

Some Severe Manifestations of Systemic Lupus Erythematosus Can Be Managed

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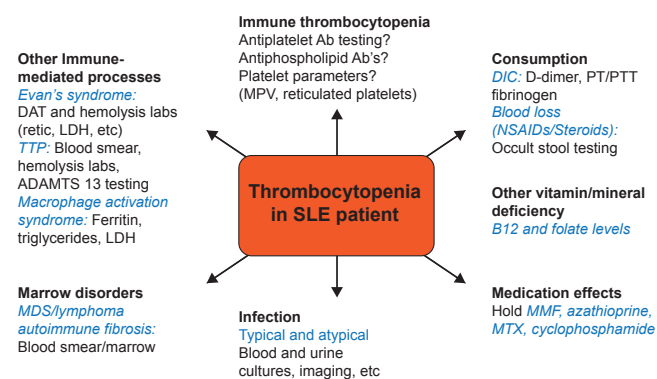
For a classification of systemic lupus erythematosus (SLE), patients must have at least one clinical and one immunologic criterion of the SLICC classification criteria, for a total of four, or must have biopsy-proven lupus nephritis. Clinical criteria include acute cutaneous lupus, chronic cutaneous lupus, oral ulcers, nonscarring alopecia, arthritis, serositis, neurologic lupus, proteinuria, and dytopenias [Petri M et al. *Arthritis Rheum* 2012]. Immunologic criteria include ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, low complement, and direct Coombs.

Michelle Petri, MD, MPH, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, pointed out that prednisone is independently associated not just with non-life-threatening organ damage (cataracts, osteoporosis), but with cardiovascular events. [Madger LS, Petri M. *Am J Epidem* 2012; Thamer M et al. *J Rheumatol* 2009]. She emphasized that even low doses of prednisone >6 mg daily increase permanent organ damage. Most mild to moderate flares will respond to intramuscular triamcinolone or to a methylprednisolone “dose pack,” helping to avoid maintenance prednisone [Danowski A et al. *J Rheumatol* 2006]. Dr. Petri recommends administering hydroxychloroquine to all patients; it reduces flares [Canadian Hydroxychloroquine Study Group. *N Engl J Med* 1991] and thrombosis [Petri M. *Scand J Rheumatol* 1996; Pierangeli SS, Harris EN. *Lupus* 1996] by half, reduces organ damage [Fessler BJ et al. *Arthritis Rheum* 2005] and lipids [Petri M. *Lupus* 1996; Wallace DJ et al. *Am J Med* 1990], improves survival [Alarcon GS et al. *Arthritis Rheum* 2005; Ruiz-Irastorza G et al. *Lupus* 2005], prevents seizures [Hanly JG et al. *Ann Rheum Dis* 2012], and triples the response to mycophenolate [Kasitanon N et al. *Lupus* 2006] in severe lupus nephritis. Vitamin D is also a safe immunomodulator for patients with SLE [Petri M. *Arthritis Rheum* 2013].

TREATMENT OF THROMBOCYTOPENIA

Brady L. Stein, MD, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA, discussed the treatment of severe thrombocytopenia in SLE. He agreed with Dr. Petri that long-term steroids have unacceptable adverse effects. Immune thrombocytopenia may result from impaired platelet production and/or increased platelet destruction mediated by autoantibodies, with subsequent splenic clearance. The differential diagnosis for thrombocytopenia in SLE is broad and a suggested diagnostic workup is summarized in Figure 1.

Figure 1. Thrombocytopenia in SLE: Differential Diagnosis and Workup



Ab=antibody; DAT=direct antiglobulin testing; DIC=disseminated intravascular coagulation; LDH=lactate dehydrogenase; MDS=myelodysplastic syndrome; MMF=mycophenolate mofetil; MPV=mean platelet volume; MTX=methotrexate; NSAIDs=nonsteroidal anti-inflammatory drugs; PT=prothrombin time; PTT=partial thromboplastin time; retic=reticulocyte count; SLE=systemic lupus erythematosus; TTP=thrombotic thrombocytopenic purpura.

Reproduced with permission from M Petri, MD, MPH.

Patient factors affect the selection of therapy for thrombocytopenia. Younger patients may be better able to tolerate splenectomy. Comorbidities, cost, and SLE activity should also be considered. The typical threshold for therapy is a platelet count <20 to 30 x 10⁹/L. For patients with antiphospholipid antibody syndrome who require anticoagulation, the threshold should be 50 x 10⁹/L.

Splenectomy is an “old” treatment that yields high responses, although it has been analyzed in small numbers of patients with SLE [You YN. *Ann Surgery* 2004]. Another option is rituximab to suppress antibody production by B cells. Rituximab has been effective in primary idiopathic thrombocytopenic purpura (ITP), but this is an off-label use, may not be durable, and may be associated with adverse reactions in SLE patients [Gudbrandsdottir S et al. *Blood* 2013; Jovancevic C et al. *Lupus* 2013; Neunert C et al. *Blood* 2011; Zaja F et al. *Blood* 2010; Godeau B et al. *Blood* 2008]. Other options are thrombopoietin agonists, like romiplostim [Kuter DJ et al. *N Engl J Med* 2010; *Lancet* 2008] and eltrombopag [Cheng G et al. *Lancet* 2011; Bussel JB et al. *Lancet* 2009], although results in SLE are anecdotal. These agents require long-term therapy and have potential side effects including thrombosis, a concern in SLE [Kuter DJ et al. *Br J Haematol* 2013; Saleh MN et al. *Blood* 2013].



TREATMENT OF NEUROLOGIC COMPLICATIONS

Julius Birnbaum, MD, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, described subtypes of posterior reversible leukoencephalopathy syndrome (PRES), myelitis, and small-fiber neuropathies in SLE. PRES is associated with visual disturbances, encephalopathies, seizures, and headaches. Risk factors for PRES are similar in patients with or without SLE, and include hypertension, renal failure, immunosuppressant use, and thrombotic thrombocytopenic purpura (TTP). SLE is associated with many concomitant risk factors for PRES.

Small-fiber neuropathies are very painful, affect unmyelinated C-fiber nerve, and, although common, are underdiagnosed in SLE. Nerve conduction studies are normal, and small-fiber deficits appear on physical examination. A punch skin biopsy showing a decreased density of small-fiber nerves in the epidermal layer is diagnostic. There are two patterns of small-fiber neuropathies in SLE: length-dependent, affecting distal-most axons, and non-length-dependent, affecting proximal dorsal root ganglia.

There are two types of myelitis in SLE: gray-matter myelitis and white-matter myelitis. The distinguishing characteristics are summarized in Table 1.

Table 1. Summary of Distinguishing Differences Between Gray-Matter and White-Matter Myelitis

	Gray-Matter Myelitis	White-Matter Myelitis
Presence of SLE disease activity	Yes	No
Relapsing disease	No	Yes
Discriminating Autoantibodies		
Anti-Ro/SSA	No	Yes
Lupus anticoagulant	No	Yes
CSF profile resembling bacterial meningitis	Yes	No
MRI Features		
Longitudinal myelitis over 3 or more vertebral segments distinguishes from MS	Yes	Yes
Cord swelling	Yes	No
Gadolinium enhancement	No	Yes
Prognosis		
EDSS≥6 (independent ambulatory capacity)	Yes, after single attack	Yes, after multiple attacks

CSF=cerebral spinal fluid; EDSS=expanded disability status scale; MRI=magnetic resonance imaging; MS=multiple sclerosis; SSA=anti-Sjogren's syndrome A; SLE=systemic lupus erythematosus.

Gray-matter myelitis is caused by catastrophic venous hypertension in which blood flow to the spinal cord is impaired and necrosis occurs. Dr. Birnbaum pointed out that 9 of 11 patients they identified had sought medical attention for the inability to void, and were ambulatory at the time. Many were sent home with a catheter. He emphasized that unexplained inability to void in patients with highly active

SLE should be taken as a sign of impending spinal cord herniation; patients should be treated immediately with pulsed intravenous steroids to avoid irreversible paraplegia.

MANAGING DERMATOLOGIC MANIFESTATIONS OF SLE

M. Kari Connolly, MD, University of California, San Francisco, California, USA, described severe cutaneous manifestations in patients with SLE, pointing out that the presentations of skin complications may be atypical or suggest other diagnoses. The differential diagnosis should include infection, drug rash, erythema multiforme, small-vessel vasculitis, bullous LE, and acute flare of SLE. Skin biopsy cannot differentiate SLE subtypes, but can differentiate SLE from other diagnoses, distinguish inflammation from scarring, and detect the presence of microthrombi or leukocytic vasculitis.

When SLE is refractory to standard therapies like antimalarials, thalidomide may be effective [Cuadrado MJ et al. *Am J Med* 2005]. It requires enrollment in a safety program due to its teratogenicity; it can also cause neuropathy [Bastuji-Garin S et al. *J Invest Dermatol* 2002]. Maintenance therapy is usually needed. Lenalidomide, a newer thalidomide analogue, is also effective; neutropenia is a significant toxicity and necessitates regular blood counts [Cortés-Hernandez J et al. *Arthritis Res Ther* 2012]. Topical steroids, tacrolimus, pimecrolimus, and retinoids, may also be effective.

Bullous LE is rare, non-scarring, and involves neutrophils rather than leukocytes. The immunomodulator dapsone is effective, but may require combination therapy with prednisone, mycophenolate, azathioprine, or rituximab [Hall RP et al. *Ann Intern Med* 1982; Ludgate MW Greig DE. *Australas J Dermatol* 2008]. Dapsone causes hemolytic anemia in 20% of patients and requires testing for glucose-6-dehydrogenase. LE panniculitis is also rare, and is associated with characteristic saucer-shaped deformities. The differential diagnosis includes subcutaneous T cell lymphoma. The associated deformities do not respond well to cosmetic surgery, lasers, or fillers, or to kenalog injections. Other SLE therapies may be effective.

Dr. Connolly said that dermatologists can help other clinicians by determining what is scar tissue and what is active disease (eg, when areas of hair loss are no longer treatable). Dermatologists are good at performing biopsies and experienced in the use of agents with which rheumatologists may be less familiar.

Some complications of SLE can be managed, including thrombocytopenia. Gray-matter myelitis that may present as an inability to void should be treated immediately to prevent permanent paraplegia. Other complications of SLE, such as atherosclerosis, a major cause of death, does not respond to statin therapy, so other therapies are needed, as they are for other symptoms that are important to patients, including fatigue and cognitive impairment.