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Case Report

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

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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

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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 aching 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-

hensive 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.

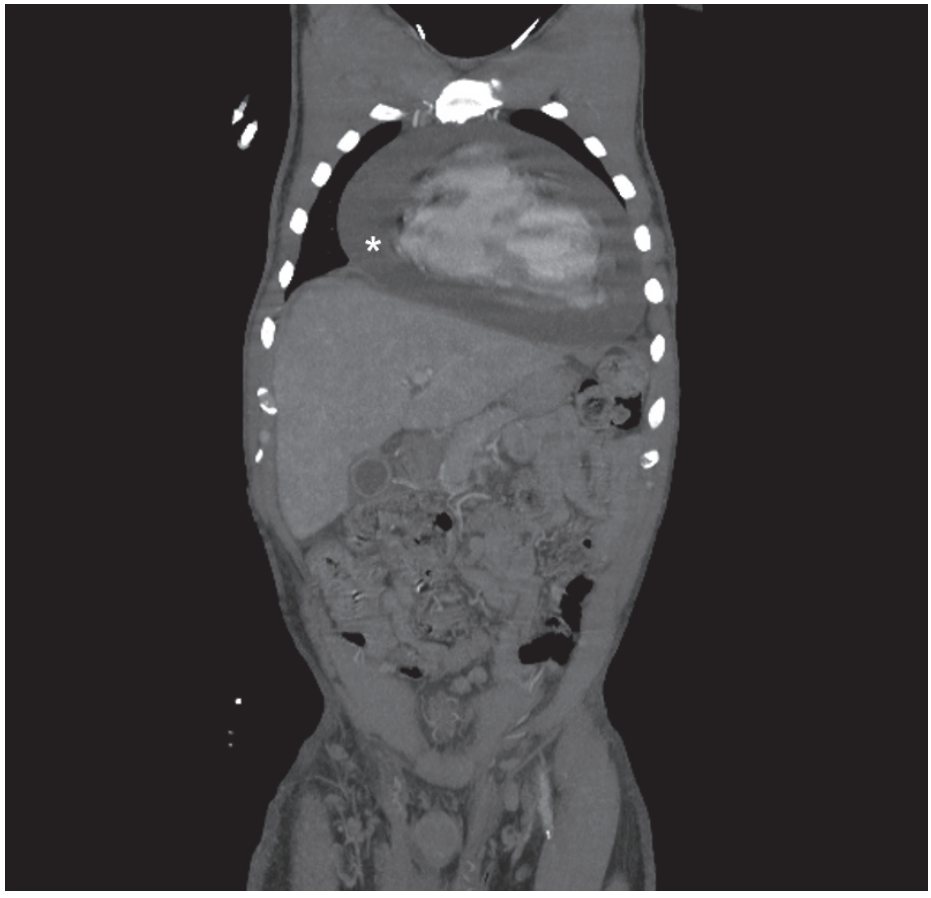

Figure 1. Computed Tomography with contrast images of the chest, abdomen, and pelvis in the coronal section at presentation
*denotes pericardial effusion; note the circumferential pericardial effusion surrounding the heart

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-

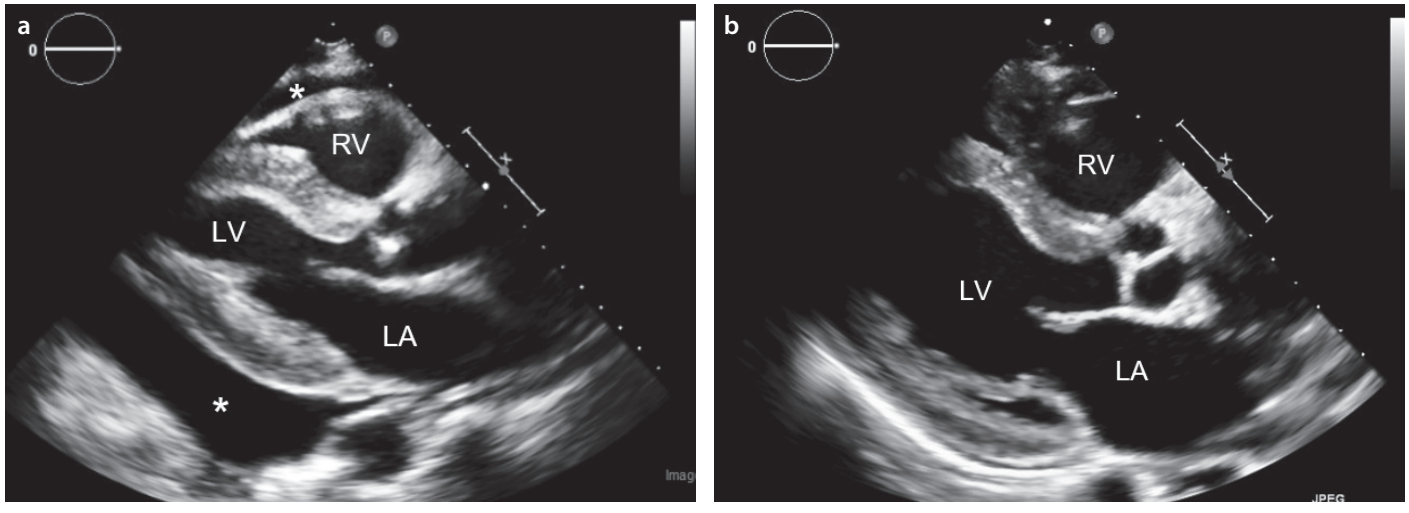

Figure 2. a, b. Two-dimensional echocardiogram (ECHO) parasternal long-axis image (a) at presentation and (b) at 3-month follow-up
*denotes pericardial effusion; RV: right ventricle; LV: left ventricle; LA: left atrium

tent with the presentation of HILS with negative ANA (3, 4).

Once we made the diagnosis of HILS, hydralazine was discontinued. A short course of colchicine and prednisone was administered. The patient noted a substantial improvement and was discharged. A follow-up ECHO performed three months later (Figure 2b) showed a complete resolution of pericardial effusion, and the patient was symptom-free upon clinical assessment.

Discussion

Up to 10% of lupus cases are drug-induced, and several medications are known to cause DILS. Prototypes include, but are not limited to, hydralazine, procainamide, methyldopa, chlorpromazine, isoniazid, and TNF-α inhibitors (5).

Hydralazine-induced lupus syndrome is a DILS caused by hydralazine and was first described in 1953 (6). Nevertheless, the exact mechanism of HILS still remains unknown. Hypothesized mechanisms include drug-induced autoimmunity via epigenetic modifications (for instance, DNA hypomethylation of T cells) and skewing of signal transduction pathways toward the reduced production of TNF-α and IL-10 to heighten autoimmunity, as reviewed in (5).

The risk of HILS is estimated to be 5%-8% per year of hydralazine use (3, 5, 7, 8). Other associated risk factors known to favor HILS include HLA-DR4 genotype, slow acetylator, female sex, daily doses of hydralazine greater than 200 mg, and therapy longer than 3 months. Our patient has been on hydralazine for 4 years at a total daily dose of up to 300 mg, putting him at the risk of developing HILS, although HILS can still develop with lower doses and shorter durations of treatment (7).

Hydralazine-induced lupus syndrome can clinically present as arthralgia, myalgia, fever, anorexia, fatigue, and sometimes with cutaneous involvements. Infrequently, serositis leading to pericardial and pleural effusions can develop. Several case reports have described HILS presenting with pericarditis and/or cardiac tamponade (1-4). Following the African American Heart Failure trials that demonstrated the mortality benefit of BiDil (combination of hydralazine and isosorbide dinitrate), hydralazine is more frequently prescribed than ever before (7, 9), and the incidences of HILS are likely to rise. As such, a high index of clinical suspicion must be present to recognize and treat HILS-related pericardial effusion without delay as it can result in high morbidity and mortality rates (1-5, 7).

Unlike classic SLE, diagnostic criteria do not exist for DILS or HILS; hence, a diagnosis is mainly clinical. The temporal relationship between the symptom onset and/or laboratory evidence of SLE and the initiation of hydralazine use are the keys to establish a diagnosis. It has been proposed that the occurrence of the clinical features of SLE after treatment with hydralazine for 3-4 weeks or longer in patients with no history of SLE and the resolution of SLE features with the discontinuation of hydralazine can be considered to be highly suggestive of HILS (5).

In up to 95% cases, HILS presents with positive ANA, positive anti-histone antibody, and negative anti-dsDNA antibody (5, 7). Based on the current literature search, this manuscript is the third of its kind to report ANA-negative HILS (3, 4). Our patient and the two other previous reported cases presented similar pericardial effusions. In fact, in (3), the patient was having recurrent pericardial effusions from HILS. Moreover, it is known that HILS can present with pericardial effusion and cardiac tamponade (1-4). The peculiar association of ANA-negative HILS with pericardial effusion should be explored in future studies to elucidate the pathological basis of HILS that may be present at the mechanistic level.

Discontinuation of hydralazine is the mainstay for the treatment of HILS. Prognosis is excellent once the causative medication is discontinued. Joint, serosal involvement, or symptomatic persistence despite the discontinuation of the offending medication are indications of a short course of NSAIDS and corticosteroids (5).

In summary, HILS should be suspected in any patient taking hydralazine who presents with vague symptoms and unexplained pericardial effusion. ANA-negative HILS has been sporadically reported in two case reports. Our report is the third to demonstrate the presence of ANA-negative HILS. Clinicians should have a high index of suspicion for HILS and be aware that ANA negativity does not rule out a HILS' diagnosis (3, 4).

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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