

Life-Threatening Complications of Systemic Lupus Erythematosus

2

Michelle Petri

Abstract The major cause of death in longstanding lupus is accelerated atherosclerosis leading to cardiovascular disease. Early in lupus, the major causes of death are active lupus and infection. Life-threatening or organ-threatening lupus is not rare. Multiple organs including skin (necrosis), hematologic (thrombocytopenia, hemolytic anemia, neutropenia, catastrophic antiphospholipid syndrome, and thrombotic thrombocytopenic purpura), heart (pericardial tamponade, myocarditis), lung (alveolar hemorrhage, pulmonary hypertension), gastrointestinal (vasculitis, pancreatitis), adrenal insufficiency, and neurologic (myelitis) may be encountered.

Keywords Catastrophic antiphospholipid syndrome • Hemolytic anemia • Myelitis • Myocarditis • Pancreatitis • SLE • Thrombocytopenia • Vasculitis

2.1 Introduction

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease. It has a strong female predominance (9:1) and predominantly is diagnosed in the 20's and 30's. SLE and its treatment lead to important morbidity and mortality. Because SLE is a multi-system disease, the following chapter will divide emergencies by organ system. For each emergency, the manifestation will be described, its evaluation detailed, and initial treatment discussed.

M. Petri

Department of Medicine, Division of Rheumatology, Johns Hopkins University School of Medicine, 1820 E. Monument St., Ste. 7500, Baltimore, MD 21205, USA
e-mail: mpetri@jhmi.edu

2.2

Cutaneous Digital Gangrene

Digital gangrene in SLE may start as small ischemic lesions but can quickly progress to digital gangrene. In the largest series, long disease duration, Raynaud's phenomenon, and elevated serum CRP were independent risk factors.¹ The differential diagnosis includes severe Raynaud's phenomenon, thromboembolic (i.e., antiphospholipid syndrome [APS]), and lupus vasculitis. Evaluation requires the assessment of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-beta₂-glycoprotein I), cardiac echocardiogram, and often arteriogram.

Treatment of digital gangrene is multifactorial. If vasospasm (Raynaud's) is involved, calcium channel blockers will be given. Other vasodilators, including topical nitrates, may be tried, as well. Intravenous prostacyclin may be needed. To prevent and treat thrombosis, low-dose aspirin (81 mg) and therapeutic doses of heparin are needed. If lupus vasculitis is present, intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min), followed by high-dose oral prednisone (1 mg/kg) is started. Digital sympathectomy, if an experienced surgeon is available, may be considered. The goal is to save as much ischemic tissue as possible. Once tissue demarcation has occurred, a hand or vascular surgeon may amputate the gangrenous areas to relieve pain and improve cosmetic appearance.

2.3

Cutaneous Necrosis

Widespread cutaneous necrosis is rare in SLE. It can occur from antiphospholipid syndrome,² SLE vasculitis, and can be induced by warfarin in patients who are Protein C deficient (because warfarin further reduces Protein C and Protein S levels). Evaluation will include assessment of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-beta₂-glycoprotein I) and biopsy of the edge of a necrotic area (to detect vasculitis). If the necrosis is due to APS, therapeutic doses of heparin are started. If necrosis is due to SLE vasculitis, IV methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) is given, followed by high-dose oral prednisone (1 mg/kg).

2.4

Thrombocytopenia

Thrombocytopenia is common in SLE and is one of the American College of Rheumatology classification criteria for SLE.³ In the Hopkins Lupus Cohort, 21% have had thrombocytopenia defined as a platelet count less than 100,000/mm³. Most thrombocytopenia in SLE

is not life-threatening, and, in fact, may be over-treated. It is rare for patients to bleed unless the platelet count is below 10,000; treatment usually is not needed unless the platelet count falls below 30,000/mm³. An exception is made in an anti-coagulated patient, in whom the goal is to keep the platelet count above 50,000/mm³. Evaluation of thrombocytopenia in an SLE patient includes assessment of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-beta₂-glycoprotein I), antiplatelet antibodies, drug toxicity, and infection. Rituximab can cause a very rare thrombocytopenia, with recovery usually within 2 weeks.

Treatment of serious thrombocytopenia requires intravenous methylprednisolone (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg). Some patients, however, may not respond. Intravenous immunoglobulin, 400 mg/kg over 5 days, is usually the next step; it may be necessary to increase the dose to 1 kg/kg to see a response. In those who still do not respond, rituximab can be considered. Maintenance therapy with azathioprine or mycophenolate is usually needed. Platelet transfusions can be given to patients who are actually bleeding, but the SLE patient's autoantibodies will rapidly destroy them. A patient who responds to intravenous immunoglobulin, but frequently relapses, is a candidate for splenectomy. Although it should not be considered a cure, most patients do improve postsplenectomy. A patient who is not a surgical candidate can be considered for splenectomy by radiation. Newer agents for thrombocytopenia, such as Promacta® (eltrombopag), have not been adequately assessed in SLE, and would not be routine in an emergent situation.

2.5

Autoimmune Hemolytic Anemia (AIHA)

AIHA is rare in SLE, occurring in only 11% of the Hopkins Lupus Cohort. Evaluation for AIHA would include a search for other causes of anemia (ferritin, B12, hemoglobinopathy, schistocytes) as well as tests to confirm hemolytic anemia (direct Coombs test, low haptoglobin, high LDH, high reticulocyte count).

Treatment of AIHA includes intravenous methylprednisolone (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg). Maintenance therapy with azathioprine or mycophenolate mofetil⁴ is then given. Danazol has been used.⁵ Refractory AIHA may require rituximab^{6,7} or splenectomy.⁸

2.6

Neutropenia

Leukopenia in SLE is common and is part of the American College of Rheumatology classification criteria. Most leukopenia in SLE is lymphopenia; neutropenia from SLE is rare, but reported.^{9,10} Evaluation of neutropenia in SLE would include anti-neutrophil antibodies

and drug toxicity (usually cyclophosphamide or other immunosuppressive drugs). Rituximab can cause both an immediate and a late neutropenia.

Neutropenia in SLE is usually not an emergency; it is often over-treated. As long as the total neutrophil count is above $1,000/\text{mm}^3$, the risk of infection is small, and no treatment is necessary. If the patient becomes neutropenic due to cyclophosphamide, or other immunosuppressive drug, it is sufficient to stop the cyclophosphamide and allow the neutrophils to recover. Granulocyte colony stimulating factor (G-CSF) should not be given to the stable patient because of the risk of SLE flares (including fatal flares).¹¹ G-CSF should be reserved for the neutropenic patient with sepsis.

2.7

Catastrophic Antiphospholipid Syndrome (CAPS)

CAPS is a rare manifestation of APS. About 40% of CAPS patients have SLE; 10% another rheumatic disease; and 50% no history of autoimmune disease. Common precipitants include infection, surgery, trauma, pregnancy, oral contraceptives, and cessation of warfarin in an APS patient. “Definitive” CAPS requires three organ involvement, and demonstration of thrombosis in the setting of antiphospholipid antibodies. “Probable” CAPS requires involvement of two organs. CAPS manifestations differ from APS. In CAPS, 48% have primary APS, 40% have SLE, and 12% have secondary APS due to another cause.¹² Evaluation of CAPS involves assessment of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti- β_2 -glycoprotein I), examination of the peripheral smear for microangiopathic hemolytic anemia and documentation of thrombosis.¹³

Treatment is truly an emergency, as mortality is as high as 50%. Treatment has three goals: to settle the “cytokine storm” (intravenous methylprednisolone pulse), treat and prevent further thrombosis (intravenous heparin), and reduce the antiphospholipid antibody burden (plasmapheresis or intravenous immunoglobulin).¹³ In recalcitrant cases, rituximab may be helpful.

2.8

Thrombotic Thrombocytopenic Purpura (TTP)

Past series of TTP in SLE may have included some patients with CAPS, as the two can present in similar fashion.^{14,15} Genetic or autoantibody-induced deficiency of the metalloproteinase ADAMTS13 is part of the pathogenesis. Classic TTP includes fever, thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, and neurologic involvement.¹⁶ Evaluation would include a peripheral blood smear for schistocytes, exclusion of infection, and drug toxicity.

Treatment of TTP in SLE is plasmapheresis or plasma exchange.¹⁷ Intravenous cyclophosphamide and rituximab have also been used.^{18,19}

2.9

Pericardial Tamponade

Pericarditis is frequent in SLE, occurring in 22% of the Hopkins Lupus Cohort. Serositis is one of the ACR classification criteria of SLE. Pericardial tamponade, however, is rare. It can occur as a presenting manifestation of SLE.²⁰ Typically, pericarditis is positional, such that the patient feels dyspneic lying flat and feels better leaning forward. Patients with tamponade may present with ascites and edema.²¹ Evaluation would include physical examination findings including pericardial rub, distant heart sounds, pulsus paradoxus, and confirmatory cardiac echocardiogram.

Treatment of life-threatening pericardial tamponade will require a pericardial tap or pericardial window. Treatment of the underlying SLE activity would include intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg).

2.10

Myocarditis

SLE myocarditis is rare, occurring in 14% in one series.²² It may be associated with myositis.²³ Patients with SLE myocarditis often present with congestive heart failure. Evaluation would include cardiac echocardiogram, which would show hypokinesis, and coronary arteriogram to rule out atherosclerosis or coronary vasculitis. On occasion, a right ventricular biopsy confirms myocarditis.²⁴

Treatment of myocarditis would include intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg).²⁵ Pulse cyclophosphamide therapy may be needed.²⁶

2.11

Pulmonary Alveolar Hemorrhage

Alveolar hemorrhage is extremely rare in SLE, with only a few case series.²⁷⁻²⁹ It presents as dyspnea, fever, hemoptysis, and chest pain. Evaluation would include chest CT and bronchoscopy.

Treatment of alveolar hemorrhage in SLE is plasmapheresis and intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg).

2.12

Pulmonary Hypertension

Pulmonary hypertension in SLE can be severe, with a poor prognosis.³⁰ Dyspnea is the most common presenting symptom. Evaluation of an SLE patient with acute severe pulmonary hypertension would require cardiac echocardiogram followed by right heart catheterization. The immediate concern is whether it is due to thromboembolic disease or due to SLE activity.

Treatment of pulmonary hypertension due to thromboembolic disease may require surgical embolectomy or thrombolytic agent or heparin. Severe pulmonary hypertension due to active SLE is treated with intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg). Chronic pulmonary hypertension can be treated in a fashion similar to idiopathic pulmonary hypertension, including sildenafil, bosentan, and intravenous prostacyclin.³¹

2.13

Pancreatitis

Pancreatitis is a rare manifestation of SLE. In the largest review, only 4% of SLE patients had pancreatitis attributed to SLE.³² Patients present with abdominal pain, fever, and electrolyte disturbances. It can be fatal, especially in pediatric patients.³³ A multivariate model found that hypertriglyceridemia, psychosis, pleurisy, gastritis, and anemia were associated with a history of pancreatitis.³² Although antiphospholipid antibodies can occur, they do not appear to be causative.

Although high-dose corticosteroids can cause pancreatitis, when SLE pancreatitis occurs, intravenous methylprednisolone 1,000 mg daily for 3 days remains the treatment of choice.

2.14

Adrenal Insufficiency

Adrenal insufficiency is a very rare manifestation of SLE. It appears in conjunction with antiphospholipid syndrome, or more commonly, in catastrophic antiphospholipid syndrome (CAPS), in whom 26% had adrenal involvement in one series.^{12,34} In CAPS, adrenal involvement is usually bilateral, due to adrenal venous infarction. Adrenal insufficiency usually presents acutely, with flank pain, nausea, vomiting, hypotension, and electrolyte abnormalities.

Treatment of CAPS is reviewed elsewhere in this chapter. Management of adrenal insufficiency is both acute, in terms of steroid, volume and electrolyte management, and chronic, with adrenal replacement, with low-dose prednisone and fluorinated steroids.

2.15

Mesenteric Vasculitis

Mesenteric vasculitis is a very rare manifestation of SLE. Patients present with fever, abdominal pain, diarrhea, vomiting, and sepsis.^{35,36} Early in the course, swollen layers of bowel may be present on abdominal CT.³⁷ A mesenteric arteriogram may show vasculitis. Occasionally, biopsy during colonoscopy may reveal vasculitis. The differential diagnosis would include atherosclerosis, pancreatitis, peptic ulcer, peritonitis, bowel infarction, and infection (such as *C. difficile* or cytomegalovirus).

Management requires both surgical resection of dead bowel and suppression of vasculitis by intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min).

2.16

Myelitis

Longitudinal myelitis in SLE occurs in two forms, one affecting gray matter (that occurs in an acute catastrophic form) and one involving white matter (that clearly resembles neuromyelitis optica).³⁸ Myelitis presents as pain, weakness, and sphincteric defects. Patients with gray matter involvement will have flaccidity and hyporeflexia, while patients with white matter dysfunction will have spasticity and hyperreflexia. Patients with gray matter dysfunction may have a prodrome of fever and urinary retention. Those with white matter involvement are more likely to have had antiphospholipid antibodies.

Treatment for SLE myelitis needs to be given within a short time after symptom onset, with intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min), followed by high-dose oral corticosteroids. There may be a role for rituximab, as well.

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