Severe Lupus Myocarditis Preceded by Mesalazine-induced Lupus

Yamashita, Mai ; Nishimura, Keisuke ; Shirasugi, Iku ; Ichise, Yoshihide ; Ueda, Yo ; Saegusa, Jun

(Citation)
Internal Medicine,62(6):929-933

(Issue Date)
2023-03-15

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/0100481669

Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9613-22
Intern Med 62: 929-933, 2023
http://internmed.jp

【 CASE REPORT 】

Severe Lupus Myocarditis Preceded by Mesalazine-induced Lupus

Mai Yamashita, Keisuke Nishimura, Iku Shirasugi, Yoshihide Ichise, Yo Ueda and Jun Saegusa

Abstract:
In drug-induced lupus (DIL), symptoms similar to those of systemic lupus erythematosus (SLE) usually resolve after discontinuation of the offending drug. A 41-year-old-woman with a history of ulcerative colitis presented with polyarthritis and myositis and was positive for anti-double stranded (ds) DNA IgG antibody. After discontinuation of mesalazine, the symptoms resolved, and the antibody titer decreased. The patient was diagnosed with DIL. Six months later, lupus myocarditis developed. After treatment with glucocorticoids, cyclophosphamide, intravenous immunoglobulin, and an intra-aortic balloon pump, she showed dramatic improvement. Patients with DIL and an immunological predisposition, such as anti-dsDNA antibodies, may have SLE and should be carefully monitored.

Key words: drug-induced lupus, lupus myocarditis, cyclophosphamide, sulfa drug, anti-dsDNA antibody, systemic lupus erythematosus

(Intern Med 62: 929-933, 2023)
(DOI: 10.2169/internalmedicine.9613-22)

Introduction

Drug-induced lupus (DIL) is a condition that presents with symptoms and serologic abnormalities similar to that of systemic lupus erythematosus (SLE). Procainamide and hydralazine are known to carry a high risk of causing DIL. Mesalazine, which is used to treat ulcerative colitis (UC) and Crohn's disease, is a sulfa drug that can induce DIL (1).

DIL generally occurs months after initiating the offending drug (2) but can be provoked even after years of continuing the offending drug (3). DIL is characterized by the resolution of symptoms after discontinuation of the offending drug. The symptoms of DIL rarely include the major complications of SLE, such as malar rash, central nervous system involvement, renal involvement, and hematologic abnormalities. Instead, DIL is characterized by a fever, arthritis, and pleuritis that resolve after drug discontinuation.

We herein report a case of DIL induced by mesalazine that was confirmed by symptom resolution and decrease in anti-double-stranded (ds) DNA IgG antibody titer after discontinuation of mesalazine. The patient experienced lupus myocarditis six months later. Although intensive supportive treatment, such as an intra-aortic balloon pump and intravenous dobutamine, was indicated, she showed dramatic improvement through immunosuppressive treatment for SLE.

Our case implies that some DIL cases with immunological predispositions can develop life-threatening systemic disorders even after mitigation of the symptoms through cessation of the offending drug. This should also raise physicians' awareness of such complications when following up similar cases.

Case Report

A 41-year-old woman was diagnosed with UC after presenting with diarrhea and bloody stools six years prior to presentation. Mesalazine was administered orally. Her intestinal symptoms and endoscopic findings improved, and mesalazine treatment was continued. Her other comorbidities were Hashimoto's thyroiditis during pregnancy and endometriosis, which were well-controlled.

Five years after initiation of mesalazine, she suffered from polyarthralgia, morning stiffness, and muscle pain. These

Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Japan
Received: February 17, 2022; Accepted: June 29, 2022; Advance Publication by J-STAGE: August 10, 2022
Correspondence to Jun Saegusa, jsaegusa@med.kobe-u.ac.jp

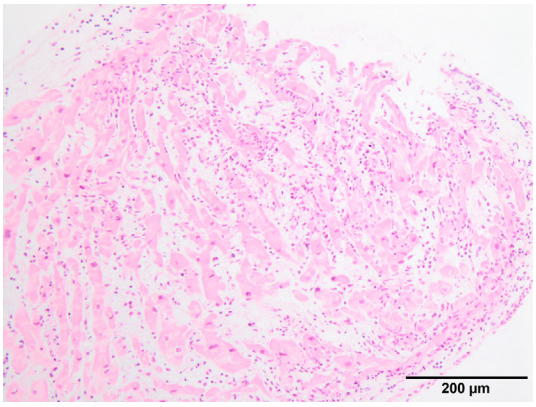

Figure 1. Historical findings of the endomyocardial biopsy. The extensive range of destruction in myocardial fibers and diffuse infiltration of mononuclear cells are shown (Hematoxylin and Eosin staining).

symptoms worsened and persisted for one year. The patient then consulted the hospital for her symptoms. A laboratory examination revealed an elevated C-reactive protein of 30.1 mg/L. The antinuclear antibody (ANA) test result was positive (2,560-fold, homogeneous pattern). Autoantibody tests were positive for anti-dsDNA IgG antibody [chemiluminescent enzyme immunoassay (CLEIA), 33.5 IU/mL] and myeloperoxidase-ANCA (16.3 U/mL). The serum complement level was normal. Short tau inversion recovery (STIR) magnetic resonance imaging of the proximal muscles revealed a high-intensity signal, and synovitis of the left shoulder was suspected. Musculoskeletal ultrasonography also suggested synovitis of both wrists and the right fingers. Histology of a forearm muscle biopsy specimen revealed infiltration of lymphocytes and plasma cells into the muscle fibers and perivascular areas in the fascia, which was consistent with myositis and fasciitis. The cardiac function at this point was normal, with no evidence of myocarditis, but echocardiography showed mild pericardial effusion. The main differential diagnoses were UC-related arthritis, systemic lupus erythematosus (SLE), and DIL.

UC-associated arthritis usually occurs during UC exacerbations (4). However, she did not present with any intestinal symptoms of UC. Considering the SLE classification criteria, her condition at that time met the 2019 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) (5) and ACR 1997 criteria (6, 7) but did not meet the Systemic Lupus International Collaborating Clinics (SLICC) criteria (8).

With the discontinuation of mesalazine, the symptoms of arthritis and myositis were relieved, and anti-dsDNA IgG antibody levels decreased, which was not consistent with the clinical course of SLE. A UC patient reportedly developed myositis during treatment with mesalazine (9). Based on previous reports of myositis, we suspected that mesalazine might be involved with the symptoms. We therefore diagnosed her with mesalazine-induced lupus. After discontinuing mesalazine, the symptoms and serological abnormalities spontaneously resolved without deterioration of her intestinal symptoms. Five months after discontinuation of the drug, the anti-dsDNA IgG antibody titer decreased to 12.5 IU/mL.

Two weeks after her last consult at our department, she began to feel fatigue, a fever, and diarrhea that persisted for two days, prompting her to visit a family clinic. The patient was transferred to the emergency department because of low blood pressure. On admission, her systolic blood pressure was 70 mmHg, and her heart rate was 160 bpm. Laboratory tests showed severe thrombocytopenia and an increased level of the following myocardial enzymes: troponin T, 1.15 ng/mL (normal <0.014 ng/mL); creatine kinase, 235 ng/mL (normal <153 ng/mL); and creatinine kinase myocardial band (CK-MB), 55 ng/mL (normal <25 ng/mL). Immunological laboratory tests showed an elevated C-reactive protein level of 81.0 mg/L, anti-dsDNA IgG antibody [enzyme-linked immunosorbent assay (ELISA)] of 213 IU/mL (normal <12 IU/mL), anti-dsDNA IgG antibody (CLEIA) of 6.4 IU/mL (normal of <12 IU/mL), and low complement C3 of 61.7 mg/dL (normal 73-138 md/dL).

Chest radiography revealed pulmonary congestion. Wide-QRS tachycardia was noted on electrocardiography, which transformed to sinus tachycardia with ST segment elevation in V1-V3 and inverted T waves in the II and aVf leads after the infusion of adenosine triphosphate. Echocardiography revealed an extremely low ejection fraction (20%) and global hypokinesis.

The patient was initially diagnosed with tachycardia-induced cardiomyopathy. On the first day of admission, continuous intravenous furosemide was administered, but her cardiac function worsened. She had low cardiac output syndrome on the second day. Intravenous dobutamine was initiated, and an intra-aortic balloon pump was introduced to support circulatory dynamics.

A Swan-Ganz catheter examination revealed a low output, pulmonary congestion, pulmonary artery wedge pressure (PAWP) of 33/32/30 mmHg, and cardiac index (CI) of 1.97 L/min/m^2. Coronary angiography revealed no evidence of coronary artery involvement. An endomyocardial biopsy showed extensive destruction of myocardial fibers and diffuse infiltration of mononuclear cells, which were compatible with acute myocarditis (Fig. 1). No evidence of multinucleated giant cells, eosinophils, or sarcoid-like granulomas was observed. Laboratory analyses of common viruses capable of inducing myocarditis [adenoviruses, coxsackievirus, Epstein-Barr virus, hepatitis C virus, parvovirus B19, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] showed no acute-phase activation.

Based on the history of DIL and laboratory data, the etiology of her myocarditis was considered to be SLE. After administering intravenous corticosteroid pulse (methylprednisolone 1,000 mg/day for 3 days) and intravenous immunoglobulin on day 2, her condition improved dramatically (Fig. 2). On day 4, the patient's low cardiac output and pulmonary congestion improved (CI, from 1.97 to 2.7 L/min/

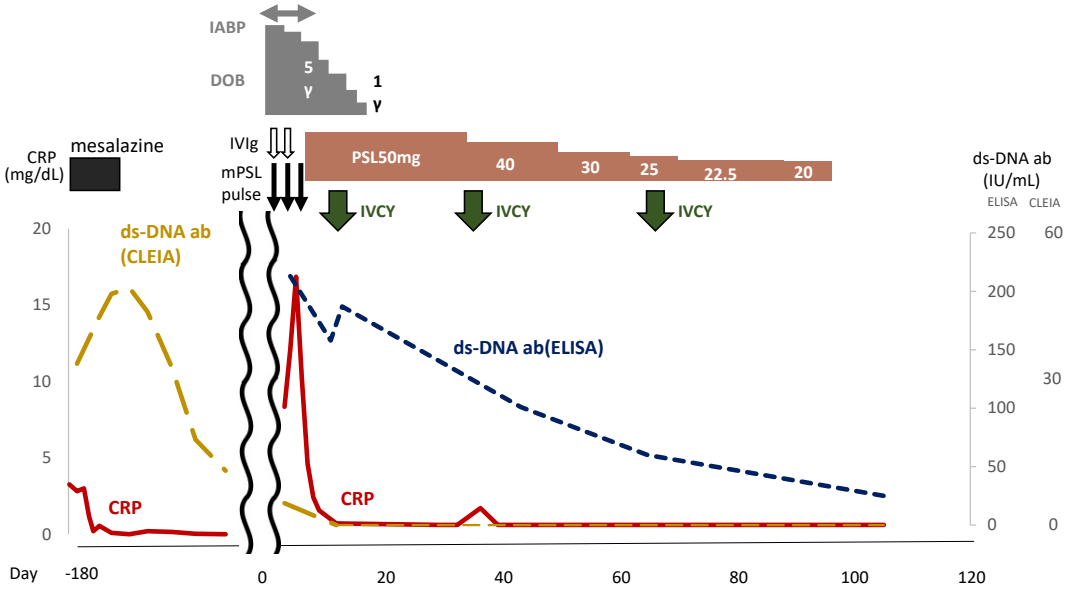

Figure 2. **Clinical course of severe lupus myocarditis preceded by mesalazine-induced lupus. CLEIA: chemiluminescent enzyme immunoassay, DOB: dobutamine, ds-DNA ab: anti-double-stranded DNA IgG antibody, EF: ejection fraction, ELISA: enzyme-linked immunosorbent assay, IABP: intra-aortic balloon pump, IVCY: intravenous cyclophosphamide, IVIg: intravenous immunoglobulin, mPSL pulse: methylprednisolone pulse, PSL: prednisolone**

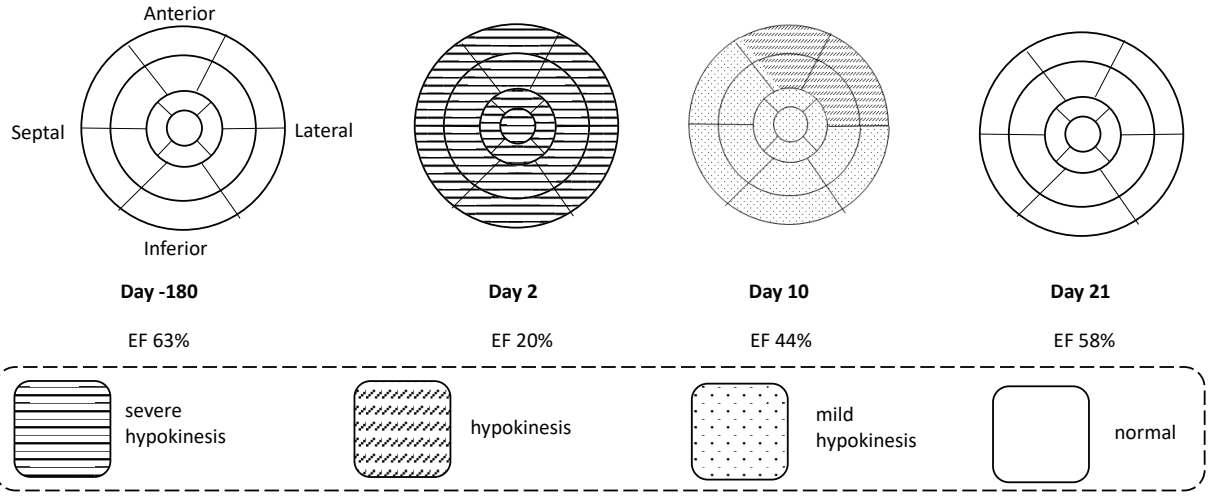

Figure 3. **Time series of echocardiographic findings showing the dramatic improvement of hypokinesis and the ejection fraction through treatment for lupus myocarditis. EF: ejection fraction**

m^2, and mean PAWP, from 30 to 20 mmHg). On day 7, supportive therapy with an intra-aortic balloon pump was no longer required. Follow-up echocardiography performed on day 10 revealed improvement in the left ventricular ejection fraction (LVEF) to 44%, but global hypokinesis anterior to the lateral wall persisted. On day 11, 800 mg/kg of intravenous cyclophosphamide (IVCY) was administered. Multidisciplinary treatment, including immunosuppressive therapy and cardiovascular management, led to an improvement in the LVEF to 58% on day 21, and hypokinesis was no longer observed (Fig. 3). The serologic abnormalities of SLE (hypocomplementemia and increased titer of the anti-dsDNA IgG antibody) also improved through the treatment. The glucocorticoid dose was reduced, and six weeks later, the patient was discharged without any mechanical support. The glucocorticoid dose continued to be tapered during outpatient care. Monthly IVCY was administered for three months, followed by azathioprine. No evidence of disease relapse was observed up to day 100.

Discussion

We encountered a case of DIL wherein the patient's symptoms (polyarthralgia and muscle pain) and serological abnormalities were resolved after the discontinuation of mesalazine. However, severe lupus myocarditis developed later.

Table. Lists of Clinical and Immunological Findings at Each Time Point of the Disease Course.

	At DIL	At SLE (myocarditis)
Clinical		
Arthritis	+	-
Myositis	+	-
Myocarditis	-	+
Immunological		
Thrombocytopenia	-	+
Hypocomplementemia	-	+
Anti-dsDNA antibody (CLEIA)	+	-
Anti-dsDNA antibody (ELISA)	N.A.	+

CLEIA: chemiluminescent enzyme immunoassay, ELISA: enzyme-linked immunosorbent assay, NA: not available

Autoimmune myocarditis, including lupus myocarditis, responds dramatically to glucocorticoids and immunosuppressive therapy, and the course of this case was consistent with previous reports (10). This is the first case report in the English literature based on a PubMed search as of May 31, 2022, to describe a case of DIL that developed severe complications of SLE after attaining symptom relief through discontinuation of the offending drug.

In DIL, symptoms and serologic abnormalities resembling SLE are induced by a certain spectrum of drugs. Sulfasalazine, a sulfa drug, is categorized as an anti-inflammatory drug and is known to induce DIL. Mesalazine, one of the main components of sulfasalazine, is thought to induce DIL less frequently than sulfasalazine; however, with the increasing number of mesalazine prescriptions for inflammatory bowel diseases, reports of DIL induced by mesalazine have also been increasing (1).

The features of DIL induced by mesalazine or sulfasalazine are consistent with those observed in the present case. The severity of DIL induced by these drugs varies among cases. Some cases have presented with arthritis, morning stiffness, and positive ANA and anti-dsDNA antibodies (11, 12). Others have shown major organ involvement, such as severe pleuropericarditis and a fever with positive ANA (13). Furthermore, lupus nephritis induced by sulfasalazine has also been reported (14). However, most cases show resolution of the symptoms with discontinuation of the drug.

In general, the prognosis of patients with DIL is good once the drug is withdrawn (2). Therefore, given the differences in prognoses between DIL and SLE, it is important to differentiate between the two (15). The patient's clinical course, namely the symptom resolution and decrease in anti-dsDNA IgG antibody titer after discontinuation of mesalazine, was consistent with DIL; however, the patient had an immunological predisposition for SLE.

Upon a review of the patient's initial presentation, there were some findings that did not correspond to typical DIL. These findings might be key for differentially diagnosing DIL cases that can later develop into SLE. First, positive anti-dsDNA antibody in DIL is relatively rare, although there have been several reports of this in sulfa-drug-induced DIL, as described above. In the present case, the presence of a positive anti-dsDNA IgG antibody result at the time of the DIL diagnosis may have been an immunological sign of possible progression to SLE. Second, mild pericardial effusion was noted on echocardiography. Serositis was not diagnosed because the patient did not complain of any symptoms associated with pleural effusion at this time. Regarding the etiology of pericardial effusion, there was no evidence of infection, malignancy, hypothyroidism, or heart failure. We believe that her pericardial effusion was immunologically induced (16). Although she had multiple immunological predispositions for SLE as described above when she was diagnosed with DIL, her symptoms were mitigated through discontinuation of mesalazine. Hypocomplementemia and thrombocytopenia were observed for the first time when she experienced lupus myocarditis, which prompted us to diagnose her with SLE for the first time (Table).

Although myositis is not a frequently reported manifestation of DIL, several reports of myositis related to mesalazine have been published. This also supports the drug-induced etiology of the patient's first presentation (9).

However, several limitations associated with the present case report warrant mention. First, during the investigations that led to the diagnosis of DIL, anti-dsDNA IgG antibody (CLEIA) was positive; therefore, anti-dsDNA IgG antibody (ELISA) was not measured. Changes in this antibody titer throughout the course of the disease therefore remain unknown. When she was diagnosed with lupus myocarditis, anti-dsDNA IgG antibody test using an ELISA was positive, whereas it was negative using the CLEIA method. Regarding the discrepancy between autoantibody detected by an ELISA and that by a CLEIA, Mai et al. reported the same findings as we did (17). They suggested differences in autoantibody reactivity to antigens coated on the plates (ELISA) or magnetic beads (CLEIA) and differences in the detection systems as possible causes of this pattern. There are various methods available for detecting anti-dsDNA IgG antibodies, and results may vary depending on the approach used (18). Second, the positivity of anti-histone antibody was unknown since it was not measured.

Conclusions

In summary, even if the presentation and clinical course seem to be consistent with DIL, careful observation is required even after resolution of DIL, as patients with predisposing immunological factors can suffer from severe manifestations of SLE. Severe symptoms of SLE, such as myocarditis, require intensive treatment. Future areas of research include the prognostic factors for DIL and the duration of follow-up after improvement of DIL.

Written informed consent was obtained from the patient for this case report.

The authors state that they have no Conflict of Interest (COI).

References

1. Katsanos K, Voulgari P, Tsianos E. Inflammatory bowel disease and lupus: a systematic review of the literature. J Crohns Colitis **6**: 735-742, 2012.
2. Vaglio A, Grayson P, Fenaroli P, et al. Drug-induced lupus: traditional and new concepts. Autoimmun Rev **17**: 912-918, 2018.
3. Pretel M, Marques L, Espana A. Drug-induced lupus erythematosus. Actas Dermo-Sifiliograficas **105**: 18-30, 2014.
4. Perez-Alamino R, Maldonado-Ficco H, Maldonado-Cocco J. Rheumatic manifestations in inflammatory bowel diseases: a link between GI and rheumatology. Clin Rheumatol **35**: 291-296, 2016.
5. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis **78**: 1151-1159, 2019.
6. Tan E, Cohen A, Fries J, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum **25**: 1271-1277, 1982.
7. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum **40**: 1725, 1997.
8. Petri M, Orbai A, Alarcón G, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum **64**: 2677-2686, 2012.
9. Naramala S, Konala V, Adapa S, et al. Recurrent inflammatory myositis as an extra-intestinal manifestations of dormant ulcerative colitis in a patient on long-term mesalamine. Case Rep Gastrointest Med **7**: 2090379, 2019.
10. Pollack A, Kontorovich A, Fuster V, Dec G. Viral myocarditis-diagnosis, treatment options, and current controversies. Nat Rev Cardio **12**: 670-680, 2015.
11. Gunnarsson I, Forslid J, Ringertz B. Mesalazine-induced lupus syndrome. Lupus **8**: 486-488, 1999.
12. Kirkpatrick AW, Bookman AA, Habal F. Lupus-like syndrome caused by 5-aminosalicylic acid in patients with inflammatory bowel disease. Can J Gastroenterol **13**: 159-162, 1999.
13. Dent MT, Ganapathy S, Holdsworth CD, Channer KC. Mesalazine induced lupus-like syndrome. BMJ **305**: 159, 1992.
14. Gunnarsson I, Kanerud L, Pettersson E, Lundberg I, Lindblad S, Ringertz B. Predisposing factors in sulphasalazine-induced systemic lupus erythematosus. Br J Rheumatol **36**: 1089-1094, 1997.
15. Araújo-Fernández S, Ahijón-Lana M, Isenberg DA. Drug-induced lupus: including anti-tumour necrosis factor and interferon induced. Lupus **23**: 545-553, 2014.
16. Beaudoin S, Gonzalez A. Evaluation of the patient with pleural effusion. CMAJ **190**: E291-E295, 2018.
17. Mai Y, Ujie H, Nishimura M, et al. Chemiluminescent enzyme immunoassay failed to detect anti-desmoglein 3 antibodies in a case of pemphigus vulgaris. J Dermatol **44**: E242-E243, 2017.
18. Mummert E, Fritzler M, Sjöwall C, Bentow C, Mahler M. The clinical utility of anti-double-stranded DNA antibodies and the challenges of their determination. J Immunol Methods **459**: 11-19, 2018.