Antinuclear antibody-negative lupus? An ominous presentation of hydralazine-induced lupus syndrome

Theodros Solomon-Tsegaye¹, Edward L. Treadwell², Reginald Obi³, Mariavittoria Pitzalis⁴

Abstract

Up to 10% of systemic lupus erythematosus (SLE) cases are drug-induced; hence, they are called drug-induced lupus syndrome (DILS). Antinuclear antibody (ANA) should be present to diagnose SLE and DILS. ANA-negative lupus is very rare; therefore, it presents a diagnostic challenge. In the medical literature, two cases of ANA-negative hydralazine-induced lupus syndrome (HILS) have been described within the last year. Here, we present the third such case of HILS with negative ANA serology in a patient who developed considerable pericardial effusion. The association between ANA-negative HILS and pericardial effusion warrants future research.

Keywords: Systemic lupus erythematosus, drug-induced lupus syndrome, hydralazine-induced lupus syndrome, antinuclear antibody, pericardial effusion

Introduction

Hydralazine-induced lupus syndrome (HILS), a drug-induced lupus syndrome (DILS), is caused by hydralazine. Unlike classic systemic lupus erythematosus (SLE), DILS does not have any diagnostic criteria. Its diagnosis mainly exhibits a clinical, and sometimes temporal, relationship between SLE onset and the start of the offending drug, which is the only clue. HILS can present vague symptoms, including arthralgia, myalgia, fever, anorexia, and fatigue. Cutaneous and serosal involvements are infrequent; rarely, pericardial or pleural effusions can be the sole manifestation of the disease (1-4). Positive antinuclear antibody (ANA) serology is the standard for SLE and DILS diagnosis. In the literature, only two cases so far have described an unusual presentation of HILS with negative ANA (3, 4). In both these cases, patients presented with pericardial effusion. In this report, we describe the third patient with HILS who presented with negative ANA, large pericardial effusion, and impending cardiac tamponade.

Case Presentation

Written informed consent was obtained from the patient.

A 53-year-old man presented to our hospital’s emergency room with the chief complaint of left-side chest and flank pain that was associated with shortness of breath lasting 2 weeks. He had an insidious dull acheing pain of moderate intensity, which was constant on his left flank area. This occasionally radiated to his left chest and left groin region without any aggravating or alleviating factors. Other associated symptoms included a new onset of dyspnea on exertion, fatigue, and generalized muscle aches. There was no fever. His medical history was significant for end-stage renal disease (ESRD), secondary to biopsy-proven membranous nephropathy, renal vein thrombosis, and hypertension. He has been on hemodialysis for 4 years and very compliant with outpatient treatments. His home medications were aspirin, amlodipine, carvedilol, hydralazine, lisinopril, and sevelamer. During his hemodialysis sessions, he also received intravenous iron sucrose and doxercalciferol.

A physical examination revealed a body temperature of 36.9°C, heart rate of 67/min, blood pressure of 175/95 mmHg, respiratory rate of 18/min, and oxygen saturation at 98% in ambient air. Breathing sounds decreased on the bilateral lung fields, whereas heart sounds were normal with no murmur or gallop. Abdominal examination was only positive for the left-side costophrenic angle tenderness. No peripheral edema or skin changes were noted.

Laboratory tests were remarkable for leukopenia, normocytic anemia, and thrombocytopenia with a WBC count of 3.3×10³/µL, hemoglobin of 9.5 mg/dL, MCV of 92 fl, and platelet count of 118×10³/µL. Compre-
Comprehensive metabolic panel showed stable ESRD with BUN of 24 mg/dL, creatinine of 7.9 mg/dL, normal electrolytes, normal liver function with total bilirubin at 0.3 mg/dL, and normal albumin and total protein at 4.6 g/dL and 7.8 g/dL, respectively. Troponin was negative, and INR was normal. Serum iron was normal at 40 µg/dL and ferritin at 487 ng/mL. Elevated ESR with 57 mm/h and CRP at 10.1 mg/L were observed. Complement C3 was low at 64 mg/dL, and C4 was normal at 15 mg/dL. ANA and anti-DNA antibody were negative. In addition, anti-histone antibody was positive.

Chest X-ray showed an enlarged cardiac silhouette, but the electrocardiogram was normal. The computed tomography of the chest, abdominal, and pelvic regions with contrast were obtained (Figure 1); they revealed a very large circumferential pericardial effusion. Transthoracic echocardiography (ECHO) was performed, which confirmed a large (3.7×2.6 cm) pericardial effusion with indentation of the right ventricle, raising concern for early evidence of tamponade physiology, as per the ECHO criteria (Figure 2a). Intriguingly, the patient never showed any clinical signs of cardiac tamponade. Cardiology was consulted, and ultrasound-guided pericardiocentesis was performed with drainage of 1000 mL straw-colored pericardial fluid. A pericardial drain catheter was placed, which was removed two days later. Pericardial fluid analysis as per Light’s criteria was an exudate, and the cytology did not show any malignant cells.

The patient’s left-side chest and flank pain gradually improved over several days following the pericardial fluid drainage. Workup was negative for common causes of pericardial effusion, including myocardial infarction, infection, hemorrhage, hypoproteinemia, liver disease, and malignancy. There was no volume overload, and uremic pericarditis was unlikely in this very compliant hemodialysis patient who had maintained normal dialysis adequacy in his outpatient unit.

The only unifying explanation for the pericardial effusion was HILS despite having negative ANA. The patient had chronically been on hydralazine for hypertension. HILS should be suspected in any patient on hydralazine presenting with unexplained effusion; moreover, in our patient, additional laboratory evidence revealed the presence of active lupus, including low C3, elevated ESR and CRP, pancytopenia, negative anti-dsDNA, and positive anti-histone antibody (5). We believe the clinical picture and laboratory findings of our patient were consis-
The authors have no conflict of interest to declare.

The authors declared that this study has received no financial support.

References
1. Carey RM, Coleman M, Feder A. Pericardial tamponade: A major presenting manifestation of hydralazine-induced lupus syndrome. Am J Med 1973; 54: 84-7. [CrossRef]
2. Chamsi-Pasha MAR, Bassiouny M, Kim ESH. Hydralazine-induced lupus syndrome presenting with large pericardial effusion. QJM 2014; 107: 305-7. [CrossRef]
3. Iyer P, Dirweesh A, Zijoo R. Hydralazine Induced Lupus Syndrome Presenting with Recurrent Pericardial Effusion and a Negative Antinuclear Antibody. Case Rep Rheumatol 2017; 2017: 1-3. [CrossRef]
4. Zeitjian V, Mehdzadeh A. ANA-Negative Hydralazine-Induced Pericardial Effusion. Case Rep Med 2017; 2017: 3521541. [CrossRef]
5. Chang C, Gershwin ME. Drug-Induced Lupus Erythematosus: Incidence, Management and Prevention. Drug Saf 2011; 34: 357-74. [CrossRef]
6. Kaufman M. Pancytopenia Following Use of Hydralazine. “Apresoline”: Report of a Case. J Am Med Assoc 1953; 151: 1488-90. [CrossRef]
7. Finks SW, Finks AL, Self TH. Hydralazine-induced lupus: Maintaining vigilance with increased use in patients with heart failure. South Med J 2006; 99: 18-22. [CrossRef]
8. Batchelor JR, Welsh KI, Tinoco RM, Dollery CT, Hughes GR, Bernstein R, et al. Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. Lancet 1980; 1: 1107-9. [CrossRef]
9. Taylor M, Taylor AL, Ziesche S, Yancy C, Carson P, D’Agostino R, et al. Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure. N Engl J Med 2004; 351: 2049-57. [CrossRef]