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When Chest Pain Reveals More: A Case of Hydrochlorothiazide-Induced Systemic Lupus Erythematosus

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Patient: Male, 57
Final Diagnosis: Drug induced lupus erythematosus
Symptoms: Anemia • arthralgia • fever • weight loss
Medication: Hydrochlorothiazide
Clinical Procedure: —
Specialty: Rheumatology





Objective: Unusual clinical course
Background: Drug induced lupus erythematosus is considered an autoimmune entity which is precipitated by medications. Hydrochlorothiazide has been recognized to cause subacute cutaneous lupus erythematosus, but very few cases of systemic drug induced lupus systemic erythematosus have been reported.

Case Report: A 57-year-old Caucasian male with a past medical history of hypertension and hyperlipidemia presented with recurrent fevers, chest pain, and dyspnea. Initial evaluation revealed diffuse ST elevations, small pericardial effusion, anemia, and leukopenia. He was initially treated with nonsteroidal anti-inflammatory drugs and prednisone for pericarditis. Six months later, he reported fatigue, arthralgias, morning stiffness, weight loss, fevers, and night sweats. Laboratory tests revealed persistent anemia and leukopenia. Extensive workup, including bone marrow biopsy and infectious evaluations, was negative. Autoimmune workup, however, revealed positive antihistone and antichromatin antibodies despite negative antinuclear antibody. A diagnosis of drug induced lupus secondary to hydrochlorothiazide was made. The medication was stopped, and prednisone was initiated resulting in marked improvement in his symptoms and hematologic abnormalities.

Conclusions: This report is one of the few known cases of systemic lupus erythematosus most likely induced by hydrochlorothiazide. Based on our finding, hydrochlorothiazide should be considered a possible offending agent when a patient presents with symptoms suspicious of drug induced lupus.

MeSH Keywords: Abnormalities, Drug-Induced • Hydrochlorothiazide • Lupus Erythematosus, Systemic

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Background

Drug induced lupus erythematosus (DILE) is a rare, lupus-like syndrome which is caused by offending medications in patients with no prior history of systemic lupus erythematosus (SLE). Symptoms and laboratory results mimic those of SLE. There are no formal diagnostic criteria for DILE, but it is widely accepted that symptoms should start after initiation or modification of a medication and resolve after cessation of that agent [1–8]. Certain serological findings such as positive antinuclear antibody (ANA), antihistone antibody, and antichromatin antibody are also seen [1–12]. The pathogenesis is thought to be multifactorial. Treatment is usually limited to cessation of the offending medication with resolution of symptoms. To date, over 80 medications have been associated with DILE [1–6]. Notable agents include procainamide, hydralazine, tumor necrosis factor inhibitors, isoniazid, and methyldopa [1–8,13]. Although hydrochlorothiazide is considered as a “possible” agent which causes DILE, very few cases have been described in literature. Herein, we report a case of hydrochlorothiazide-induced DILE with new onset pericarditis and severe inflammatory arthritis, leukopenia, neutropenia, repeatedly negative ANA, but strongly positive antihistone and antichromatin antibodies.

Case Report

A 57-year-old male presented to the Emergency Department with sudden onset of severe substernal chest pain. The pain was intermittent, non-radiating, worsened by exertion, and improved with rest and aspirin. One week prior to presentation he reported occasional shortness of breath and a fever of 38.3°C (101°F) which resolved. Past medical history included hypertension and hyperlipidemia. He had no surgeries in the past. Current medications were losartan 100 mg daily, hydrochlorothiazide 25 mg daily (started 15 years prior), aspirin 81 mg daily and atorvastatin 20 mg daily. There were no recent dose adjustments or new medications. Family history was nonsignificant. He denied tobacco, alcohol, or illicit drug use. Vitals on admission were blood pressure 105/58 mmHg, pulse 81 beats/min, temp 36.5°C (97.7°F), respiratory rate 20 breaths/min, SpO₂ 99% on room air and body mass index (BMI) 30.68 kg/m². His physical examination was within normal limits.

Electrocardiogram (ECG) showed diffuse ST elevations. Laboratory tests showed anemia, leukopenia, and elevated inflammatory markers. Peripheral blood smear showed leukopenia with absolute neutropenia, microcytosis, and anisocytosis with normal platelets. ANA screen by immunofluorescence and titer was negative. Echocardiogram showed normal left ventricular size and systolic function with ejection fraction of 55–60%. A small circumferential pericardial effusion was noted without evidence of cardiac tamponade. Chest x-ray (CXR) was

unremarkable and troponin was negative. Two sets of blood cultures showed no growth.

The patient was initially treated with aspirin and nitroglycerin for presumed acute coronary syndrome. He was seen by the interventional cardiologist and underwent coronary angiography which showed normal coronaries with preserved ejection fraction. Because of the small pericardial effusion and diffuse ST elevations in ECG, he was started on nonsteroidal anti-inflammatory drugs and steroids for pericarditis. On day 2, he developed asymptomatic atrial fibrillation and was started on a diltiazem drip. Gastroenterology was consulted for the microcytic anemia and recommended outpatient colonoscopy. The patient's last colonoscopy was 5 years prior and showed 1 tubular adenomatous polyp in the ascending colon with the recommendation for follow-up endoscopies. In addition, patient was seen by hematology/oncology for the anemia and leukopenia who recommended bone marrow biopsy if the blood counts did not improve in a few weeks. Patient improved symptomatically with steroids and was discharged home with a 5-day steroid taper, diltiazem, nebivolol and his home medications were resumed.

Five days after discharge, the patient was admitted again with recurrent chest pain. Repeat echocardiogram showed small/moderate pericardial effusion suggestive of recurrent pericarditis which was presumed to be from premature cessation of steroids. Laboratory tests revealed persistent anemia and elevated inflammatory markers. He was discharged home on prednisone 30 mg daily for 2 weeks and colchicine 0.6 mg twice daily. Two weeks after discharge, he followed up with his cardiologist who proceeded with a slow prednisone taper over 4 weeks (20 mg daily for 2 weeks followed by 10 mg daily for 2 weeks). Repeat C-reactive protein (CRP) was checked to assess response and remained elevated. His colchicine was continued for 3 months.

Six months following initial presentation, he presented to his primary care physician with complaints of fever, fatigue, joint pain and swelling, morning stiffness, unintentional 40-pound weight loss, loss of appetite, low grade fevers, night sweats, and shortness of breath. Physical examination revealed swelling of bilateral metacarpophalangeal (MCP) and proximal interphalangeal joints (PIP). Range of motion in his joints was severely reduced. Repeat laboratory tests showed anemia and leukopenia with persistent severe neutropenia (see Table 1 for laboratory findings). ECG showed sinus rhythm. He was referred to oncology with concern for malignancy and admitted for further workup.

Given the constellation of symptoms of malaise, weight loss, loss of appetite, low grade fever, joint pains, anemia, leukopenia, and neutropenia, the differential diagnosis was broad.

Table 1. Laboratory findings.

Test	Reference range	Day 1	Day 6	Day 21	6 months later	7 months later (a month after stopping medication and starting steroid)	8 months later
Hemoglobin (g/L)	13–17	9.4	9.9		9.1	12.0	12.0
White blood count (cells/L)	3.7–10.3×10 ⁹	2.9×10 ⁹	5×10 ⁹		1.4×10 ⁹	1.3×10 ⁹	2.3×10 ⁹
Absolute neutrophil count (cells/L)	1.6–6.1×10 ⁹	1.59×10 ⁹	3.3×10 ⁹		0.18×10 ⁹	0.6×10 ⁹	0.69×10 ⁹
MCV (fL)	79–98	77	77		71	76	83
Platelets (cells/L)	155–269×10 ⁹	179×10 ⁹	250×10 ⁹		302×10 ⁹	172×10 ⁹	246×10 ⁹
Ferritin (pmol/L)	67–898	1159					
Iron (umol/L)	8.9–31.5	5.19					
TIBC (umol/L)	44.5–80.5	35.26					
Iron saturation (%)	20–55	15					
Folate (nmol/L)	16.5–59.15	31.72					
Vitamin B12 (pmol/L)	155.71–698.14	680.99					
ESR (mm/hr)	0–20	48	22		49	16	
CRP (mg/L)	<5	91.3	64.4	1.4	69	16	
ANA	Negative	Negative (immunofluorescence)			Negative on three occasions (immunofluorescence and ELISA)		
Antihistone antibody (U)	0–0.9				2.5		
Antichromatin antibody (U)	0–19				30		11

It included chronic viral infections, acute leukemia, myelodysplastic syndrome, lymphoma, drug induced, and rheumatological conditions like SLE or rheumatoid arthritis. ANA was rechecked and was negative by immunofluorescence. He also underwent extensive infectious workup including human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein Barr virus (EBV), herpes simplex virus (HSV), parvo virus, hepatitis B, hepatitis C which were all negative. Computed tomography (CT) chest and abdomen were negative for masses or lymphadenopathy. He underwent bone marrow biopsy. Pathology showed hypercellular marrow (90%) with erythroid and megakaryocytic hyperplasia with normal male karyotype and negative Fluorescence *in situ* hybridization (FISH) analysis. Workup for paroxysmal nocturnal hemoglobinuria was also negative. The patient was referred to rheumatology. Physical examination revealed severe swelling of his joints including MCPs, PIPs, ankles, and feet in a bilateral distribution. Range of motion in his joints was severely reduced. A comprehensive autoimmune

workup was notable for positive anti-histone and anti-chromatin antibodies but also negative for ANA, anti-centromere antibody, anti-Smith antibody, anti-neutrophilic cytoplasmic antibodies (ANCA), rheumatoid factor, anti-cyclic citrullinated peptide antibody, anti-ribonucleic protein, anti-Scl 70 antibody, anti-Ro, and La antibodies. Complete blood count (CBC) showed persistent anemia and leukopenia. Urinalysis was unremarkable. X-rays of the hands, feet, knees, and ankles showed mild degenerative changes with no erosions. Following initial rheumatologic workup, ANA was checked a fourth time, this time by enzyme linked immunosorbent assay (ELISA), and was again negative.

This patient's clinical presentation of low-grade fevers, weight loss, inflammatory arthritis and pericarditis along with anemia, leukopenia with neutropenia, positive antihistone and antichromatin antibodies, and negative infectious and hematologic workup lead us to a diagnosis of exclusion. Although the

patient had a negative ANA, his symptoms, physical examination, and additional blood work, particularly positive anti-histone and anti-chromatin antibodies, were consistent with systemic lupus, most likely drug induced. hydrochlorothiazide was the most likely culprit of his presentation and was discontinued immediately. Because of the patient's severity, the decision was made to start him on a 1-month prednisone taper. At his 1-month follow-up visit, his anemia and leukopenia significantly improved. On his 3-month follow-up, inflammatory markers normalized, and anti-chromatin antibody normalized. The patient, however, reported persistence of arthralgias and his laboratory tests showed neutropenia. Hydroxychloroquine 200 mg twice daily was initiated as we anticipated this drug caused a systemic reaction. On hydroxychloroquine, the patient's symptoms continued to improve.

Discussion

SLE is a rare but well-known multisystem connective tissue disorder. It is estimated that up to 10% of cases were related to medications [3,14]. DILE is considered an autoimmune entity caused by medications which triggers a lupus-like syndrome. Many differences are noted between systemic lupus erythematosus and DILE. Over 80 medications from over 10 different drug classes have been recognized as causing a lupus like syndrome [1–5]. The first report of hydrochlorothiazide-induced subacute cutaneous DILE was published in 1983. Since then, few cases of hydrochlorothiazide-induced systemic lupus erythematosus have been described in literature [15,16].

Although established criteria exist for the diagnosis of SLE, no formal or universal diagnostic criteria for DILE have been established. DILE is considered a syndrome which causes symptoms and laboratory and serologic findings consistent with SLE. These findings should be related to drug exposure and usually develop after months and quite commonly, years of treatment [5]. There are no symptoms which are specific for DILE, but resembles a milder lupus like syndrome presentation usually [4]. DILE tends to affect older individuals and there is no gender predilection. Laboratory results in DILE and SLE are similar but with some distinct differences. Unlike in SLE, complement levels are typically normal in DILE. Markers of inflammation are notoriously elevated in both disorders. In contrast to SLE, hematologic involvement is unusual and can be seen in 5–25% of DILE cases [1].

Serologic characteristics of DILE can also vary. The presence of antinuclear antibodies in DILE, as in SLE, is seen in as many as 90–95% of cases but negative cases do exist [17,18]. In contrast with SLE, anti-dsDNA antibodies are rare but anti-single stranded DNA antibodies can be seen [4]. The autoantibody specificity in DILE, in contrast to SLE, is largely restricted to histone containing antigens such as anti-histone and anti-chromatin antibodies, which are seen frequently [9–11,19]. Treatment for DILE consists of discontinuation of the offending drug. Glucocorticoids and other immunosuppressive agents such as antimalarials can be used in more severe cases [1]. Prognosis is excellent.

Based on the patient's symptoms and laboratory findings, he was diagnosed with drug induced lupus secondary to hydrochlorothiazide. He did not meet diagnostic criteria for SLE. The offending medication was discontinued, and the patient was initially started on glucocorticoids. His hematologic abnormalities and inflammatory markers improved significantly but had not normalized. In addition, he was reporting persistent arthralgias, so he was started on hydroxychloroquine with improvement.

Conclusions

Drug induced lupus erythematosus due to hydrochlorothiazide, to our knowledge, is rarely reported. Our patient presented with a more severe case of DILE with hematologic and pericardial involvement. Diagnostic evaluation revealed positive antihistone and antichromatin antibodies but negative ANA. Cessation of the hydrochlorothiazide, the offending medication, resulted in marked improvement, although not resolution, of the clinical picture. Therefore, steroids and hydroxychloroquine were initiated which helped relieve the patient's arthralgias. This report is one of the few known cases of drug induced lupus erythematosus due to hydrochlorothiazide and with pericardial involvement. Hydrochlorothiazide remains a commonly prescribed medication for the treatment of hypertension, and although not frequently reported, it should be considered when a patient presents with symptoms suspicious for drug induced lupus.

Conflicts of interest

None.

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