DOI: 10.7860/JCDR/2020/44121.13906

Case Report

Internal Medicine Section

Seronegative Lupus- A Wolf in Sheep's Skin

ERAM NAHID[1], SAUMYA GUPTA[2], DEEPAK GAUTAM[3], INDRAJEET SINGH GAMBHIR[4]

ABSTRACT

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory multisystem autoimmune disease. Most of the SLE cases are seropositive, but rare (5%) seronegative SLE cases can also present with complications. Hepatic involvement SLE is multifactorial like hepatotoxic drugs, steatohepatitis, viral hepatitis and Autoimmune Hepatitis (AIH). However, the differentiation between lupus-related hepatitis and AIH remains a challenge to the clinician because of many similar features. It is very difficult to differentiate whether hepatitis is due to autoimmune involvement or purely lupus related on the basis of clinical and biochemical parameters. The patient must fulfill ACR criteria for SLE and International Autoimmune Hepatitis Group (IAIHG) criteria for AIH. Histological diagnosis is considered to be definative in differentiating SLE-related hepatitis and AIH. The cardiac manifestations of SLE are multiple with pericardial disease being the most common. While pericardial effusion is rarely haemodynamically significant, the occurrence of subsequent constrictive pericarditis is even less frequent with only occasional reports in the literature. Authors described a case of a 17-year-old female with Antinuclear Antibody (ANA) negative active SLE (seronegative) with AIH and constrictive pericarditis. The patient responded well to the conservative management initially but later developed drug induced myelosuppression and bilateral pneumonia and succumbed.

Keywords: Autoimmune hepatitis, Antinuclear Antibody, Constrictive pericarditis

CASE REPORT

A 17-year-old female presented with complaints of fever on-and-off for 3 months, multiple joint pain for 2 months (large joints, no morning stiffness), associated with swelling and pain in joints, chest pain (central and pleuritic) for 20 days, chest pain was persistent, aggravated by deep breathing or coughing and nonradiating. Nonproductive cough was present for 3 days and amenorrhea for 3 months.

On examination PR was 86/min, BP was 120/80 mm Hg, RR was 18/min, pallor present, erythematous macular rashes were present over malar areas bilaterally and eye lids, bilateral lower lung fields had decreased air entry. Other general physical and systemic examination was normal. The patient was investigated and results have been summarised in [Table/Fig-1]. In view of deranged Liver Function Test, autoimmune liver profile (ELISA) was sent and it turned out to be strongly positive ((Anti-Smith Antibody [Anti-SMA] and anti F-ACTIN antibody). In view of The Systemic Lupus International Collaborating Clinics (SLICC) 2012 and IAIHG criteria, a diagnosis of seronegative lupus with AIH with constrictive pericarditis was kept [1].

Patient was started on tab hydroxychloroquine, tab prednisone 60 mg/day and azathioprine 50 mg/day. After 3 days of starting this treatment patient developed features of psychosis in the form of irrelevant talking, restlessness, running out of bed and emotional lability. Since, these complaints were not present initially and started only after treatment was initiated, a possibility of drug induced psychosis was kept. Steroids are known to cause psychosis at higher doses therefore dose of steroid was reduced to half i.e., 30 mg/day. On reducing the dose, symptoms of psychosis improved within 2 days. To confirm the aetiology, again the patient was challenged with 60 mg of prednisolone which was followed by development of psychotic features in 2-3 days and resolved on reducing the dose. Patient was finally prescribed tab hydroxychloroquine 400 mg/day, tab prednisone 30 mg/day and azathioprine 50 mg/day and responded well to treatment and she was discharged with following laboratory profile [Table/Fig-2], repeat ANA test was also negative.

Patient was kept on monthly follow-up. Her rash cleared, joint pain resolved, repeat 2D echocardiography suggested Ejection Fraction-65%, mitral valve inflow variation of 28%, septal bounce present. Patient was planned for pericardiectomy but the patient developed bilateral pneumonia with drug induced myelosupression 3 months later and succumbed.

DISCUSSION

SLE is an autoimmune disease that may affect any organ of the body. In SLE organs and cells undergo damage mediated by tissue binding auto antibodies and immune complexes [1]. This disease is characterised by the production of various auto antibodies such as ANA, Anti-double stranded DNA antibodies (Anti-dsDNA), anti Sm antibodies, anti Ro/La antibodies, antihistone antibodies, anti RNP antibodies. ANA are present in more than 98% of the patients with lupus. Anti-double stranded DNA antibody and anti Sm antibodies are specific for lupus. But these are not essential for the diagnosis. ANA negative SLE was first introduced by Koller SR et al., with five cases with clinical features similar to SLE [2]. But with the introduction of HEp-2 cells (a rapidly dividing human epithelial cell line) as a substrate for ANA determination has significantly increased the sensitivity and standardisation of the assay. ANA negative lupus in HEp-2 era is extremely rare [3-5]. SLE is a multi-system autoimmune disorder of unknown aetiology with varied clinical presentations. Kidneys are the most common organs to be involved. Cardiac manifestations develop in the bulk of patients with SLE at some point during the course of the disease. In most of the patients involvement of Cardiovascular system has become the major cause of death. Cardiac manifestations of lupus may involve the pericardium, myocardium, endocardium, valvular apparatus, conducting system and coronary vessels [6,7]. The aetiology of pericarditis in SLE may be active disease, uremia or infection [8,9]. Common clinicopathological types of lupus pericarditis include acute fibrinous, serous, chronic focal adhesive,

Date	07/12/2017	13/12/2017	19/12/2017	25/12/2017
Hb (gm/dL)	9.8	8.9		
TLC (/mm^3)	3600 (N=71%, L=23%)	3020		
Platelet (/mm^3)	1.4L	1.14L		
MCV (fl)	76	75		
Creatinine/Urea (mg/dL)	0.6/20	0.5/32		
NA/K (meq/l)	135/4.1			
SGOT/SGPT (units/l)	146/101	**1500/271**	**2905/582**	**1464/745**
TB/DB (mg/dL)	1.4/0.5	**4.6/4**	**4.9/3.7**	**4.3/4**
TP/ALB (Total Protein/Albumin)		**6.8/2.9**		
LDH (Lactate Dehydrogenase)(units/l)	911			
FE/TIBC (Iron/Total Iron Binding Capacity) (mcg/dL)	28/240			
CPK (Creatine Phosphokinase)	387		147	
Alkaline Phosphatase (ALP)	236	1048	688	500
Urine R/M	1-2 PUS CELLS, ALBUMIN in traces 0-1 RBC	**Digital Chest X-ray**	**B/L pleural effusion**	
2D Echo Cardiography		**Constrictive pericarditis,** Pericardial thickening 6.8 mm Mitral valve inflow variation=32% Septal bounce +nt		
INR/aPTT		1.46/48		
Colour Doppler HPVS and USG abdomen		normal		
24 hour urinary protein		79 mg/day		
Pleural Fluid Analysis		Cells-2161/mm^3 Protein-4.02 gm Sugar-128 mg LDH-5487 iu AFB, gram stain and culture-negative		
Fundus		fluffy cotton wool spots present s/o active vasculitis		
ECG		Low voltage complexes		
HBsAg, Anti HCV, HIV		Negative		
Positive Direct coombs test IgM Anticardiolipin Antibody, IgG weakly +ve C3, C4 low	**Negative** ANA, Anti-dsDNA, Anti SM Antibody Lupus anticoagulant, anti B2 glycoprotein Anti scl-70, anti Jo-1, Anti U1RNP, Anti RO/SSA, Anti LA/SSB Ana was equivocal both by ELISA and indirect immunoflorescence (HEp-2)	Serum was used for all these tests. ANA was done both with ELISA and IIF assays using HEp-2 Cells		

[Table/Fig-1]: Laboratory profile during admission.

On discharge 7/01/2018	
Hb	10.3 gm/dL
TLC	6270/mm^3
Platelet Count	1.5 lacs/mm^3
MCV	83 fl
SGOT/SGPT	450/232
TB/DB	2.9/2.3
PT/INR/aPTT	12.3/0.96/23
Creatinine/Urea	0.6/36
10/02/2018	
SGPT/SGOT	123/144
TB/DB	1.2/0.6
Hb	11 gm/dL
TLC	7600/mm^3
Platelet Count	1.98 lacs/mm^3
Joint pain and rash resolved	
2D-echo (5/03/2018)	Ejection Fraction-65%, mitral valve inflow variation of 28%, septal bounce +nt
4/04/2018	
TLC	2630/mm^3
Hb	6 gm/dL
Platelet Count	84000/mm^3

Chest x ray PA view	Bilateral lower lobe pneumonia
Clinical presentation	Fever and cough with minimal expectoration for 4 days and shortness of breath for 2 days o/e- patient was drowsy, E4V5M6, RR-40/min, BP-80/40 mmhg, SpO2-68% on room air

[Table/Fig-2]: Laboratory profile on discharge.
Hb: Haemoglobin; TLC: Total leucocyte count; SGOT/SGPT: Aspartate transaminase/Alanine transaminase; MCV: Mean corpuscular volume; TB/DB: Total bilirubin/Direct bilirubin; PT: Prothrombin time; aPPT: Partial thromboplastin time; INR: International normalised ratio

generalised adhesive and haemorrhagic pericarditis. Suppurative and constrictive pericarditis are less frequently reported [6,7]. Renal involvement is common in lupus patients with pericarditis. Hepatic involvement in patients with SLE is considered to be rare and if present hepatotoxic drugs, coincident viral hepatitis, Non-Alcoholic Fatty Liver Disease (NAFLD), concurrent AIH should be ruled out. Clinical and biochemical data may not clearly differentiate whether hepatitis is due to autoimmune involvement or purely lupus-related. A 90-95% of SLE patients are positive for ANA and its titer is one of the key diagnostic criteria for SLE. But ANA positivity is not mandatory for the diagnosis [10]. The cases of ANA-negative lupus were first described by Koller SR et al., in 5 patients [2]. Cutaneous manifestation, particularly photosensitivity was the predominant feature in first few cases of seronegative SLE [11]. The diagnosis of SLE is based on characteristic clinical features and auto antibodies. The current criteria are meant for classification and estimation of the

probability that the disease is SLE. The 2012 SLICC criteria says any combination of four or more criteria, with at least one in clinical and one in immunological category, reported at any time during an individual's history, makes SLE the likely diagnosis [1]. The 2012 SLICC criteria for diagnosing AIH in SLE, the patient must fulfill ACR criteria for SLE and IAIHG criteria [Table/Fig-3] for AIH [12,13] (our patient had a score of 15). Histological evidence is considered to be conclusive in differentiating SLE related hepatitis and AIH. Auto-antibodies may help in differentiating these two entities. ANAs can be found in both these conditions; however, antismooth muscle and antimitochondrial antibodies are rare in SLE-related hepatitis (<30%) and often found in low titers. This patient had no renal impairment, proteinuria or oedema, thus making the pericarditis more likely to be the result of the active lupus process. Our patient initially presented with pyrexia of unknown origin complicated with hepatic impairment and cardiac involvement. Despite seronegativity and absence of renal involvement, she was diagnosed as SLE [4,9,10]. If patient fulfils criteria for SLE despite seronegativity, diagnosis and treatment should not be delayed as 5-10% of SLE patient are seronegative and SLE is still a disease with significant morbidity and mortality.

Required parameters	Score
Female	+2
Ratio of serum alkaline phosphatase to aminotransferase activities (in IU/l) <3.0	+2
Total serum globulin or gammaglobulin or IgG: upper limit=1.0-1.5	0
Autoantibodies (titers ANA/SMA/LKM-1); adults >1:80; children >1:20	+3
Seronegative for markers hepatitis A, B and C	+3
No history of recent hepatotoxic drug usage or parenteral exposure to blood products	+1
Alcohol average consumption <25 g/day	+2
Other autoimmune disease in patient	0
Liver histology	-5
Additional parameters Complete response to therapy	+2
Interpretation Before treatment >15 10-15 After treatment >17 12-17	 Definite Probable Definite Probable
Pre-treatment score was 15 for the patient	

[Table/Fig-3]: Evaluation of Autoimmune Hepatitis (AIH) in the patient as per International Autoimmune Hepatitis Group (IAIHG) scoring system.

CONCLUSION(S)

The introduction of HEp-2 cells as a substrate for ANA determination has significantly increased the sensitivity and standardisation of this assay. ANA negative lupus in HEp-2 era is extremely rare. But if the patient fulfils ACR or SLICC criteria for SLE then despite seronegativity, diagnosis should not be delayed as 5-10% patients of SLE are seronegative and delay in diagnosis and initiation of appropriate management can lead to grave prognosis. This case makes us understand that a high degree of clinical suspicion together with the laboratory picture is essential for timely diagnosis and management and while managing patients with immunosupressants, drug induced complications must be carefully monitored and necessary precautions should be explained to the patients. In present case patient was managed conservatively, but developed drug induced myelosuppression with bilateral pneumonia and succumbed.

REFERENCES

[1] Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-86.
[2] Koller SR, Johnston CL Jr, Moncure CW. Lupus erythematosus cell preparation-antinuclear factor incongruity. A review of diagnostic tests for systemic lupus erythematosus. Am J Clin Pathol. 1976;66:495-505.
[3] Kavanaugh A, Tomar R, Reveille J, Solomon DH, Homburger HA. Guidelines for clinical use of the antinuclear antibody test and tests for specific autoantibodies to nuclear antigens. American College of Pathologists. Arch Pathol Lab Med. 2000;124:71-81.
[4] Worrall JG, Snaith ML, Batchelor JR, Isenberg DA. SLE: A rheumatological view. Analysis of the clinical features, serology and immunogenetics of 100 SLE patients during long-term follow-up. Q J Med. 1990;74:319-30.
[5] De Zoysa HDJ, Peranantharajah T, Aravinthan N, Nisahan B. A young lady with seronegative systemic lupus erythematosus. Int J Clin Rheumatol. 2017;12(2):38-40.
[6] Tarner IH, Lange U, Madlener K, Classen K, Kandolf R, Sperzel JKH, et al. Der Wolf im Schafspelz: Atypischer systemischer Lupus erythematodes (SLE) mit führender kardiovaskulärer Symptomatik [A wolf in sheep's clothing: Atypical systemic lupus erythematosus (SLE) presenting as cardiovascular disease]. Med Klin (Munich). 2010;105(4):300-04. doi:10.1007/s00063-010-1048-0.
[7] Jain D, Halushka MK. Cardiac pathology of systemic lupus erythematosus. Journal of Clinical Pathology. 2009;62:584-92.
[8] Jacobson EJ, Reza MJ. Constrictive pericarditis in systemic lupus erythematosus: Demonstration of immunoglobulins in the pericardium. Arthritis Rheum 1978;21:972-74.
[9] Cervera R, Font J, Pare C, Azqueta M, Pérez-Villa F, López-Soto A, et al. Cardiac disease in systemic lupus erythematosus: prospective study of 70 patients. Ann Rheum Dis. 1992;51:156-59.
[10] Ferreiro JE, Reiter WM, Saldana MJ. Systemic lupus erythematosus presenting as chronic serositis with no demonstrable antinuclear antibodies. Am J Med. 1984;76:1100-15.
[11] McHardy KC, Horne CH, Rennie J. Antinuclear antibody-negative systemic lupus erythematosus-how common? J Clin Pathol. 1982;35:1118-21.
[12] Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International AutoimmuneHepatitis Group Report: Review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999;31(5):929-38.
[13] Hochberg MC. Updating the American College of Rheumatology of revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of General Medicine, Institute of Medical Sciences BHU, Varanasi, Uttar Pradesh, India.
2. Assistant Professor, Department of General Medicine, Institute of Medical Sciences BHU, Varanasi, Uttar Pradesh, India.
3. Associate Professor, Department of General Medicine, Institute of Medical Sciences BHU, Varanasi, Uttar Pradesh, India.
4. Professor, Department of Geriatric Medicine, Institute of Medical Sciences BHU, Varanasi, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Saumya Gupta,
Assistant Professor, Department of General Medicine, Institute of Medical Sciences BHU, Varanasi-221005, Uttar Pradesh, India.
E-mail: g_saumya@yahoo.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 19, 2020
- Manual Googling: Jun 22, 2020
- iThenticate Software: Jul 24, 2020 (12%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Mar 18, 2020**
Date of Peer Review: **May 01, 2020**
Date of Acceptance: **Jun 23, 2020**
Date of Publishing: **Aug 01, 2020**