Fleischer ring on slit lamp microscopy. Serum immunoglobulin G and M levels were increased 3608 and 152 mg/dL, respectively. The patient showed 6 out of 11 American College of Rheumatology (ACR) criteria for SLE which classified her as definite SLE [1]. Renal biopsy revealed class IIIA (focal proliferative) kidney disease

according to the International society of nephrology and renal pathology society 2004 classification. Renal biopsy, on light microscopy (Figure 1) showed 6/14 (42.8%) glomeruli with segmental increase in endocapillary cellularity with mesangial expansion and mild neutrophilic infiltration, focal tubular atrophy and necrosis, mild chronic inflammatory infiltrate in interstitium, focal fibrosis and unremarkable vessels. Immunofluorescence showed full house pattern (deposition of IgG, C3, IgA, IgM, C1q and fibrinogen) of immunoglobulin deposition both in mesangium and capillary walls (Figure 2). Liver biopsy showed maintained lobular architecture with mild chronic inflammatory infiltrate in portal tracts with predominantly lobular inflammation and mild cholestasis (Figure 3). Patient was diagnosed to be having lupus nephritis class IIIA with nephrotic syndrome with lupus hepatitis. In the view of class IIIA lupus nephritis with lupus hepatitis, methyl prednisolone 500 mg/day for three days was given followed by 30 mg/day oral prednisolone. Liver function tests (serum bilirubin and SGOT/SGPT) normalized within two weeks. After two weeks, she was managed on the line of lupus nephritis according to Euro-Lupus regimen [2]; cyclophosphamide was given 500 mg intravenously every two weeks for six doses as induction therapy and azathioprine 2.0 mg/kg/day was used as maintenance therapy after two weeks of last cyclophosphamide injection. After six months her serum creatinine was 0.9 mg/dL, 24-hour urine protein was 160 mg/day and liver enzyme levels were within normal limit. After one year follow-up, her serum creatinine was 0.8 mg/dL, 24-hour urine protein was 86 mg/day and liver enzyme levels were within normal limit.

DISCUSSION

One to four percent patients of SLE have jaundice, and it is usually secondary to hemolysis, hepatitis or pancreatitis [3]. Ten to thirty-one percent patients of SLE have hepatomegaly [3]. Elevated liver enzyme levels greater than three times normal are rare in case of active lupus [3]. Infections, salicylates or NSAIDs are responsible for most of the cases [3]. In this case, the patient had active lupus nephritis, hepatomegaly, markedly elevated serum bilirubin and liver enzymes. The incidence of SLE associated hepatitis is difficult to ascertain. Piga et al. reported 5.8% incidence of lupus hepatitis in their study of 242 patients of SLE during a mean follow-up of 72.2 months [4]. Efe et al. reported 4.7% incidence of autoimmune liver disease in SLE patients [5]. Literature shows that anti-ribosomal P-proteins are strongly associated with “lupus hepatitis”, while these antibodies are found in only 10% of patients with SLE without liver disease [6]. This test was found to be positive in our case patient. No drug, alcohol, or other cause is found in approximately one-third of patients with abnormal liver tests in SLE [3]. The biopsy picture of lupus hepatitis shows predominantly lobular

inflammation with maintained lobular architecture and mild chronic infiltrate in portal tracts [3]. There is paucity of lymphoid infiltrates and absence of plasma cells in liver biopsy of lupus hepatitis [7]. Liver biopsy of our case patient showed features suggestive of lupus hepatitis. There are three subclasses of AIH in literature. Type 1 AIH is the most common type worldwide (80% cases) and is associated with ANA and/or smooth muscle antibodies (SMA) [8]. Anti-liver/kidney microsomal 1 (Anti-LKM1) antibodies are positive in Type 2 AIH [8]. Type 3 is the least common type of the disease. Anti-soluble liver/liver pancreas antigen (anti-SLA/LP) is present in serum of the patients of Type 3 AIH [8]. The criteria for the diagnosis of AIH in adult patients have been given by the International Autoimmune Hepatitis Group (IAIHG) [9]. Both laboratory and liver histology features are required for the diagnosis and conditions that resemble AIH should be excluded [7] (Table 2). Atsumi et al. reported two cases of severe hepatic involvement without inflammatory changes in systemic lupus erythematosus and found that corticosteroid therapy is effective in lupus hepatitis [10].

Table 2: Differentiating features of Lupus associated hepatitis and autoimmune hepatitis in SLE [4–10].

	Lupus-associated hepatitis	Autoimmune hepatitis
Incidence	5.8%	4.7%
ANA+	Most of the patients	80% Type I AIH
Complement C3, C4	low in active disease	Usually normal
Smooth muscle antibody (SMA)	May be positive	Usually positive in Type I AIH
Anti-liver/kidney microsomal 1 antibodies	Negative	Positive in Type 2 AIH
Anti-soluble liver/liver-pancreas antigen	Negative	Positive in Type 3 AIH
Anti-ribosomal P antibody	Positive	Negative
Histology	Lobular, rarely-periportal, paucity of lymphocytes mild chronic inflammation	Periportal, piecemeal necrosis, plenty of lymphocytes, plasma cell infiltration, interface hepatitis
Response to steroids	Positive response	Positive response
Progression	Histopathologically benign	May progress to cirrhosis

CONCLUSION

Lupus associated hepatic disease must be differentiated from hepatitis caused by drugs, toxins, viral and other autoimmune diseases. Liver histology may be necessary to confirm a diagnosis of lupus hepatitis or autoimmune hepatitis if liver enzymes are increased in the scenario of active systemic lupus erythematosus.

Author Contributions

Sham Sunder – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Satyanand Sathi – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Himanshu Mahapatra – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Rajesh J – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

Anurag Gupta – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Prabhu K – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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