

## Successful treatment using cyclosporine in a patient with rhupus complicated by aplastic anaemia: a case report and review of the literature

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### ABSTRACT

*Systemic lupus erythematosus (SLE) co-morbid with rheumatoid arthritis (RA) is known as "Rhumus syndrome" and is estimated to be present in between 0.01 and 2% of SLE and RA patients. The occurrence of aplastic anaemia in a patient with rhupus is very rare and a treatment for this condition has not been reported. A 52-year-old woman presented complaining of nausea and dizziness during the preceding month. She had been treated for rheumatoid arthritis for 16 years. At the time of presentation, she had a malar rash, multiple arthritis, pancytopenia, pleural effusion, proteinuria, and positive anti-nuclear and anti-dsDNA antibodies. A kidney biopsy revealed ISN/RPS class IV-G (A) lupus nephritis. Bone marrow aspiration and biopsy showed aplastic anaemia with no evidence of viral infection. The patient was successfully treated using cyclosporine and prednisolone and she remained symptom-free at the one-and-a-half-year follow-up. To our knowledge, this is the first report of a successful treatment using cyclosporine in a patient with rhupus complicated by aplastic anaemia.*

### Introduction

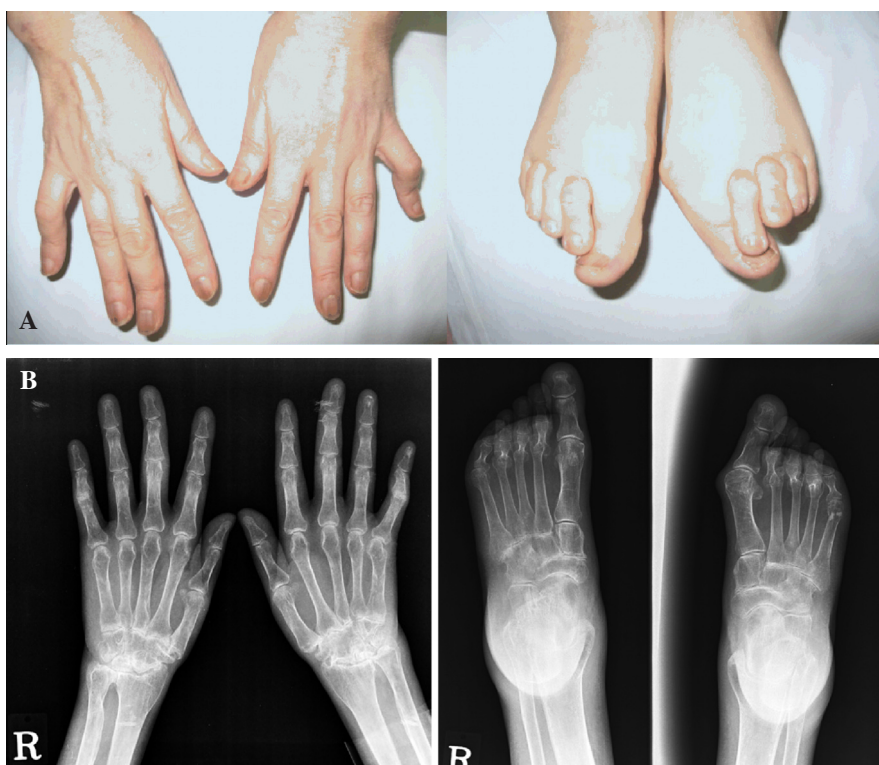
Comorbid systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), known as "Rhumus syndrome", is rare. An overlap in these conditions has been debated because SLE and RA have distinct genetic backgrounds and an inverse pathophysiological relationship (1). However, recent genetic studies have uncovered candidate genes associated with a predisposition to autoimmune disease in general, referred to as shared autoimmunity (2). The prevalence of rhupus is estimated to be between 0.01 and 2% in SLE and RA (3), and its clinical features are erosive arthropathy, rheumatoid nodule, serosal involvement, and haematological alteration with mild renal damage. Among the various clinical features of rhupus, proteinuria and thrombocytopenia are significantly associated with an increased risk of mortality (4). However, the occurrence of aplastic anaemia in a patient with rhupus has not been pre-

viously reported, and no treatment for this condition has been described in the literature. Here we report the successful treatment of a patient with rhupus associated with aplastic anaemia using cyclosporine.

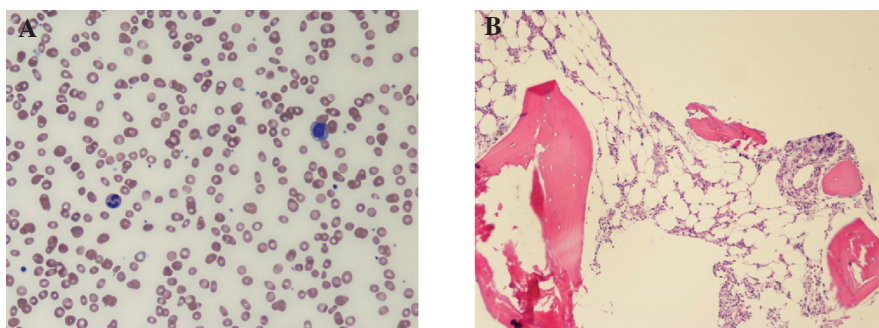
### Case report

A 52-year-old woman presented complaining of nausea, vomiting, and dizziness during the previous month. She had a 16-year history of rheumatoid arthritis and had undergone treatment with low-dose corticosteroids and non-steroidal anti-inflammatory drugs in her local clinic. She had an allergic reaction to sulfa drugs including sulfasalazine, and methotrexate was intermittently medicated for gastrointestinal discomfort. Treatment with leflunomide had been stopped several months earlier because she developed leukopenia. On admission, the patient's temperature was 37.3°C, pulse rate was 88 beats/min, and blood pressure was 130/80 mmHg. She had a chronically ill general appearance, and had anaemic conjunctivae and malar rash on both cheeks. Splenomegaly was palpated, and lymphadenopathy and hepatomegaly were not detected. She had pitting oedema on both lower extremities. On musculoskeletal examination she had tenderness and swelling in both elbows, wrists, knees, and ankles. Additionally, the patient had Boutonniere deformity in both fifth fingers, hallux valgus deformity in left first metatarsophalangeal joint, and hammer toes in both feet (Fig. 1A). Her chest x-ray showed pleural effusion with mild pulmonary oedema. X-rays of her hands, elbows, knees, and feet revealed multiple deformities including joint space narrowing, bony erosion, joint subluxation, and ankylosis (Fig. 1B). Laboratory examination showed a decreased white blood cell count of 2500/ $\mu$ L with 57.7% neutrophils and 6.1% lymphocytes, haemoglobin 4.5 g/dL, platelet count 55,000/ $\mu$ L, reticulocyte count 2.56%, reticulocyte production index 0.32, total protein 5.4 mg/dL, and albumin 2.1 mg/dL. Urinalysis showed 3+ proteinuria and 24-hour urine protein was 2.82 g/day. Liver and renal function tests were normal.

Competing interests: none declared.



**Fig. 1.** The patient had (A) Boutonniere deformity on both fifth fingers and hallux valgus deformity on the left first metatarsophalangeal (MTP) joint, and hammer toes. (B) Both hand x-rays showed carpal bone erosion and joint space narrowing, joint space narrowing on the proximal interphalangeal (PIP) joints, and subluxation on the fifth PIP joints. Both foot x-rays showed hallux valgus deformity of left first MTP joint, dislocation of the 2-4th MTP joints, and subluxation of the fifth MTP joints.



**Fig. 2.** (A) The peripheral blood smear showed pancytopenia and normochromic normocytic anaemia and thrombocytopenia without definitive abnormal cells. (B) Bone marrow aspiration and biopsy revealed hypocellular marrow with a cellular density of 10-30% and several fatty globules without neoplastic infiltration or significant myelofibrosis.

Her rheumatoid factor was increased to 69.3 IU/mL (normal range 0-15 IU/mL), and her anti-cyclic citrullinated peptide (CCP) was 200 U/mL (normal range <2.9 IU/mL). Her antinuclear antibody test was positive at a dilution of 1:320 with a homogenous pattern, the anti-dsDNA antibody titer was 170 IU/mL (normal range <7 IU/mL), and anti-Ro (SS-A) antibody titer was 194 U/mL. Anti-Sm, anti-RNP, and anti-La antibodies were negative. C3, C4, and

CH50 were decreased to 18.6 mg/dL, 6.69 mg/dL, and 7.2 U/mL, respectively. Serological tests for Epstein-Barr virus, cytomegalovirus, parvovirus B19, hepatitis A, hepatitis B, and hepatitis C were negative.

A peripheral blood smear showed pancytopenia with a left shift to myelocytes without definitive abnormal cells (Fig. 2A). Bone marrow aspiration and biopsy revealed hypocellular marrow with a cellular density of 10-30% and many fatty

globules without neoplastic infiltration or significant myelofibrosis (Fig. 2B), findings that are compatible with aplastic anaemia. The patient had persistent proteinuria; thus, we performed a kidney biopsy. Light microscopy findings showed endocapillary hypercellularity, leukocyte infiltration, and glomerular sclerosis, and electron microscopy revealed electron-dense subendothelial and mesangial deposits (Fig. 3). These findings correspond to class IV-G (A) lupus nephritis using the ISN/RPS classification of lupus nephritis. The patient fulfilled seven criteria of the 1982 American College of Rheumatology (ACR) classification criteria for SLE, characterised by malar rash, arthritis, pleuritis, nephritis, leukopenia, lymphopenia, thrombocytopenia, positive anti-nuclear antibody test, and the presence of anti-dsDNA antibody. Furthermore, she presented with morning stiffness, symmetric arthritis of more than three joints including hand joints, radiologic changes, and positive rheumatoid factor, which are compatible with the 1987 ACR criteria for the classification of RA. Thus, based on these findings, the patient was diagnosed as having rhus, and the results of the bone marrow studies suggested that the rhus was accompanied by aplastic anaemia.

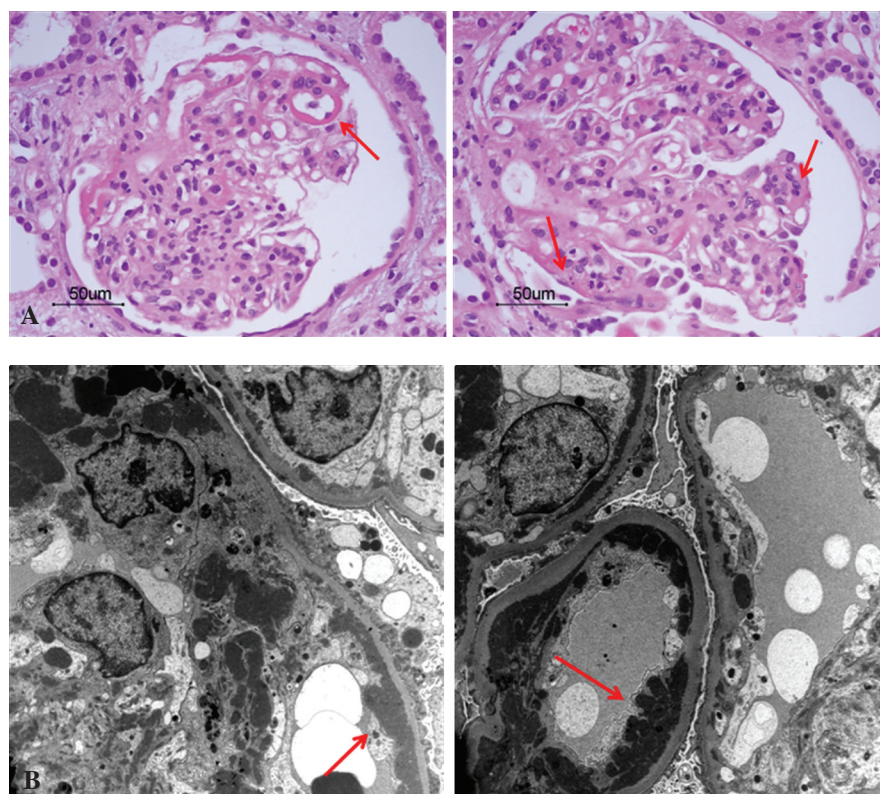
We started treatment with prednisolone at a dose of 1 mg/kg body weight per day, cyclosporine at a dose of 100 mg/day, and hydroxychloroquine for lupus nephritis, arthritis, and aplastic anaemia. The white blood cell and platelet counts began to improve after 2 weeks of treatment, and 2 months later, the patient's white blood cell and platelet counts had increased to 5900/ $\mu$ L and 174,000/ $\mu$ L, respectively. As the cell counts improved, methotrexate was added to decrease the dose of corticosteroids. The patient's 24-hour urine protein decreased to 1.82g/day after 2 months and to 0.57g/day after 4 months of treatment. We were able to taper oral prednisolone to 7.5 mg/day after 6 months of treatment with no evidence of disease recurrence; the same dose of cyclosporine was continued throughout the treatment period. At the one-and-a-half-year follow-up, the patient remained in remission with re-



spect to normal renal function with no proteinuria, no active arthritis, and near normal cell counts with the exception of a low haematocrit value (haemoglobin 8~9 g/dL).

### Discussion

Rhupus is a rare condition, in which clinical characteristics of RA and SLE occur at the same time. However, the existence of an overlap in these conditions is controversial because they have opposing underlying pathophysiological mechanisms; Th1 cytokines predominate in RA and Th2 cytokines are dominant in SLE, and the two conditions have distinctly different genetic backgrounds. However, recent genetic studies have identified several genes associated with an increased risk for both RA and SLE. Findings from the Multiple Autoimmune Disease Genetics Consortium (MADGC) have shown that clinically distinct autoimmune diseases such as RA, SLE, type I diabetes, and Hashimoto's thyroiditis may share a common set of susceptibility genes (5). Several candidate genes, such as *PDCD1*, *SLC22A4*, and *PTPN22*, have been suggested to predispose to various autoimmune diseases, supporting the hypothesis of shared autoimmunity (6). In addition to this genetic evidence, observational studies in several cohorts support the concept of shared autoimmunity. The observed prevalence of rhupus is higher than the expected prevalence calculated from the chance concurrence of SLE and RA (4, 7). Family members of SLE patients are as likely to develop RA as family members of RA patients (8), and one retrospective cohort study reported that 33% of the SLE patients had at least one other autoimmune disease, and 3.49% of those patients had RA (9). Furthermore, recent immunologic studies have shown that rhupus patients have both anti-CCP antibodies, in similar frequencies and titers to those reported in RA patients, and anti-dsDNA and anti-Sm antibodies, in similar frequencies to those in SLE patients (10). Thus, it is likely that rhupus is not a simple overlap between RA and SLE, nor a variant of either condition, but belongs to a broad clinical spectrum of autoimmune disease (1).



**Fig. 3.** Results of the kidney biopsy. (A) Light microscopy revealed endocapillary hypercellularity, leukocyte infiltration, and glomerular sclerosis in the glomeruli (arrows). (B) Electron microscopy showed electron-dense subendothelial and mesangial deposits (arrows) that are compatible with ISN/RPS class IV-G (A) lupus nephritis.

Several case studies have found that RA symptoms are more severe and SLE symptoms are less severe in patients who had rhupus than in patients who had RA or SLE alone (3, 7, 11, 12). The predominant RA manifestation in patients with rhupus is erosive arthritis, with almost half of the patients having rheumatoid nodules. SLE manifestations in these patients are characterised by mucocutaneous and haematological involvement with mild renal damage, and more than 50% of the patients have serositis. In rhupus patients, proteinuria and thrombocytopenia are independent risk factors for increased mortality (4). Cohen *et al.* (7) and Brand *et al.* (12) reported renal involvement in up to 63% of patients with rhupus, while Panush *et al.* (11) and Simon *et al.* (3) found low prevalence levels of around 16% and 22%, respectively. Because drug-induced nephropathy and amyloidosis may cause nephritis in patients with rhupus, drug history and kidney biopsy findings are important for differentiating renal involvement from drug-

induced nephropathy and amyloidosis. Although our patient had a long history of RA, we were unable to locate relevant medication history and kidney biopsy findings.

Haematological abnormality is not a common feature of RA. In contrast, anaemia, leukopenia, and thrombocytopenia are relatively common symptoms in SLE, and are reported in up to two-thirds of patients. However, aplastic anaemia is a rare and serious complication in patients with SLE that is mediated by cytotoxic T lymphocytes either directly via the Fas pathway or indirectly through interferon gamma or tumour necrosis factor. Furthermore, circulating autoantibodies against pleuri-potent stem cells have been implicated in the development of aplastic anaemia (13). Although aplastic anaemia associated with rhupus has not been previously reported, similar pathomechanisms may underlie its development. Moreover, the favourable response to cyclosporine in our patient supports an immune-mediated mechanism for aplastic anaemia in rhupus.

Although the disease course of comorbid aplastic anaemia and SLE differs from idiopathic aplastic anaemia, and the prognosis is generally good with long-standing remission, an acceptable treatment option for these patients has not been established. Various treatments have been tried in patients with aplastic anaemia associated with SLE. Plasmapheresis, high-dose methylprednisolone, androgen, cyclophosphamide, antithymocyte globulin, and cyclosporine have been used, based on the degree of cytopenia and involvement of other organs in individual case reports. Cyclosporine, in particular, has been advocated for the management of patients with life-threatening bone marrow failure in whom immunosuppressive therapy with antithymocyte globulin and high-dose methylprednisolone had failed (14). In one case report, a patient with SLE and associated aplastic anaemia was successfully treated using cyclosporine following unsuccessful treatment with high-dose corticosteroids and cyclophosphamide pulses (15). No treatment option has been reported for patients with rhupus and comorbid aplastic anaemia; thus, we administered oral cyclosporine to our patient and were able to induce long-term remission. To our knowledge, the present case is the first to report cyclosporine as a successful treatment for a patient with rhupus and co-occurring aplastic

anaemia. We believe our case report has important implications for clinical practice. Physicians should be aware of the possibility of overlapping autoimmune symptoms, even after the diagnosis of a specific autoimmune disease has been established. More importantly, cyclosporine should be considered for the treatment of a patient with rhupus associated with aplastic anaemia.

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