Unusual Presentations of Systemic Lupus Erythematosus

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KEYWORDS

• Systemic lupus erythematosus • Adolescence • Lupus • Pediatrics

KEY POINTS

- Adolescents with systemic lupus erythematosus (SLE) may present with unusual signs and symptoms.
- Understanding and recognition of uncommon SLE presentations allow prompt diagnosis and management.
- Specific histologic, laboratory, and imaging findings in the appropriate clinical context will lead to a diagnosis of SLE.
- SLE during adolescence may mimic other diseases, leading to delays in diagnosis and treatment.
- SLE should be considered in the differential diagnosis of a wide variety of signs and symptoms.

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that most commonly begins in adolescence and early adulthood and can involve nearly any organ system in the body.[1] The diagnosis is clinical, primarily based on signs and symptoms and supported by characteristic laboratory test results. Several classification criteria for SLE have been developed,[2–4] and the European League Against Rheumatism/American College of Rheumatology 2019 criteria[4] is the most recent (**Box 1**). Although SLE will often present with the characteristic clinical and laboratory abnormalities emphasized in these criteria, unusual manifestations may sometimes be the first to appear. This review discusses several of the less common presenting manifestations of SLE, focusing on clinical, laboratory, and imaging features. This discussion of the treatment of SLE is limited to specific therapies targeting unusual manifestations. Further information regarding the overall management of SLE can be found in several references,[1,5] and a comprehensive list of unusual

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Box 1
EULAR/ACR criteria for classification of systemic lupus erythematosus

Entry Criterion	ANA titer >/ = 1:80	
Clinical Domains		Points
Constitutional	Fever	2
Hematological	Leukopenia	3
	Thrombocytopenia	4
	Coombs + Autoimmune hemolytic anemia	4
Neuropsychiatric	Delirium	2
	Psychosis	3
	Seizure	5
Mucocutaneous	Nonscarring alopecia	2
	Oral ulcers	2
	Subacute cutaneous or discoid lupus	4
	Acute cutaneous lupus	6
Serosal	Pleural or pericardial effusion	5
	Acute pericarditis	6
Musculoskeletal	Joint involvement	6
Renal	Proteinuria > 0.5 g/24 h	4
	Renal biopsy class II or V nephritis	8
	Renal biopsy class III or IV nephritis	10
Immunologic Domains		
Antiphospholipid antibodies	Anticardiolipin	2
	Anti-β2-glycoprotein 1 lupus anticoagulant	
Complement	Low C3 or C4	
	Low C3 AND C4	
SLE-specific antibodies	Anti-dsDNA	
	Anti-Smith	

Requires presence of entry criterion, ≥1 clinical criterion, and ≥10 points. Within each domain only the highest weighted criterion is counted toward the total score. Occurrence of criterion on at least one occasion is sufficient; criteria need not occur simultaneously.

Adapted from Petty RE et al, editors: *Textbook of Pediatric Rheumatology*, ed 8, Philadelphia, 2021, Elsevier (Table 23.2, p 296), with permission.

presentations of SLE is listed in **Box 2**, including additional manifestations not specifically discussed here.

HEMATOLOGIC MANIFESTATIONS

Lupus Anticoagulant Hypoprothrombinemia Syndrome

Lupus anticoagulant hypoprothrombinemia syndrome (LAHS) is caused by an acquired factor II (prothrombin) inhibitor in combination with a lupus anticoagulant. Despite the presence of the prothrombotic lupus anticoagulant, nonneutralizing antiprothrombin antibodies result in the rapid clearance of prothrombin-antibody complexes from the serum, leading to hypoprothrombinemia and subsequent bleeding.[6,7] LAHS occurs in all ages with SLE and seems to be more frequent in children and adolescents.[7] Symptoms may range from mild mucocutaneous bleeding including epistaxis, gum bleeding, menorrhagia, ecchymoses (**Fig. 1**), and hematochezia to severe life-threatening bleeding.[8] Additional signs and symptoms of SLE are not always present, and the evidence of associated SLE may be restricted to laboratory test findings. Laboratory testing will reveal a prolonged prothrombin time and activated partial thromboplastin time, an elevated lupus anticoagulant, and factor II

Box 2
Uncommon systemic lupus erythematosus manifestations in adolescence

Musculoskeletal	Myositis
	Tenosynovitis
Vascular	Leukocytoclastic vasculitis
	Cryoglobulinemia
	Livedo reticularis
Hematologic	Hypoprothrombinemia
	Catastrophic antiphospholipid syndrome
	Thrombotic microangiopathy
Neuropsychiatric	Aseptic meningitis
	Cognitive dysfunction
	Mood disorders/psychiatric disease
	Pseudotumor cerebri
	Acute inflammatory demyelinating polyradiculoneuropathy
	Cranial neuropathy
	Neuromyelitis optica
	Mononeuropathy multiplex
	Myasthenia gravis
	Chorea
	Transverse myelitis
Cardiovascular	Coronary artery disease/myocardial infarction
	Libman-Sacks endocarditis
Pulmonary	Pneumonitis
	Pulmonary hypertension
	Diffuse alveolar hemorrhage
	Shrinking lung syndrome
Gastrointestinal	Enteritis
	Pancreatitis
	Protein-losing enteropathy
Ocular	Keratoconjunctivitis sicca
	Orbital pseudotumor
	Ulcerative keratitis
	Uveitis
	Episcleritis scleritis
	Optic nerve disease
	Ocular motor abnormalities
	Retinopathy
Dermatologic	Panniculitis
	Bullous lupus

Modified from Petty RE et al, editors: *Textbook of Pediatric Rheumatology*, ed 8, Philadelphia, 2021, Elsevier (Table 23.4, p 301), with permission.

deficiency.[7,8] Hypocomplementemia, elevated anticardiolipin antibodies, and additional autoantibodies characteristic of SLE may also be present. Treatment includes controlling bleeding, when necessary, with fresh frozen plasma, red blood cell transfusions, and factor concentrate as well as immunomodulators to decrease antibody and inhibitor formation.[6,8] Rituximab may be particularly effective, and plasmapheresis has been used in severe cases.[7]

Catastrophic Antiphospholipid Syndrome

Catastrophic antiphospholipid syndrome (CAPS) is a rare life-threatening variant of antiphospholipid syndrome (APS) (<1% of all patients with APS), characterized by multiple small vessel occlusions resulting in multiorgan failure associated with elevated

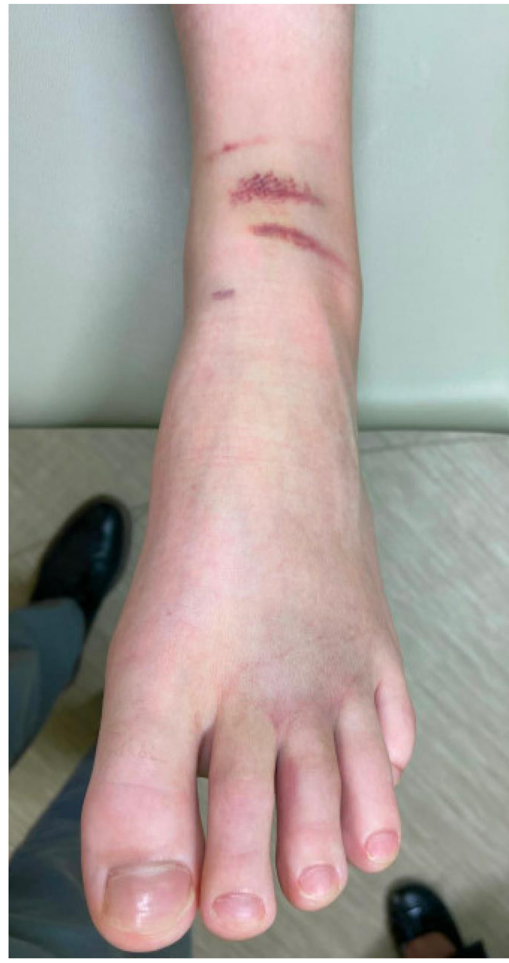

Fig. 1. Soft tissue hemorrhage in lupus anticoagulant hypoprothrombinemia syndrome.

serum antiphospholipid antibodies.[9] Although it can occur in isolation, up to 30% of pediatric patients with CAPS are also diagnosed with SLE.[9,10] Diagnostic criteria for CAPS are listed in **Box 3**. In children and adolescents, the most commonly affected organs include the kidneys and lungs, with many additional organ systems potentially affected by both APS and CAPS (**Box 4**).[11] Other associated signs and symptoms may include livedo reticularis, arthritis, leukopenia, and thrombocytopenia.[9,11] The mortality rate is high (24%–50%), and therefore, prompt recognition and treatment of CAPS is critical.[9,11] Therapy targets the elimination of precipitating factors, treatment of ongoing thrombotic processes with anticoagulation, and suppression of commonly associated cytokine storm.[9] Immunomodulators such as cyclophosphamide or rituximab have been demonstrated to be effective in improving survival.[9,11,12]

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) has been reported in 2% to 3% of those with SLE, with 15% to 60% of childhood and adolescent SLE–associated TMA occurring at the

Box 3
Criteria for the classification of catastrophic antiphospholipid syndrome

1. Evidence of involvement of 3 or more organs, systems, and/or tissues
2. Development of manifestations simultaneously or in less than 1 week
3. Confirmation by histopathology of small vessel occlusion in 1 or more organs/tissues
4. Laboratory confirmation of the presence of antiphospholipid antibodies (APLA)

Definite CAPS
All 4 criteria present

Probable CAPS
- All 4 criteria except only 2 organs, systems, and/or tissue involvement
- All 4 criteria except for absence of laboratory confirmation more than or equal to 6 weeks apart because of early death of patient or never tested for APLA before CAPS
- 1, 2, and 4 criteria present
- 1, 3, and 4 criteria present + development of third event in more than 1 week but less than 1 month despite anticoagulation.

Adapted from Petty RE et al, editors: *Textbook of Pediatric Rheumatology*, ed 8, Philadelphia, 2021, Elsevier (Table 24.1, p 331), with permission.

Box 4
Venous and arterial thrombosis manifestations of antiphospholipid syndrome in children and adolescents

Site of Vessel Involvement	Clinical Manifestations
Limbs	Deep vein thrombosis
	Ischemia/gangrene
Skin	Livedo reticularis, chronic leg ulcers, superficial thrombophlebitis
Large veins	SVC or IVC thrombosis
Lungs	Pulmonary embolus, pulmonary hypertension
Brain	Cerebral venous sinus thrombosis
	Cerebral infarction, transient ischemic attack, acute ischemic encephalopathy
Eyes	Retinal vein thrombosis
	Retinal artery thrombosis
Liver	Budd-Chiari syndrome, portal vein thrombosis
	Hepatic infarction
Kidney	Renal vein thrombosis
	Renal artery thrombosis, renal thrombotic microangiopathy
Adrenal glands	Hypoadrenalism, Addison disease
Heart	Myocardial infarction
Spleen	Splenic infarction
Gut	Mesenteric artery thrombosis
Bones	Bone infarction

Abbreviations: IVC, inferior vena cava; SVC, superior vena cava.

Adapted from Petty RE et al, editors: *Textbook of Pediatric Rheumatology*, ed 8, Philadelphia, 2021, Elsevier (Table 24.2, p 336), with permission.

onset of SLE.[13] TMA can occur as the result of an inhibitor of a disintegrin and metalloprotease with thrombospondin-type motif (ADAMTS13), equivalent to thrombotic thrombocytopenic purpura[14]; however, some instances of TMA are hypothesized to be complement mediated with a normal or only minimally reduced ADAMTS13.[15] The diagnosis should be suspected in patients with SLE with the combination of acute thrombocytopenia and hemolytic anemia, fevers, rapidly worsening renal insufficiency, and/or neurologic involvement.[16] A peripheral smear will reveal abundant schistocytes characteristic of a microangiopathy. Plasmapheresis is an effective treatment of TMA in addition to glucocorticoids and immunomodulation, and prognosis is favorable when recognized and treated early.[14] Eculizumab, a terminal complement inhibitor, has also demonstrated efficacy when ADAMTS13 levels are not severely reduced.[15,17,18]

DERMATOLOGIC MANIFESTATIONS

Lupus Panniculitis

In 2% to 5% of patients with SLE, the first skin finding may be panniculitis.[19,20] Lesions appear as recurrent tender erythematous indurated nodules and plaques in the deep dermis and subcutaneous tissues with initial local swelling followed by subsequent scarring and lipoatrophy[20](**Fig. 2**). In children and adolescents, the face is the most common affected location, with areas of higher fat composition such as the breasts, upper thighs, and buttocks also frequently affected.[21] Histopathology reveals lobular

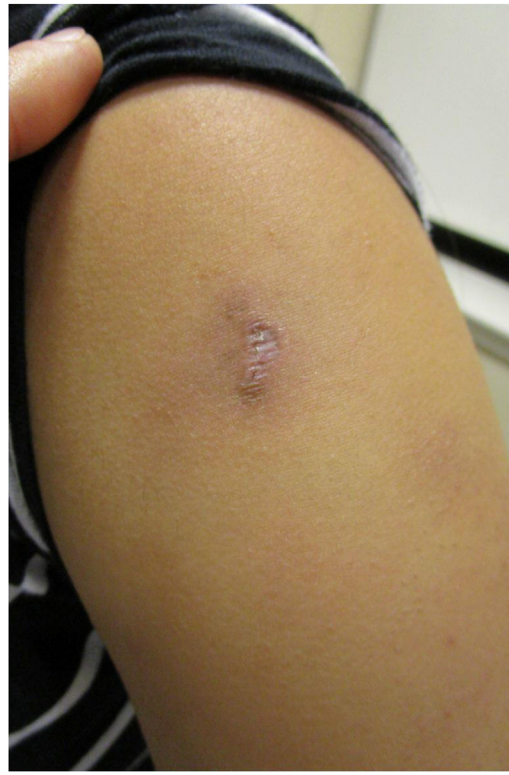

Fig. 2. Lupus panniculitis. (*Courtesy of* Kristen Holland, MD, Medical College of Wisconsin.)

dense lymphoplasmacytic and histiocytic patchy infiltrates, hyaline fat necrosis, mucin deposition, and lymphocytic vasculitis in fat lobules.[20] Specific findings that are suggestive of SLE-associated panniculitis include vacuolar changes at the dermal-epidermal interface, periadnexal lymphocytic infiltrates, interstitial deposition of mucin in the reticular dermis, and lymphoid follicles with reactive germinal centers in the subcutis.[19] Direct immunofluorescence may reveal immunoglobulin (Ig) G, IgM, and complement 3 (C3) deposition in the basal membrane of overlying skin.[22] Lupus panniculitis may occur in isolation or in association with SLE, and when associated with SLE, treatment with hydroxychloroquine and glucocorticoids is often effective.[21] For refractory cases, additional immunomodulators are used. If left untreated, profound lipoatrophy can lead to severe disfigurement.[23,24]

Bullous Lupus

Vesiculobullous lesions are exceedingly rare manifestations of SLE, occurring in less than 5% of patients.[25] Bullous lupus (BSLE) represents only 2% to 3% of all subepidermal autoimmune bullous skin diseases.[25] Antibodies targeting type VII collagen result in weakened basement membrane-dermal adhesion with subsequent subepidermal blistering.[25] Widespread blistering lesions appear that can resemble large burns (**Fig. 3**). These are most commonly present on the upper trunk, neck, and other sun-exposed areas.[22] Mucosal surfaces can be affected, particularly the oropharynx, and can potentially compromise the airway. Biopsy reveals a neutrophil predominant infiltrate and multiple immunoglobulins and immune complexes along the basement membrane zone.[22] Direct immunofluorescence characteristically reveals IgG, IgM, IgA, and C3 at the dermal-epidermal junction and the absence of eosinophils, differentiating BSLE from other bullous diseases.[22] Treatment with dapsone is effective, with a dramatic response in the first 24 to 48 hours of use.[25] In contrast to other cutaneous manifestations of SLE, glucocorticoids and hydroxychloroquine have limited efficacy for BSLE, and methotrexate, cyclophosphamide, and mycophenolate mofetil all have modest efficacy.[25] In refractory cases, rituximab has had promising results.[22] Lesions typically heal with residual hyperpigmentation, scarring, or milia, and recurrences are common.[22]

CENTRAL NERVOUS SYSTEM MANIFESTATIONS

Chorea

Chorea as an initial manifestation of SLE is unusual (incidence 0.6%–2.3%).[26,27] It is defined as involuntary purposeless rapid, jerky, forceful movements. Patients may

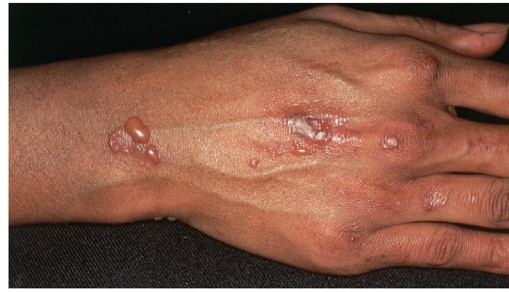

Fig. 3. Bullous lupus. (*From* Lee, Lela A.; Werth, Victoria P. Lupus Erythematosus. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. 4th ed. Elsevier; 2018: Fig 41.16 p 671. with permission.)

have difficulty walking or remaining upright. Loss of coordination of tongue or hand muscles may result in dysarthria and difficulties grasping objects or writing.[26] Movements are typically discrete but can sometimes seem to flow more consistently and resemble athetosis and often worsen with stress and excitement.[28,29] The exact pathogenesis in those with SLE remains unclear, but possible explanations include direct antineural antibody–mediated damage to phospholipid-containing structures in the basal ganglia and reversible ischemia.[26,28] MRI may demonstrate focal findings such as vasculopathy or demyelination, particularly hyperintensities in the basal ganglia on T1-weighted images.[26,28] PET may reveal hypermetabolism in the contralateral striatum.[29] However, in most of the cases neuroimaging studies are typically normal or nonspecific.[28] Cerebrospinal fluid (CSF) analysis is nonspecific, typically disclosing findings characteristic of inflammation within the CNS, including pleocytosis, elevated protein, elevated IgG and IgG index, and oligoclonal bands.[26,29] SLE-associated chorea usually responds very well to treatment with glucocorticoids and hydroxychloroquine, and when refractory, immunomodulators such as azathioprine, cyclophosphamide, and intravenous immunoglobulin have been effective.[29–31] Prognosis is favorable with rapid resolution of symptoms often within days of starting therapy.[30]

Acute Transverse Myelitis

Acute transverse myelitis (ATM) occurs in approximately 1% to 2% of those with SLE and can be an initial manifestation (39% of all SLE-associated ATM).[32–34] The peak incidence among pediatric patients occurs in adolescence, and the severity of symptoms varies depending on the number of spinal cord segments involved.[35] Weakness, sensory changes, and bowel and bladder dysfunction are common.[32,35] Symptoms may progress within a few hours or may gradually develop over a few weeks. The specific pathologic mechanism of transverse myelitis in SLE remains unknown. An increased incidence of antiphospholipid antibodies (APLAs) has been reported, suggesting thrombosis as a possible explanation.[36] The small longitudinal arterial blood vessels in the thoracic spine may be more vulnerable to thrombosis and ischemia, a possible explanation for the predominance of involvement of this area in patients with SLE.[32] Demyelinating lesions visualized on MRI and high IgG levels in the CSF may be present.[35] Treatment is predominantly anticoagulation if APLAs are present in addition to immunomodulators such as cyclophosphamide and glucocorticoids.[33] Recurrences within the first several months are common, with 21% to 55% of patients reporting at least one recurrence.[35]

Systemic Lupus Erythematosus–Associated Psychosis

Acute psychosis is present in 2% to 24% of patients with SLE with neuropsychiatric disease and typically occurs within a year after the onset of SLE.[37,38] The pathogenesis is unclear and postulated to be secondary to autoantibody-mediated cerebral vasculopathy and/or direct neuronal damage.[37–39] Symptoms of SLE-associated psychosis are not unique to SLE and include auditory and visual hallucinations, delusions, and acute confusional states.[38,40] The presence of visual distortions, such as objects moving or changing shape and color, and retained insight earlier on in disease course have been reported to be more suggestive of SLE-associated psychosis than other causes.[40] Psychosis is also more likely to occur in the setting of other systemic manifestations of SLE. CSF analysis may reveal pleocytosis, elevated protein, and oligoclonal bands.[39,41] MRI may demonstrate hyperintensities in the white matter, particularly the frontal cortex, and/or diffuse cortical atrophy.[39,41] The diagnosis may be challenging because these findings are nonspecific, and patients with SLE may have coincidental psychiatric illnesses that are not directly secondary to SLE. The exclusion of infectious, metabolic,

and thrombotic causes and the presence of additional clinical and laboratory features of active SLE will be most suggestive of SLE-associated psychosis. Treatment includes antipsychotics, glucocorticoids, and cyclophosphamide acutely followed by maintenance treatment, most often with mycophenolate mofetil or azathioprine.[37] Intravenous Ig, plasmapheresis, and rituximab have been reported to be effective in refractory cases.[37,38] Prognosis is typically good with recurrences uncommon.[39]

GASTROINTESTINAL MANIFESTATIONS

Lupus Enteritis

Although relatively unusual, acute abdominal pain in children and adolescents as a manifestation of SLE is most commonly caused by lupus enteritis.[42–45] It is thought to occur secondary to immune complex deposition and inflammation and/or thrombosis of intestinal blood vessels. The clinical manifestations vary widely from mild nonspecific abdominal pain, nausea, vomiting, and diarrhea to severe gastrointestinal (GI) bleeding, peritonitis, and ascites.[44] Laboratory test results and radiographs are often nonspecific. Computed tomography (CT) may be useful diagnostically with the identification of (1) engorgement of mesenteric vessels (comb sign), (2) diffuse thickened bowel wall with peripheral rim enhancement (target sign), and/or (3) increased attenuation of mesenteric fat[44](**Fig. 4**). The jejunum is most frequently involved followed by the ileum.[45] Glucocorticoids, bowel rest, and hydration are often effective with immunomodulators used for refractory disease.[44,45] Surgical interventions are necessary for those with the rare complications of intestinal necrosis or perforation. Overall prognosis is good; however, mortality rates increase when recognition is delayed.[44,45]

Pancreatitis

Pancreatitis occurs in approximately 5% to 6% of children and adolescents with SLE, often early in the course of disease.[46–48] Possible pathologic mechanisms of

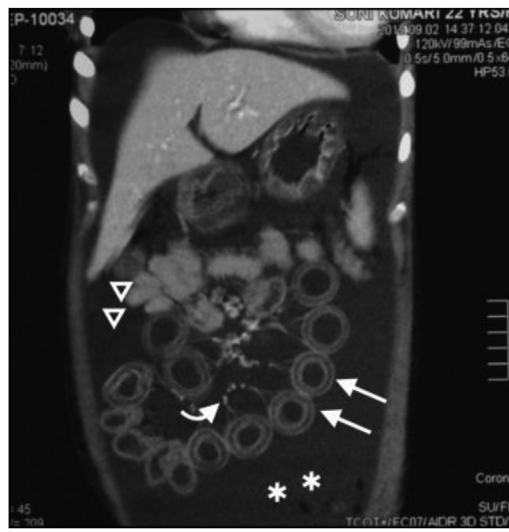

Fig. 4. Computed tomography abdomen of a patient with lupus enteritis showing "target sign" of small intestinal loops with circumferential wall thickening (*straight arrows*) compared with normal bowel loops (*open arrowheads*). Also noted are mesenteric vasculature leading to loops (*curved arrows*) and massive ascites (*asterisks*). (*From* Patro PS et al. "Presumptive Lupus Enteritis." The American Journal of Medicine 2016; 129(11):278; with permission.)

SLE-related pancreatitis include vascular ischemia and damage secondary to vasculitis, immune complex deposition, and microthrombi secondary to APLAs and antipancreas autoantibodies.[49–51] Children with pancreatitis present with generalized abdominal pain, fevers, and nausea or vomiting. CT or MRI may reveal pancreatic edema, necrosis, or peripancreatic fluid collections.[48] Acute pancreatitis typically occurs in patients with increased overall lupus activity; therefore, additional clinical findings and abnormal laboratory test results such as low complements and cytopenias are often present.[48] The mortality rate of pancreatitis in children has been reported to be 2% to 21%,[46,50] and early treatment with glucocorticoids, immunomodulators for severe or refractory disease, nutritional support, and pain management are essential.[48]

Systemic Lupus Erythematosus–Related Protein-Losing Enteropathy

Protein-losing enteropathy (PLE) presents with peripheral edema, ascites, diarrhea, and hypoalbuminemia.[52] Differentiation from other more common causes of protein loss in SLE such as nephrotic syndrome may be challenging. Laboratory test results such as hypocomplementemia, elevated stool alpha-1-antitrypsin, and the absence of proteinuria may be most helpful in confirming the presence of PLE associated with SLE.[43,53] CT of the abdomen often reveals prominent mucosal patterns due to edema, spiculation, or thickened folds/nodules indicative of lymphangiectasia.[53] Technetium-labeled serum albumin scintigraphy may also reveal leakage of albumin into the intestine.[53] Small bowel biopsies are typically normal. The pathogenesis is unclear and possibly due to increased vascular permeability due to complement-/cytokine-mediated damage and intestinal vessel vasculitis or intestinal lymphangiectasia.[53] Relapse is common when treated with glucocorticoids alone; therefore, additional immunomodulators are often necessary.[43,53]

OPHTHALMOLOGIC MANIFESTATIONS

Systemic Lupus Erythematosus Retinopathy

Nearly one-third of the patients with SLE develop ophthalmic symptoms, and retinal involvement is the second most common ophthalmologic manifestation (incidence 3%–29% of adult lupus patients).[54,55] Retinopathy may present with acute painless vision loss or visual field defects as an initial manifestation of SLE; however, it may also occur silently; therefore, routine funduscopic examination is prudent for all patients with SLE.[54,56] Pathogenesis is theorized to be the result of immune complex deposition, leading to occlusion of the retinal vessels and localized inflammatory vasculitis.[56] Cotton wool spots, macular edema, perivascular exudates, retinal hemorrhages, or microaneurysms may be seen on funduscopic examination (**Fig. 5**).[55] As with other SLE manifestations, management of retinopathy includes glucocorticoids and immunosuppression.[54] Rituximab has resulted in rapid improvement in several patients.[54,57,58] Adjunctive periocular and intraocular glucocorticoids, panretinal photocoagulation, intravitreal antivascular endothelial growth factor injections, and vitrectomy have also been used to halt neovascularization.[54,57,58] Although retinal involvement is uncommon in children and adolescents with lupus, it poses a severe threat to vision and thus prompt recognition and treatment is critical.

PULMONARY MANIFESTATIONS

Shrinking Lung Syndrome

Shrinking lung syndrome (SLS) has a prevalence in SLE of 0.5% to 1.1%.[59–61] Despite typically occurring as a later complication, it has been documented at initial diagnosis in 9% of children and adolescents with SLE.[61] The pathogenesis remains unknown,

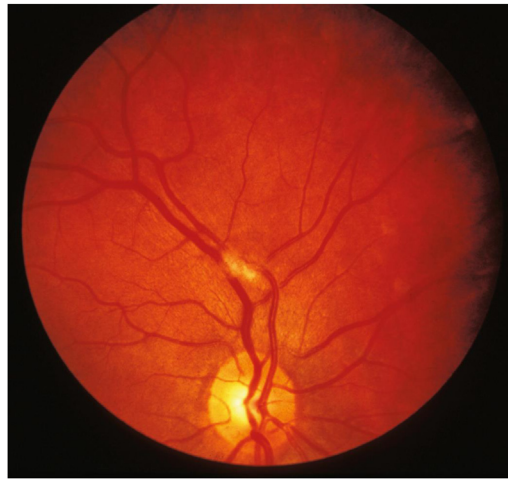

Fig. 5. Lupus retinitis cotton wool spot in the posterior retinal pole. (*Adapted from* Petty RE et al, editors: *Textbook of Pediatric Rheumatology,* ed 8, Philadelphia, 2021, Elsevier (Fig 23.20, p 320), with permission.)

and it is hypothesized that chronic pleural inflammation results in pain, with deep breathing leading to inhibition of diaphragmatic activation and ultimately chronic lung hypoinflation and decreased lung compliance.[61] Patients will develop progressive exertional dyspnea of variable severity and/or pleuritic chest pain. Because of the nonspecific nature of these symptoms, diagnosis of SLS is often delayed.[59,61,62] Hypoinflation may be evident on chest radiograph, and high-resolution CT may reveal elevated hemidiaphragms and reduced lung volumes in the absence of parenchymal lung disease or vascular pathology.[59,61] Pulmonary function tests (PFTs) reveal a restrictive ventilatory defect with reduced total lung capacity and diffusion capacity of the lungs for carbon monoxide.[60] Glucocorticoids and immunomodulators such as cyclophosphamide, rituximab, or belimumab have been effective.[61,63] Prognosis is favorable, with patients showing significant clinical improvement and stabilization or improvement in PFTs, although a persistent chronic restrictive defect is common.[62] Progression to respiratory failure or death is very uncommon.[59]

SUMMARY

SLE commonly presents during adolescence and may present with unusual clinical features in potentially any organ system. SLE should therefore be considered as part of the differential diagnosis for a wide variety of signs and symptoms. Early recognition allows appropriate treatment and ultimately decreased morbidity and mortality.

CLINICS CARE POINTS

- Children and adolescents with SLE may not present with characteristic signs and symptoms.
- Unusual SLE manifestations may mimic many other diseases, leading to delays in diagnosis and treatment.
- Specific laboratory, histologic, and imaging findings can help to diagnose SLE.

- Recognition of unusual SLE presentations allows for prompt diagnosis and better long-term outcomes.
- SLE should be considered in the differential diagnosis of a wide variety of signs and symptoms.

DISCLOSURE

The authors have nothing to disclose.

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