*Case Report*

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# Acute diffuse alveolar haemorrhage accompanied by gastrointestinal bleeding in a patient with serious systemic lupus erythematosus: A case report

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**Abstract**

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects many organs, but multisystem dysfunction is rare. Here, we report a case of a 29-year-old woman who was initially diagnosed with SLE complications including lupus nephritis, lupus encephalopathy, renal hypertension, thrombocytopenia, anaemia and hyperkalaemia. She recovered following treatment with high dose methylprednisolone, intravenous immunoglobulin (IVIG) and continuous renal replacement therapy (CRRT). However, a few days after hospital discharge, she developed gastrointestinal bleeding. Although intensive treatment was administered, the patient deteriorated rapidly and had a progressive decline in oxygen saturation followed by diffuse alveolar haemorrhage and acute left heart failure. Inotropic therapy, mechanical ventilation, blood transfusion, CRRT, antibiotics, intravenous glucocorticoids and other support therapies were initiated and gradually the

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patient's vital signs stabilized and haemoptysis subsided. This case report emphasises that complications of SLE can occur at any stage of the disease, especially in patients with active SLE. Therefore, it is important for clinicians to be aware of the rare presentations of SLE and its complex management. For multisystem dysfunction, early intensive treatment with high dose corticosteroids and cyclophosphamide is advocated.

**Keywords**
Systemic lupus erythematosus, gastrointestinal bleeding, diffuse alveolar haemorrhage, lupus nephritis

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## Introduction

An autoimmune disease, systemic lupus erythematosus (SLE) affects joints and many organs including the skin, kidneys, lungs and nervous system.[1] Availability of self-antigens, activation of the innate immune system, dysfunction of the adaptive immune system are thought to promote the progression of SLE.[2,3] The complications of SLE are protean and severe and may include lupus pneumonitis, lupus encephalopathy, intestinal pseudo-obstruction, gastrointestinal bleeding and vasculitis.[4–7] It is important for clinicians to recognize SLE and its complications early on in its course and treat the disease promptly and intensively.[8] We report here on a rare case of multisystem damage in a 29-year-old Chinese woman with SLE.

## Case report

The patient was a 29-year-old woman who had initially been diagnosed with SLE when she was 20 years old based on American College of Rheumatology (ACR) criteria.[9] At that time, the signs and symptoms included clinical findings (i.e., intestinal obstruction) and laboratory results (i.e., positive antinuclear antibodies (ANA), mouth ulcers, photosensitivity and history of butterfly rash). Following gastrointestinal decompression and treatment with methylprednisolone (60 mg/day) the patient recovered well. During a long period tapering off corticosteroids, the patient did not experience any vomiting, abdominal pain or skin rashes and laboratory data were normalized. At the age of 24 years and with strict blood pressure (BP) and urinary protein monitoring, the patient became pregnant and gave birth to a healthy boy. Following the birth, the patient was well and was prescribed prednisolone 2 mg/day and hydroxychloroquine 0.2g/day as maintenance therapy.

Five years later, on 16 December 2016, the patient was hospitalized after experiencing fatigue and vomiting for several days. Physical examination showed she was 80 kg, had a full moon face, her abdomen was soft with absence of bowel sounds and she had slight abdominal tenderness without rebound tenderness. Her BP, heart rate and respiratory rate were 177/113 mmHg, 130 beats/min, 18/min, respectively. She did not have a fever, cough or dyspnoea but had slight oedema of the lower extremities. Her laboratory results were as follows: haemoglobin, 5.9 g/dl; platelet count, 42,000/mm$^3$; creatinine, 307.2 μmol/l;

serum potassium, 6 mmol/l: erythrocyte sedimentation rate (ESR), 140 mm/h; C reactive protein (CRP),19.0 mg/l. She was given methylprednisolone (1mg/kg/day) intravenously for three days and her ECG was monitored. In addition, she received high concentrations of glucose (10%) and insulin (10U) intravenously and sodium polystyrene sulfonate (30 g/day) orally to reduce potassium levels. She also received nifedipine (30 mg/day) and glyceryl trinitrate (2 mg/day) to reduce her BP.

Three days later, laboratory results showed the presence of the following: rheumatoid factor (30.0 IU/ml); ANA (+++ [1 : 1000]); antibodies against double stranded-DNA (+++ [1 : 100]); anti–ribonucleoprotein antibodies (+++); anti-Sjogren's syndrome A antibodies (60KD) (+++); anti-Ro antibodies (52KD) (+++); complement 3 (0.22 g/l); complement 4 (0.05 g/l); $CD4^+$ lymphocyte subsets (37.00%); $CD8^+$ lymphocyte subsets (14.60%); anticardiolipin antibodies (ACA, 26.4 RU/ml); anti-beta 2 glycoprotein 1 antibodies (11.9 RU/ml). Her urinary volume was 400 ml/24h, protein levels were 908.0 mg/24h and creatinine was elevated at 398.8 $\mu$mol/l. An ultrasound scan of chest and abdomen showed small amounts of both pericardial ascites and peri-renal effusion. Some pulmonary inflammation was evident on a chest radiograph and multiple small infraction lesions in the brain were visible on an MRI scan (Figure 1). The patient was diagnosed with lupus nephritis, lupus encephalopathy, renal hypertension, thrombocytopenia, anaemia and hyperkalaemia. Her SLE disease activity index (SLEDAI)[10] score was 27(severe, $\geq$14) and she had rapidly worsening renal function.

High dose methylprednisolone (500 mg/day, three days), intravenous immunoglobulin (IVIG, 20g/day, five days) combined with continuous renal replacement therapy (CRRT) was initiated. In addition, washed red blood cells (RBC) were transfused to reverse the severe anaemia. After three days, oedema of the extremities gradually decreased, CRP levels fell to near normal values (2.4 mg/l) and urinary volume

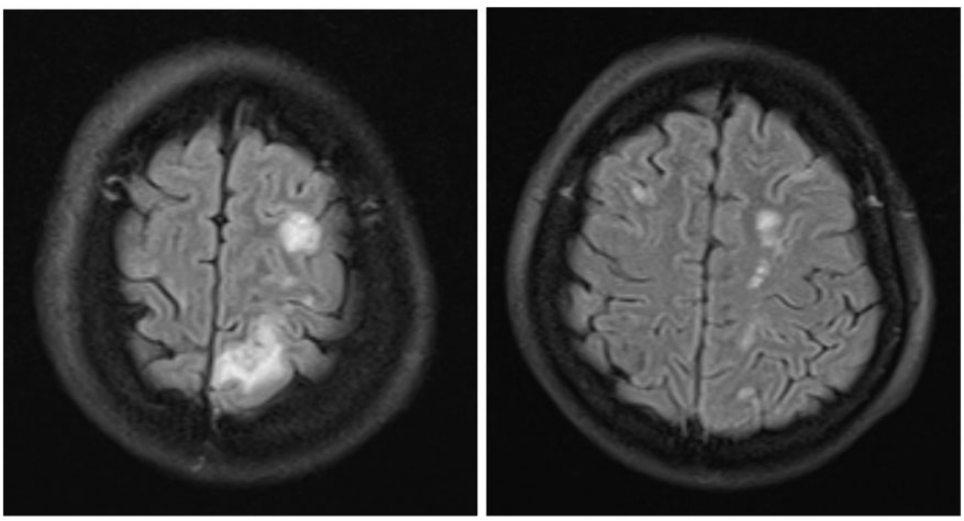

**Figure 1.** T2-weighted cranial MRI scans showing multiple small infraction lesions in bilateral frontal lobes, left parietal lobe and occipital lobe.

increased to 1000 ml/24h. However, proteinuria, anti-dsDNA antibodies and BP remained elevated and the patient had refractory ascites. Analysis of the urinary sediment showed 30–50 RBC per high-power field (HPF) and 1–2 granular casts per HPF. A bolus injection of cyclophosphamide (0.4 g) was administered intravenously and double filtration plasmapheresis (DFPP) was used for the highly active SLE. Nifedipine (60 mg/day), carvedilol (25 mg/day) and methylprednisolone (1 mg/kg/day) were also administered as maintenance therapy. The patient gradually improved and her ANA and ESR levels decreased. However, platelets (18,000/$mm^3$), haemoglobin (5 g/dl) and fibrinogen (0.94 g/l) were low and a few sporadic petechiae were observed on the lower extremities. The DFPP was stopped and IVIG (20 g/day, five days) combined with plasma transfusion were introduced to prevent bleeding.

After five days, the platelet count and haemoglobin recovered to 108,000/$mm^3$ and 6.7 g/dl, respectively. However, the patient developed a dry cough and computed tomography (CT) scan showed mild pulmonary inflammation. Following ceftriaxone (2 g/day) for seven days, symptoms and infection improved. On January 10th 2017, the patient received another bolus injection of cyclophosphamide (0.4g) intravenously and following this treatment levels of CRP, ESR, ANA, haemoglobin, platelets, leukocytes and liver transaminases returned to normal levels and the patient was later discharged from hospital.

On 21st January 2017 (two days after discharge), the patient was readmitted to hospital because of repeated melena and abdominal pain. Laboratory results showed platelets, CRP, ANA, perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic-ANCA and ESR levels were near normal values. Nevertheless, the patient's condition worsened and was accompanied by severe gastrointestinal bleeding and her haemoglobin levels fell rapidly to 3.9 g/dl. Blood volume supplementation and haemostasis therapy were implemented. A colonic endoscopy showed signs of bleeding in the small intestine with hyperaemia, oedema and multiple petechiae on the mucosal surface (Figure 2). Contrast enhanced abdominal CT showed thickened small intestinal walls and a large quantity of ascites (Figure 2). Diagnostic paracentesis showed clear peritoneal fluid and laboratory analysis showed that the effusions were transudative and negative for bacteria or atypical cultures. Methylprednisolone was decreased to 40 mg/day and human serum albumin (20g/day) was administered intravenously. In addition to the gastrointestinal bleeding, the patient developed a fever and persistent dry cough. A comprehensive diagnostic work-up for signs of infection (i.e., blood, sputum and urine cultures) was negative but a pulmonary CT scan showed signs of multiple bilateral inflammation of the lungs. In spite of meropenem (1g tds), her pulmonary symptoms worsened.

Despite intensive therapy which included methylprednisolone, IVIG, urapldil, cefoperazone/sulbactam, torasemide, meropenem and other supporting treatments, the patient experienced dyspnoea and eventually developed severe haemoptysis and acute left heart failure. Notably, although she was receiving oxygen at 10 l/min, her oxygen saturation decreased to 77% and brain natriuretic peptides (BNP) levels were elevated (1867.3 pg/mL). A pulmonary CT scan showed diffuse bilateral alveolar filling patterns and patches of infiltration (Figure 3). Following additional inotropic therapy, mechanical ventilation, blood transfusion and CRRT, the patient's vital signs gradually recovered and haemoptysis

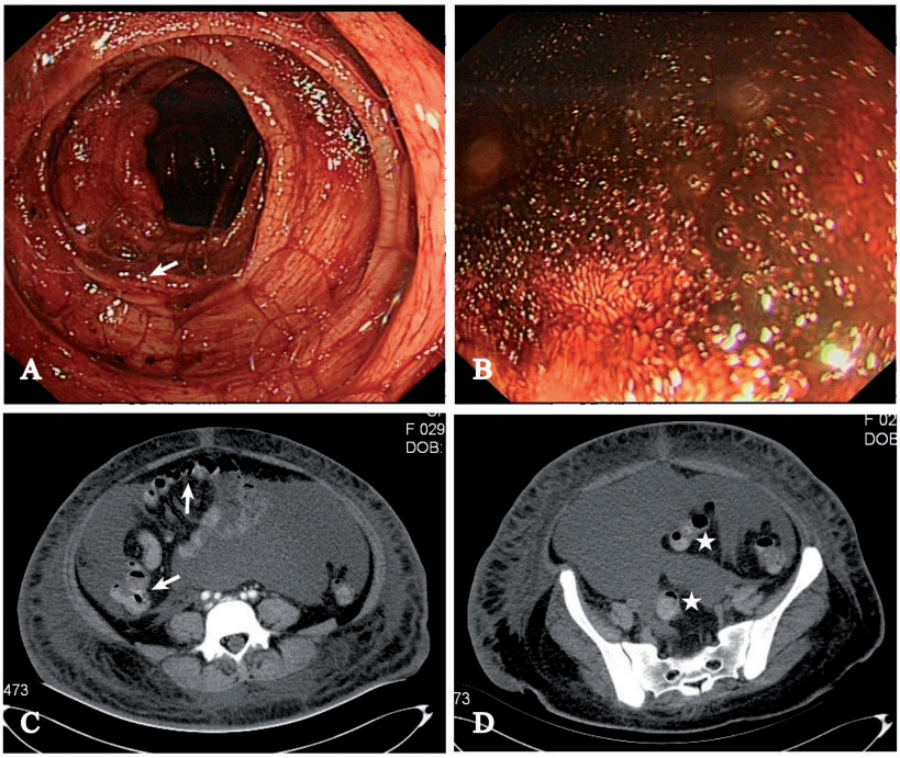


**Figure 2.** Endoscopy of the colon showing small intestine active bleeding combined with oedema (A) and hyperaemia(B). Enhanced computed tomography (CT) scans of the abdomen showing small intestinal wall was thickened (C, indicated by white stars) with associated marked enhancement (D, indicated by white arrows).

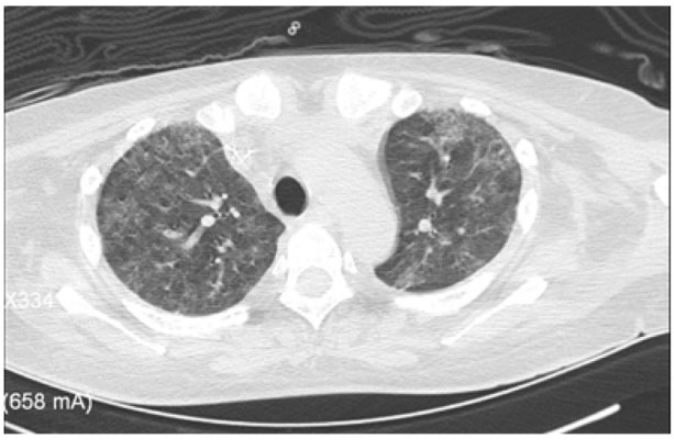

**Figure 3.** Pulmonary CT scan showing diffuse bilateral alveolar filling pattern and patches of infiltration.

subsided. The patient's kidney and heart function continued to improve following daily maintenance therapy with oral prednisolone and with azathioprine.

## Discussion

This case report describes a rare manifestation of SLE in that the patient had multisystem dysfunction. The patient initially presented with proteinuria, haematuria, elevated creatinine and laboratory results showed high titres of ANA, anti-dsDNA and ACA. She was diagnosed with lupus nephritis, lupus encephalopathy, renal hypertension, thrombocytopenia, anaemia and hyperkalaemia. Following intravenous methylprednisolone and cyclophosphamide, DFPP and other supportive treatment her SLEDAI scores improved and renal function gradually recovered. Lupus nephritis is one of the most common complications of SLE and many patients experience renal function problems long before serological abnormalities become apparent.[11] Importantly, circulating autoantibodies to cellular antigens and immune deposits in the vascular wall are characteristics of SLE which activate the inflammatory reaction and lead to cell proliferation and inflammatory leucocyte infiltration.[12]

Soon after discharge from hospital, the patient developed gastrointestinal bleeding with abdominal pain and no signs of infection. Contrast enhanced CT of the abdomen confirmed vasculitis, another common complication of SLE.[13] However, tests for ANCA were negative. Nevertheless, multisystem inflammation and haemorrhage accompanied by high titres of ANAs in the peripheral blood can help in the identification of vasculitis.[14] The mechanism of ANCA-negative vasculitis is unclear but it could involve immune complex deposition and microvascular thrombosis associated with anti-phospholipid antibodies which would then exacerbate mucosal damage and lead to extensive gastrointestinal bleeding.[6,15] The fact that our patient responded well to immunosuppressive therapies supports this theory.

Although intensive treatment was administered, the patient deteriorated rapidly and had a progressive decline in oxygen saturation followed by diffuse alveolar haemorrhage (DAH) and acute left heart failure. Although DAH is a rare complication of SLE it is life-threatening when accompanied by cardiac dysfunction.[16] A large retrospective study in China involving 2133 inpatients with SLE indicated that the incidence of DAH was 1.4%, and the mortality rate was 62%.[17] The disease may occur as a consequence of capillary basement membrane destruction caused by immune complex deposition which allows red blood cells to enter the alveolar spaces. Infiltration of hemosiderin-laden macrophages and development of emboli may also be involved.[18] Pulmonary vascular inflammation and microthrombi may lead to the pulmonary arterial hypertension.[19] Patients with DAH may experience dyspnoea, haemoptysis, bilateral pulmonary infiltrates and consequences of a sudden drop in haemoglobin levels.[20] It is important to identify DAH in patients with SLE and distinguish it from a lung infection, pulmonary embolism, heart failure or acute lupus pneumonitis. Clinically, DAH often coexists with nosocomial infections but focusing on the pulmonary infections and ignoring DAH may lead to high mortality rates in patients with SLE.[21]

Corticosteroids are the mainstay of treatment for SLE and its complications. IVIG and plasma exchange are another two therapies frequently used in clinical practice.[22] Notably, several studies have shown beneficial therapeutic effects of plasmapheresis in patients with highly active SLE, including those with lupus nephritis combined with vasculitis, DAH, gastrointestinal bleeding, lupus encephalopathy,

thrombotic microangiopathy and antiphospholipid syndrome.[23–25] Antiphospholipid syndrome is characterized by hypercoagulability and the presence of antiphospholipid antibodies.[26] This present case report confirms that corticosteroids combined with IVIG and subsequent plasmapheresis are effective in the treatment of a patient with severe SLE complicated by multisystem dysfunction.

In conclusion, complications of SLE can occur at any stage in the course of the disease especially in patients with active SLE. Accurate diagnosis and early intensive treatment with high-dose corticosteroids and cyclophosphamide may prove beneficial in patients with multisystem dysfunction. In addition, appropriate application of CRRT, DFPP combined with intravenous injections of IVIG may improve recovery and renal outcome. It is important for clinicians to be aware of the rare presentations of SLE and its complex management.

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## Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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