Dermatologic Manifestations of Systemic Diseases in Childhood

Fatima I. Quddusi, MD,* Molly J. Youssef, MD,*† Dawn Marie R. Davis, MD*†

*Department of Pediatric and Adolescent Medicine and
†Department of Dermatology, Mayo Clinic, Rochester, MN

PRACTICE GAP

It is crucial for pediatricians to maintain awareness of cutaneous signs and symptoms of systemic diseases to allow for prompt recognition and adequate management of such disorders in children.

OBJECTIVES *After completing this article, readers should be able to:*

1. Identify the classic dermatologic manifestations of common systemic diseases in children.
2. Understand the epidemiology, etiology, and likely mechanisms of these dermatologic findings.
3. Enlist the best diagnostic tests for quick and definitive diagnosis while minimizing risk to the patient.
4. Outline the standard management approach for acute and long-term follow-up of these diseases.
5. Coordinate an impactful multidisciplinary care approach and deliver appropriate education to the patient and family.

INTRODUCTION

The integument can serve as a diagnostic window to pathophysiologic changes of internal organ systems, offering timely and valuable clues to a systemic disease process. It is the largest organ of the human body, continuously regenerates, and is readily accessible for comprehensive examination. Systemic diseases influence multiple organs and often pose a diagnostic challenge due to their occult and/or diverse clinical presentations. Cutaneous features frequently serve as the initial or most prominent indicator of systemic disease, often allowing earlier diagnosis and intervention, eluding potentially debilitating complications of such illnesses. Furthermore, they might be the only markers of clinical disease in otherwise asymptomatic patients. (1)(2)(3)

Several studies have estimated the prevalence of skin disease to be 15% to 20% in the general population; 12% of pediatric dermatology consultations are

AUTHOR DISCLOSURE Drs Quddusi, Youssef, and Davis have no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ACLE	acute cutaneous lupus erythematosus
AE	acrodermatitis enteropathica
ANA	antinuclear antibody
CBC	complete blood cell
CCLE	chronic cutaneous lupus erythematosus
CDC	Centers for Disease Control and Prevention
CLE	chilblain lupus erythematosus
COVID-19	coronavirus disease 2019
DH	dermatitis herpetiformis
DLE	discoid lupus erythematosus
EN	erythema nodosum
HLA	human leucocyte antigen
HSP	Henoch-Schönlein purpura
IBD	inflammatory bowel disease
IgA	immunoglobulin A
IVIg	intravenous immunoglobulin
JDM	juvenile dermatomyositis
KD	Kawasaki disease
LCH	Langerhans cell histiocytosis
LE	lupus erythematosus
MIS-C	multisystem inflammatory syndrome in children
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCLE	subacute cutaneous lupus erythematosusSLE systemic lupus erythematosus
PG	pyoderma gangrenosum
TNF	tumor necrosis factor
TTG	tissue transglutaminase

for diagnosis or management of systemic diseases. (4) Studies also note a considerable lack of confidence regarding recognition of dermatologic manifestations of systemic diseases among pediatricians and other primary care providers. Approximately 50% of patients referred to dermatologists by other medical providers receive a different diagnosis on evaluation. Access to dermatologic care can be challenging due to a maldistribution and undersupply of dermatologists in the United States. (5)(6) Thus, it is imperative for pediatric providers to maintain awareness of the cutaneous signs of particular systemic diseases to optimize patient care quality and effectively use available health-care resources. (4)(7)(8)(9)(10)

The purpose of this review is to encapsulate the dermatologic manifestations of systemic diseases in childhood. Because this is a vast topic with a multitude of diseases to review, we include common, confusing, and timely (ie, multisystem inflammatory syndrome in children [MIS-C]) disorders only. Additional review articles focusing on specific subsets of cutaneous manifestations (eg, infection induced, connective tissue, nutritional, gastrointestinal, genetic) would be of value.

The epidemiology, pathogenesis, diagnostic evaluation, and preferred management of each disease are reviewed based on the best medical literature to date. The diseases are arranged in alphabetical order, and a systematic approach to their dermatologic findings is summarized in Table 1.

ACRODERMATITIS ENTEROPATHICA

Acrodermatitis enteropathica (AE) is a rare disorder associated with zinc deficiency with an incidence of 1 in 500,000 children. (11) Most cases are caused by an autosomal recessive mutation in the gene encoding for zinc-ligand binding protein ZIP4 (zinc or iron regulator transporter-like protein), resulting in altered keratinocyte metabolism. The gene mutation is broadly distributed in the population such that inherited AE has no predilection for sex or race. Cases with a genetic etiology manifest early in infancy, characteristically days to weeks after weaning in breastfed infants. (12) A positive family history might be noted. (13) Patients can also develop AE from inadequate zinc intake (anorexia nervosa, bulimia nervosa, fad diet) or malabsorption (cystic fibrosis, inflammatory bowel disease, and excessive alcohol intake). (14)(15)(16)(17) Thus, it is imperative to consider this disorder in all pediatric patients based on history and demographics. The cutaneous manifestations are identical regardless of etiology. AE is characterized by periorificial dermatitis, alopecia, and diarrhea; however, this triad is present in only 20% of patients. (18)

Patients initially present with symmetrical, erythematous to orange, scaly, crusted patches or plaques. Occasionally, vesicles or bullae can form. At first, perioral, anogenital, and acral areas are affected, but in the absence of adequate treatment, plaques erupt on the periorificial areas of the face (eyes, nostrils), abdomen, inguinal area, and thighs (Fig 1). Alopecia (typically diffuse), glossitis, gingivitis, stomatitis, onychodystrophy, and paronychia constitute additional mucocutaneous findings and usually indicate advanced disease. Superficial bacterial (commonly *Staphylococcus aureus*) and fungal (*Candida albicans*) infections are common and can mask the traditional signs of AE. Refractory diarrhea, failure to thrive, and neuropsychiatric features (irritability, anorexia, and depression) are common extracutaneous manifestations of AE and indicate prolonged deficiency. (14)(15)(16)(19)

Diagnosis is based on physical examination findings and is confirmed with a serum zinc level of 50 μg/dL or less (≤7.65 μmol/L). Proper technique and equipment can reduce the potential risk of sample contamination in plasma zinc testing. (18) Low levels of serum alkaline phosphatase, a zinc-dependent enzyme, can also indicate the diagnosis. Some patients might have low serum albumin levels depending on etiology. (14)(15) Rapid clinical improvement after adequate zinc supplementation confirms the diagnosis of AE, especially in resource-limited areas. (20)

Skin biopsy can be performed when the diagnosis is uncertain or an alternative diagnosis is suspected (which is typically diagnosed by pathologic confirmation). Histopathological analysis reveals necrosis of keratinocytes, cytoplasmic pallor, vacuolization, and confluent parakeratosis in the superficial layers of the epidermis. Psoriasiform hyperplasia occurs in resolving or chronic cases. (15)(21)

Optimal management requires early diagnosis, zinc supplementation, and appropriate medical management and counseling based on patient needs (gastroenterology evaluation, dietary counseling, etc). Replacement therapy with 3 mg/kg per day of elemental zinc is recommended. Genetic deficiency will require lifelong supplementation, along with periodic monitoring of plasma zinc levels every 3 to 6 months. (15)(22) Nausea, vomiting, and gastric hemorrhage are well-known adverse effects of zinc therapy. Accidental overdose of zinc can prove fatal due to multiorgan failure. (23) A subset of patients with AE might benefit from genetic counseling.

Table 1. Snapshot of Classic Dermatologic Findings with Respect to Age at Presentation, Location, and Histologic Features Associated with Common Systemic Diseases of Childhood

SYSTEMIC DISEASE	MOST COMMON AGE	HISTOLOGIC FEATURES OF PRESENTATION	DERMATOLOGIC LOCATION	FINDINGS
Acrodermatitis enteropathica	Infancy	Red to orange scaly plaques; alopecia (diffuse)	Perioral, acral, anogenital (symmetrical)	Keratinocyte necrosis, confluent parakeratosis, psoriasiform hyperplasia in resolving cases
Dermatitis herpetiformis	Adolescence, but can affect infants/children	Pruritic, clustered red papules and vesicles ± mucosal erosions	Extensor surfaces (elbows, forearms, back, buttocks, knees)	Neutrophilic infiltrate and fibrin deposits at tips of dermal papillae, followed by subepidermal blisters in later cases; IgA deposition in dermal papillae (on direct immunofluorescence)
Erythema nodosum	Adolescence, but can occur in childhood	Symmetrical, tender, red to violaceous subcutaneous nodules	Anterior shins; less commonly other extensor surfaces	Neutrophilic inflammatory infiltrate, septal edema, Miescher granulomas, no true vasculitis in adipose tissue
Henoch-Schönlein purpura	Early childhood (4–6 y)	Red, edematous papules evolving into palpable purpura; nonpitting edema of hands and feet	Lower limbs, buttocks, belt line (pressure-dependent areas common)	Leukocytoclastic vasculitis, IgA-dominant immune complex deposition in postcapillary venules, capillaries, and arterioles
Inflammatory bowel disease	Childhood or adolescence	Symmetrical, tender, red to violaceous subcutaneous nodules (EN); violaceous, deep ulcer with rolled border (PG); genital edema; oral ulcers, edema and/or pustules; lip edema; violaceous plaques, ulcerating nodules, and knifelike fissures (metastatic Crohn's disease)	Anterior shins (EN); legs, peristomal (PG); genitalia; oral mucosa; intertriginous and lower extremities (metastatic Crohn's disease)	Neutrophilic infiltration of dermis and hypodermis, noncaseating granulomas in metastatic Crohn's disease
Juvenile dermatomyositis	School age (5–10 y)	Red to violaceous papules/patches; heliotrope rash (eyelids); Gottron papules (extensor surfaces and dorsal hands); shawl sign (chest, shoulders, back); holster sign (lateral thighs); ragged cuticles	Face, trunk, extremities	Perivascular inflammatory infiltrate, fibrin deposits in vessel lumen
Langerhans cell histiocytosis	Age 1–3 y	Red to brown crusted papules; intractable diaper dermatitis ± petechiae	Trunk, groin, face, and scalp	Langerhans cells (round to oval mononuclear cells with a "coffee-bean" nuclear groove and no dendritic processes

Continued

Table 1. Snapshot of Classic Dermatologic Findings with Respect to Age at Presentation, Location, and Histologic Features Associated with Common Systemic Diseases of Childhood (Continued)

SYSTEMIC DISEASE	MOST COMMON AGE	HISTOLOGIC FEATURES OF PRESENTATION	DERMATOLOGIC LOCATION	FINDINGS
LE (ACLE, CCLE, SCLE)	Late childhood to adolescence	ACLE: Red scaly facial rash, nose and cheeks ("butterfly rash"), papular or vesicular eruption, oral/nasal plaques or erosions; CCLE: coin-shaped patches with keratotic spikes with eventual pigmentary changes, scarring, scarring alopecia (discoid LE); indurated nodules (LE profundus); purple papules over the digits (chilblain LE); SCLE: scaly annular plaques	ACLE: Face, sun-exposed areas (can also be generalized), oral CCLE: scalp, face, ears (discoid LE); scalp, proximal extremities, breasts, trunk, buttocks (LE profundus); digits (chilblain LE); SCLE: sun-exposed areas	Epidermal hyperkeratosis, vacuolar interface changes, dermal mucin and mononuclear cell–predominant inflammatory infiltrate in perivascular spaces, perifollicular spaces, and along the dermal-epidermal junction
Neonatal LE	Neonatal	Periorbital erythema ("raccoon eyes"); Annular scaly plaques, discoid lesions, scarlike lesions, telangiectasias, mucosal ulcerations	Periorbital, often sun-exposed areas	Similar to LE as listed above
Multisystem inflammatory syndrome in children	Late childhood to adolescence	Diffuse, erythematous rash and mucositis	Face, trunk, abdomen, extremities	Nonspecific inflammatory infiltration

ACLE=acute cutaneous lupus erythematosus, CCLE=chronic cutaneous lupus erythematosus, EN=erythema nodosum, IgA=immunoglobulin A, LE=lupus erythematosus, PG=pyoderma gangrenosum, SCLE=subacute cutaneous lupus erythematosus.

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis (DH) is a noninfectious autoimmune skin eruption due to gluten sensitivity. The misnomer alludes to the tendency of small blisters to appear in clusters, similar to a herpes simplex virus rash. (24)(25) Although gluten sensitivity is fairly common, DH is not consistently present such that the annual incidence rate is 0.4 to 3.5 per 100,000 people; only 4% of patients with DH are children and adolescents, with a slight male predominance. (26)(27)(28) Several studies demonstrate that carriers of human leukocyte antigens (HLAs) DQ2 and DQ8 exhibit a strong predisposition to DH. (29) The association of DH with gluten-sensitive enteropathy was first outlined in 1966, when it was described in relation to celiac disease. (30) Both of these entities share a unique tissue transglutaminase (TTG)–dependent immune response to gliadin peptides found in wheat, rye, and barley, with anti-TTG antibody–mediated immune complexes depositing in the dermis, subsequently allowing formation of blisters. (31) Several environmental factors also contribute to development or exacerbation of DH (amount of gluten ingested, intake of iodine-containing substances such as shellfish, and exposure to triiodomethane used in dental procedures). (32)(33)(34)(35)

Patients typically present with clusters of erythematous papules and vesicles on the extensor surfaces of the elbows, forearms, back, buttocks, and knees (Fig 2). The rash is strikingly symmetrical in most patients. Less commonly, the scalp, face, and groin can also be involved. DH lesions are intensely pruritic; thus, the primary morphology is often replaced by excoriations and erosions. Oral manifestations are uncommon and include erythematous macules and erosions on the mucosa accompanied by a burning or sore sensation. Enamel defects along with delayed eruption of teeth can be present. (33)(36) Rarely, pediatric patients demonstrate palmoplantar purpura and petechiae. (37) Subclinical or mild gastrointestinal symptoms characteristic of celiac disease, such as abdominal bloating, cramps, diarrhea, or constipation, are evident in approximately 90% of patients with DH but frequently attributed to other factors. (38) DH can also manifest before onset of typical gastrointestinal manifestations of celiac disease. (39)(40) Patients with gluten-sensitive enteropathy have an increased risk of hypothyroidism, type I diabetes mellitus, and non-Hodgkin lymphoma. (38)

After initial clinical suspicion, skin biopsy of an intact vesicle is conducted to confirm the diagnosis. Histopathologic analysis reveals neutrophilic infiltrate and fibrin deposition

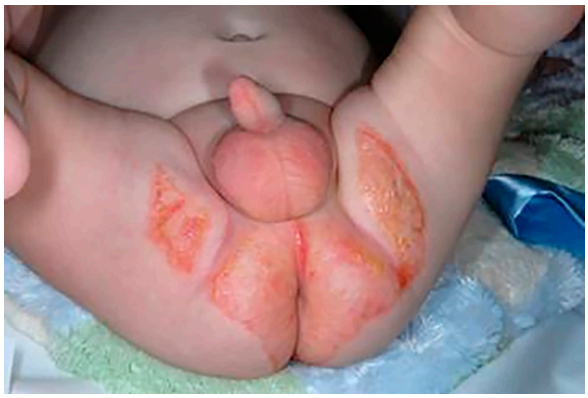

Figure 1. Symmetrical, erythematous plaques and patches of acrodermatitis enteropathica in the anogenital area, inguinal area, and thighs.

of the dermal papillae, with subepidermal blisters in mature lesions. These findings closely resemble other cutaneous blistering disorders, especially bullous pemphigoid and linear immunoglobulin A (IgA) bullous dermatosis, and should be differentiated accordingly. Clinical signs and symptoms can mimic urticaria, atopic dermatitis, and scabies. (36) The gold standard for diagnosis of DH is direct immunofluorescence of biopsy tissue, depicting IgA antibodies in the tips of dermal papillae and along the basement membrane of the perilesional skin. (38) Serologic testing provides further confirmation of DH and gluten-sensitive enteropathy, with IgA TTG antibodies and IgA endomysial antibodies being highly specific.

Treatment of DH consists primarily of gluten avoidance and appropriate gastrointestinal evaluation. (41) A gluten-free diet often resolves the skin eruption. When additional treatment is required to achieve skin clearance, 0.5 to 2 mg/kg per day of dapsone given orally is suggested as the patient transitions to a gluten-free diet. Subsequently, it can be tapered off over 4 to 6 weeks and discontinued thereafter. If clinical improvement does not occur, dapsone can be given as an adjunct therapy. In addition, it can be reinstituted to manage severe recurrences of DH. Routine complete blood cell (CBC) counts, liver function tests, renal function tests, and screening for glucose-6-phosphate dehydrogenase deficiency is recommended before initiation of therapy. (42)

ERYTHEMA NODOSUM

Erythema nodosum (EN) is the most frequent form of panniculitis, a group of inflammatory disorders primarily involving subcutaneous fat. (43) It has a rare incidence before the second decade of life and is exceptional before 2 years of age. There is a familial predominance related to the presence of HLA haplotype (HLA-B8, HLA-A11, and HLA-B51) without any predilection for sex or race. (44)(45)(46)

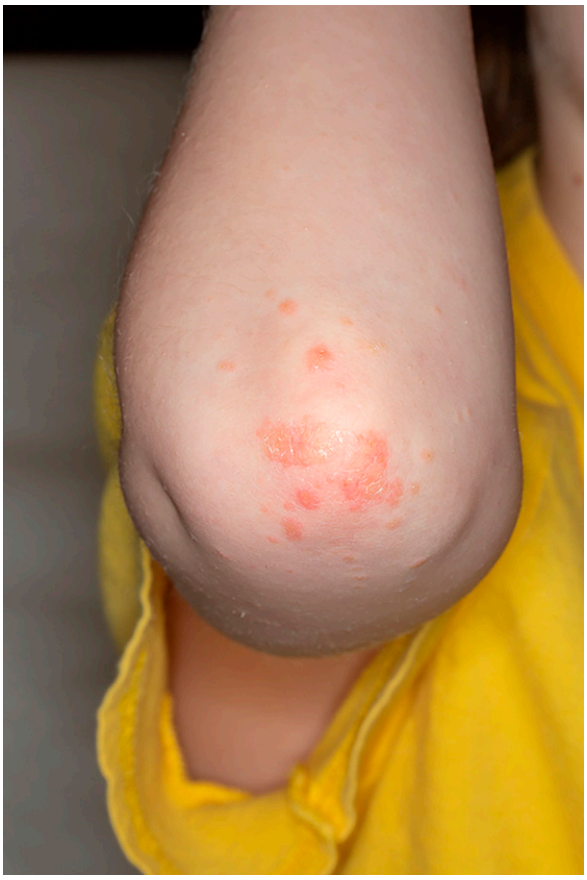

Figure 2. Erythematous papules and vesicles of dermatitis herpetiformis on the extensor surface of the forearm and elbow.

There is no identifiable underlying etiology in approximately 50% of patients. (47) The remainder seems to occur as a consequence of an infectious process, with β-hemolytic *Streptococcus* as the leading cause worldwide, followed by *Mycobacterium tuberculosis* in endemic areas. Rare cases due to other viral, bacterial, protozoal, and fungal infections have been reported. (44)(48) EN can also be a sign of inflammatory bowel disease, Behçet disease, and sarcoidosis, and it was recently reported in a 3-year-old girl with Kawasaki disease (KD). (45)(49) Other inciting factors, include pregnancy, underlying malignancy (consider the possibility if there is chronic recurrence or relapse despite an optimal treatment regimen), and medications (especially oral contraceptives and certain antibiotics). (50)(51)(52)(53)

EN is characterized by the acute onset of symmetrical, tender, erythematous to violaceous, subcutaneous nodules. The anterior shin is the most common location, with the extensor surface of the forearms, trunk, and thighs occasionally

involved (Figs 3 and 4). Rarely, unilateral disease has been documented. (54)(55) Nodules are characteristically round to oval, 1 to 5 cm in size, easily palpable, warm, and firm. Fluctuance and serous exudate can develop with time, along with coalescence to giant nodules. Nodules usually persist for 2 to 8 weeks and heal without scarring or ulceration. A bruise can remain, referred to as "erythema contusiformis," but is an inconsistent finding. New outcroppings are expected and frequent, with cycles lasting up to 6 weeks. (50)(56)(57) A prodrome of low-grade fever, malaise, weight loss, arthralgia and cough may occur 1 to 3 weeks before disease onset. (58)

Rare forms of EN include EN migrans and palmoplantar EN. The migrans variant is subacute, unilateral, and less painful, with a centrifugal distribution and central clearing. (59) Palmoplantar involvement is most common after exercise. All EN forms share similar histopathological features. (60)

Diagnosis is usually clinical, with biopsy confirmation as needed. Histopathological analysis shows neutrophilic and lymphohistiocytic infiltration of the dermal adipose tissue, along with septal edema, radial granulomas (Miescher granulomas),

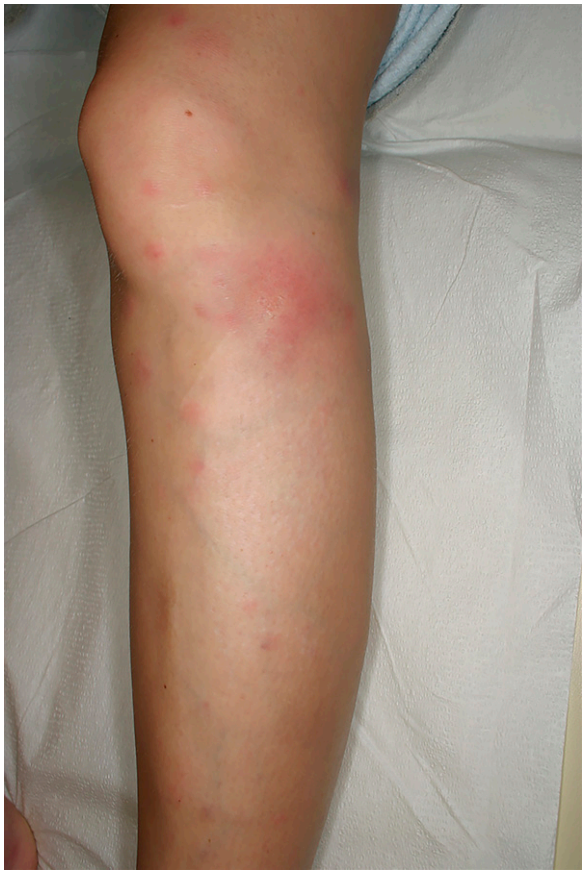

Figure 3. Symmetrical, tender, erythematous subcutaneous nodules of erythema nodosum on the anterior shin.

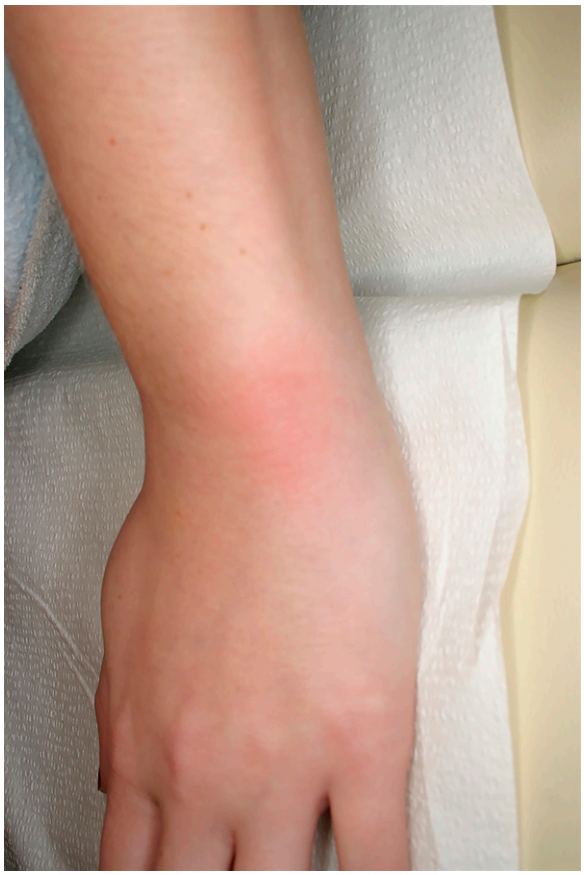

Figure 4. Cutaneous findings of erythema nodosum on the extensor surface of the forearm.

and absence of true vasculitis. (61)(62) Laboratory investigation for an infectious etiology can be performed as needed (CBC count, rapid streptococcal antigen test, throat swab culture, antistreptolysin O titer, anti-DNAase, antihyaluronidase, Mantoux skin test, stool culture, and/or polymerase chain reaction assay), and suspect medications should be discontinued. A pregnancy test is recommended in postpubertal females. (45)(50)(63)

The differential diagnosis of EN is broad and includes EN leprosum, child abuse, factitial disease, insect bites, Henoch-Schönlein purpura (HSP), urticaria, erythema induratum, fat necrosis, and cutaneous polyarteritis nodosa. (48)(64) Recurrences seldom occur but can be found in drug-induced cases of EN. (45)(59)

Treatment is supportive with bed rest, leg elevation, and nonsteroidal anti-inflammatory drugs (except aspirin). In severe cases, systemic corticosteroids can be used. In addition, the underlying cause must be sought and if one is identified, must be managed accordingly. (44)(50) Oral dapsone, hydroxychloroquine, colchicine, potassium iodide, and topical heparin have been used as well. (65) Use of oral tetracycline has been suggested in refractory cases. (66)

HENOCH-SCHÖNLEIN PURPURA

HSP, recently referred to as IgA vasculitis, is the most common systemic vasculitis in childhood. It has an incidence of 20 per 100,000 children, with most cases occurring between 4 and 6 years of age. (67)(68)(69) There is a slight male predominance; the disease is more prevalent in the Asian and white populations, especially in individuals of European descent. (70) The disease typically manifests in fall and winter, often preceded by an upper respiratory tract infection, commonly group A streptococcus. (71) Certain medications and insect bites are other possible inciting factors. Of note, no causal relationship has been established between vaccinations (eg, meningococcal vaccine and human papillomavirus vaccine) and vasculitides, including HSP. (72)(73) Clinical findings similar to HSP have been found in conjunction with familial Mediterranean fever as well. (74)

HSP is an immune-mediated inflammatory disease characterized by IgA1-containing immune complexes inside the walls of small vessels of affected organs, including the kidneys, skin, joints, and small intestine. (75)

The hallmark clinical features are palpable purpura (in the absence of thrombocytopenia or coagulopathy), arthritis/arthralgias, and abdominal pain along with varying degrees of proteinuria, microscopic or macroscopic hematuria, and sometimes hypertension. Typically, skin and joint findings are the earliest signs. Cutaneous manifestations include erythematous, asymptomatic edematous papules and urticarial wheals distributed bilaterally over pressure-dependent areas, such as the lower limbs, buttocks, and belt line (Figs 5 and 6). The face, trunk, and forearms can be involved at any age but are more commonly seen in infants and nonambulatory children. The lesions are well-defined and tend to occur in "crops." Eventually they coalesce to form ecchymoses. Palpable purpura less than 10 mm in diameter is a pathognomic feature of HSP; however, the literature does report cases without palpable lesions. Eruptions last for up to 10 days and self-resolve without residual scars. A brown discoloration might be present on resolution, which can take days to weeks to fade. Localized, subcutaneous, nonpitting edema over the dorsal surfaces of the hands, ankles, and feet is present in 50% of patients. Pitting edema secondary to kidney disease or severe protein-losing enteropathy can accelerate these findings. Blistering eruptions, koebnerization, and capillary fragility can occur. (76)(77)(78)(79)(80) Skin biopsy shows leukocytoclastic vasculitis with IgA-predominant immune complex deposition in postcapillary venules, arterioles, and capillaries. (81)

Figure 5. Palpable purpura in the absence of thrombocytopenia on the anterior surfaces of the thighs and lower legs in Henoch-Schönlein purpura.

Diagnosis is typically clinical, with renal and/or skin biopsy conducted in unusual cases. Consensus criteria developed in 2005 identify cutaneous findings without thrombocytopenia or coagulopathy as a mandatory criterion for HSP in pediatric patients, along with 1 or more of the following: abdominal pain, joint findings, renal disease, leukocytoclastic vasculitis, or membranoproliferative glomerulonephritis with IgA deposition. (82)

Differential diagnosis includes cutaneous small vessel vasculitis, acute hemorrhagic edema of infancy, microscopic polyangiitis, KD, Rocky Mountain spotted fever, and bacterial endocarditis. (69)(77)

Treatment is supportive with optimal hydration, pain control, bed rest, elevation of extremities, and periodic surveillance for development of any complications. Corticosteroids are used in severe cases. Most children undergo complete resolution within 4 weeks without long-term sequelae. Recurrence is commonly associated with HSP nephritis. Follow-up visits with urinalysis and blood pressure measurements are generally recommended weekly or biweekly for the first 2

Figure 6. Henoch-Schönlein purpura–specific cutaneous findings extending over the posterior surface of the bilateral legs.

months, followed by every other month for the first year after initial presentation once the disease seems to be subsiding. Any concerning test results should be evaluated with a serum creatinine level. For persistent hypertension, proteinuria, or renal insufficiency, referral to a pediatric nephrologist is reasonable. (78)(79)(83)(84)

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD), a unique combination of Crohn's disease and ulcerative colitis, is an immune-mediated systemic inflammatory disorder triggered by changes in the gut microbiota and certain environmental factors in genetically predisposed individuals. Approximately 5% to 25% of cases occur in the pediatric population, with a slight male predominance and often a strong family history. (85)(86)(87)(88)(89)(90)

Typically, diarrhea (bloody or nonbloody), abdominal pain, growth failure, delayed puberty, and systemic symptoms (fever, fatigue) raise concern for IBD. However, extraintestinal manifestations can develop before IBD diagnosis or during management of known disease. (91)(92)(93) Approximately 15% of extraintestinal manifestations are cutaneous. (94)

EN is the most common dermatologic finding, with a prevalence of 8% in Crohn's disease and 3% in ulcerative colitis. EN induced by IBD rarely occurs before gastrointestinal symptom onset, parallels underlying intestinal activity, and lasts for 3 to 6 weeks. Such cases are usually a single episodic cycle when the underlying intestinal disease is treated and monitored adequately. (91)(95)(96)(97)

The second most common cutaneous finding in IBD is pyoderma gangrenosum (PG). Approximately 4% of cases occur in children, with a mean age at onset of 14 years. Cases in infancy have been reported. (98)(99) PG exhibits a female predominance and is more commonly associated with ulcerative colitis. Initially, an erythematous, painful papule or pustule forms, rapidly evolving into a violaceous, deep ulcer with a rolled border. The leg is a common site, in addition to a stoma site, if present. Progression leads to an atrophic, cribriform scar. PG lesions show varying morphology over time, denoted as pustular, ulcerative, bullous, and vegetative subtypes. PG can erupt due to pathergy, such that the head and perineal area are affected, particularly in young children. Pathergy refers to altered tissue reactivity that occurs in response to minimal trauma. (100) Histopathology exhibits sterile neutrophilic inflammatory dermatoses in the dermis and subcutaneous tissue. Treatment regimens are many, including corticosteroids, tacrolimus, and tumor necrosis factor (TNF) antagonists. Mechanical trauma must be avoided along with appropriate wound care. In case of peristomal PG, dermatologists and skilled ostomy nurses should be consulted. The disease course lasts several months, with recurrence in 25% of patients. As with EN, underlying gastrointestinal disease control is imperative. Immunologic disorders such as IgA gammopathy, human immunodeficiency virus, and leukemia can also manifest PG and must be excluded. (91)(95)(96)(101)(102)

Genital edema might be the only presenting sign of IBD and usually involves prominent genital swelling (Fig 7). Erythema and erosions can be present. Genital signs are typically bilateral, although unilateral disease can occur and includes erythema, swelling, and erosions of the perianal area (Fig 8), perineum, penis, scrotum, clitoris, labia, and vulva. Warty plaques or a pedunculated mass can form with disease progression. (103)

Oral lesions are common in IBD and can manifest before gastrointestinal symptoms in approximately 50% of patients, including the pediatric population (Fig 9). (104)(105) Aphthous stomatitis, especially if recurrent and extensive, tends

Figure 7. Genital edema in inflammatory bowel disease.

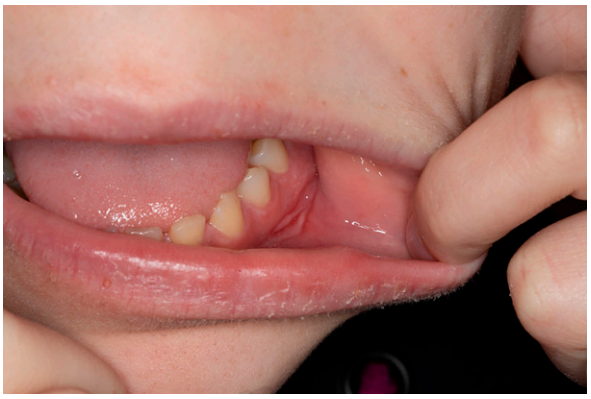

Figure 9. Oral lesions in a child diagnosed as having inflammatory bowel disease.

to manifest frequently with Crohn's disease. (106) Affected oral mucosa exhibits nodular granulomatous swelling with a characteristic cobblestone appearance and mucosal tags. In addition, orofacial granulomatosis, a chronic or refractory swelling of oral mucosa with characteristic histologic features of noncaseating granulomas, can be found in conjunction with Crohn's disease. (107) Pyodermatitis-pyostomatitis vegetans describes a combination of pustular and vegetating plaques affecting the skin and oral mucosa simultaneously or consecutively. Sometimes genital areas become affected as well. Pyodermatitis-pyostomatitis vegetans occurs frequently with ulcerative colitis and usually responds well to corticosteroids and azathioprine. (108)(109) Therefore, children with unexplained or persistent oral mucosal lesions should undergo a detailed oral as well as genital and rectal examination, along with appropriate blood tests (CBC count, iron levels, erythrocyte sedimentation rate) and biopsy procedures (if needed), to rule out the possibility of underlying IBD. (107)

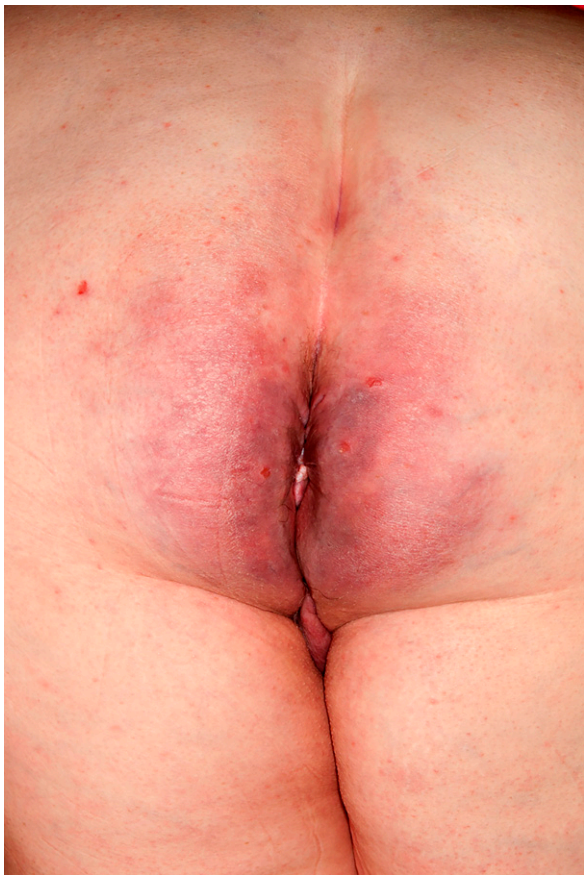

Figure 8. Cutaneous findings in the perianal area of a patient with inflammatory bowel disease.

Metastatic Crohn disease, a form of granulomatous dermatitis, is a rare finding in pediatric patients with Crohn disease. It comprises erythematous, violaceous plaques, abscess, swelling, and ulcerating nodules and fissures, often in a knifelike pattern on the lower extremities and intertriginous areas. Bowel management with corticosteroids, immunosuppressive agents (eg, azathioprine, cyclosporine), and TNF antagonists is the mainstay of treatment. (110)(111)

On rare instances, pediatric patients with IBD can develop hidradenitis suppurativa, a chronic, recurrent inflammatory disorder of hair follicles mainly involving sites with apocrine glands, including the axillae and the inguinal and perianal areas. (112)

Psoriasis is more common in patients with IBD than in the general population. In addition, psoriasiform dermatitis is common in IBD as an adverse effect of anti-TNF treatment (known as "paradoxical reaction"). This is particularly curious because anti-TNF treatment is also used to successfully manage refractory generalized psoriasis. As such, psoriasiform skin eruptions along the extensor surfaces of the forearms, scalp, face, trunk, knees, and joint flexures in patients with IBD should be investigated by a dermatologist for etiologic clarification and treatment

suggestions, as anti-TNF medication-induced skin disease can necessitate changing systemic medications. Having to change medications can be disappointing if the bowel disease is under good control. (113)

Distinct nutritional dermatoses can occur in IBD secondary to deficiency of vitamins (A, C, E, K, and B_{12}) and essential trace elements (zinc). (96) Cutaneous small vessel vasculitis, polyarteritis nodosa, epidermolysis bullosa, and alopecia have also been observed. (111)

JUVENILE DERMATOMYOSITIS

Juvenile dermatomyositis (JDM) is the most frequent form of childhood idiopathic inflammatory myopathy, with an annual incidence of 2 to 4 cases per 1 million children. (67)(114) The mean age at onset is 5 to 10 years, with a female-to-male ratio of 2:1. (115) Certain alleles, including HLA 8.1 ancestral haplotype (AH8.1), HLA-DRB1*3:01, and TNF-α-308A, have been associated with an increased risk of JDM. (116)(117) It has also been observed in response to an underlying infectious process, mainly of respiratory or gastrointestinal origin. (118)

JDM is a systemic vasculopathy primarily involving both muscle and skin; however, skin-limited disease is also common (eg, dermatomyositis sine myositis). A heliotrope rash is a discrete, red-purple macular rash located over the upper eyelids; it can involve the nose, malar area, and upper lip as well. Another hallmark feature is Gottron papules (Fig 10), which are erythematous to violaceous papulosquamous lesions generally located over the dorsal surface of the metacarpophalangeal and interphalangeal joints; they can also involve the extensor surfaces of the elbows, knees, and medial malleoli. Secondary changes such as scale, crust, erosion, ulceration, telangiectasia, and hypopigmentation or hyperpigmentation can develop in later stages of the disease. In dark-skinned individuals, hyperpigmentation can mask underlying erythema such that the lesions must be palpated to confirm blanchable erythema. The Gottron sign is the presence of flat erythematous to violaceous lesions with a similar distribution and clinical course as Gottron papules. Macular erythema in discrete or confluent distribution can manifest over the upper anterior chest and anterior neck, called the "V-sign." The "Shawl sign," a less frequent cutaneous eruption, is a macular erythematous rash located over the posterior neck, upper arm, and lateral arms (similar to a shawl distribution). Cutaneous features of JDM often develop before muscle weakness but can manifest concurrently as well. Exposure to sunlight, especially to ultraviolet light radiation, exacerbates skin findings of JDM. (119)(120)(121) Patients can also develop focal patches of nonscarring alopecia, erythema, and inflammation on the scalp (Fig 11). (122) Subcutaneous calcification and ulceration of overlying skin can develop in chronic, often untreated, cases of JDM. (123) Nail fold capillary dilatation, loss of capillaries, and distinct branching capillary loops (bushy loops) can also be present, causing roughened cuticles. (124)(125)

Symmetrical proximal muscle weakness is an integral component of JDM. Functional limitations increase as the disease progresses. Children are often fatigued and experience an intermittent low-grade fever. Acanthosis nigricans along with insulin resistance and type 2 diabetes mellitus can develop as well. (126)

Histopathological analysis of muscle tissue reveals a perivascular inflammatory infiltrate, necrosis of fibers, endothelial thickening, reduced capillary density, and an exaggerated activity of major histocompatibility complex class I molecules. Skin biopsy can reveal similar vascular changes, perivascular inflammatory infiltrate, vacuolar interface changes of the basal keratinocytes, dermal mucin, and occasional vascular fibrin thrombi. (119)(120)

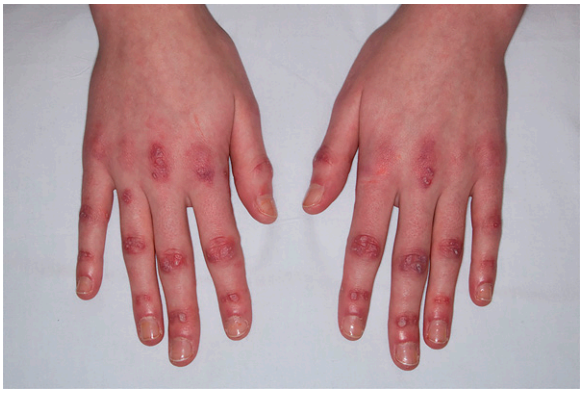

Figure 10. Gottron papules, as seen in juvenile dermatomyositis.

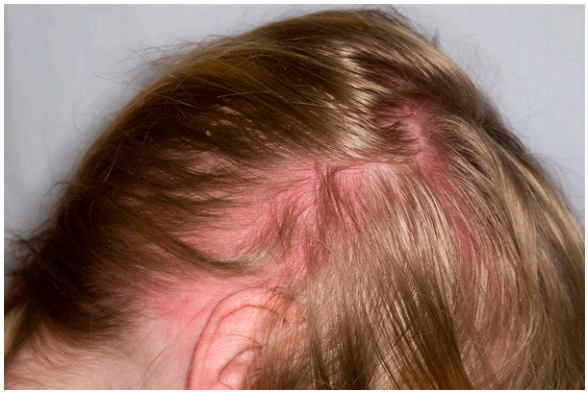

Figure 11. Scalp findings, including erythema and inflammation, in a child with juvenile dermatomyositis.

In 2017, the European League Against Rheumatism/American College of Rheumatology revised and formulated criteria for the diagnosis of adult and pediatric idiopathic inflammatory myopathies with and without invasive tests (eg, muscle biopsy). (114) After initial clinical suspicion, serum levels of muscle enzymes indicative of muscle damage and inflammation (creatine kinase, lactate dehydrogenase) and inflammation (C-reactive protein, erythrocyte sedimentation rate) are typically ascertained. (127)(128)(129) Measurement of myositis-specific autoantibodies, magnetic resonance imaging, electromyography, and muscle biopsy can be performed in atypical cases. (130)

Initial treatment involves high-dose oral prednisolone (2 mg/kg per day) with methotrexate (15 mg/m^2, subcutaneous injection) and folic acid. (131) In severe cases, intravenous methylprednisolone or intravenous cyclophosphamide can be used. Intravenous immunoglobulin (IVIg) is used in refractory cases. Mycophenolate mofetil, tacrolimus, hydroxychloroquine, rituximab, and anti-TNF agents have also been used. Physical and occupational therapy, sunscreen, and adequate psychosocial support are vital for successful management of JDM. (127)(132) Skin-limited disease, or skin involvement persisting despite systemic treatment, is improved by topical corticosteroids and calcineurin inhibitors. (133)(134)(135)

LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH) describes a clonal proliferation and infiltration of myeloid progenitor cells (Langerhans cells) into multiple organs, resulting in inflammation and tissue damage. It has an annual incidence of 2 to 9 cases per million children, with most occurring between 1 and 3 years of age. There is a slight male predominance and an increased incidence in Hispanics and individuals of Northern European descent. (136)(137)(138)(139)(140)

The underlying pathogenesis of LCH is unclear. However, the discovery of a BRAF V600E mutation in patients with LCH poses LCH as a possible form of inflammatory myeloid neoplasia. (141)

LCH encompasses a vast clinical spectrum ranging from solitary organ involvement to widespread disseminated disease. In general, patients belong to either single-system LCH, with single organ/system involvement (further categorized into unifocal or multifocal depending on the number of sites involved), or multisystem LCH, where 2 or more organs/systems are affected, with or without participation of high-risk organs (liver, spleen, hematopoietic system). Bone is the most commonly affected organ, followed by skin in 39% of LCH patients. (142) Skin-only disease tends to occur in approximately 12% of patients. (143)(144) In children, cutaneous manifestations are present in 53% of multisystem LCH. Typical features include erythematous to brown crusted papules and papulovesicles, 1 to 10 cm in size, located on the trunk, groin, face, and scalp (Figs 12 and 13). Scalp lesions resemble seborrheic dermatitis and can be mistaken for "cradle cap" and/or scabies in infants. Another frequent presentation is severe, intractable diaper dermatitis in younger children. Lesions can develop ulcerations or erosions and can be confused with fungal or bacterial skin infections. Petechiae can become evident; hypopigmentation is common in dark-skinned individuals. (144)(145)(146)(147)(148)(149) A varicella-like eruption and purpuric rash resembling the classic "blueberry muffin" rash are atypical variants of LCH. (150)(151) Certain nail findings (onycholysis, longitudinal grooving, purpuric striae of nail bed, paronychial erythema, and swelling) have been identified, particularly in the pulmonary form of LCH. (152) Histopathology reveals a dense dermal infiltrate of Langerhans cells along with variable numbers of eosinophils, neutrophils, lymphocytes, and histiocytes. Immunohistochemical staining is positive for CD1a, CD207 (Langerin), and S100. Birbeck granules are seen with electron microscopy, confirming the presence of Langerhans cells when necessary. (138)(145)(146)(147)(148)

Definitive diagnosis is contingent on confirmation of hallmark histopathological findings and positive immunohistochemical staining of the involved skin. Note that a substantial number of skin-only LCH progresses to systemic involvement shortly after diagnosis. Therefore, comprehensive organ surveillance is warranted on diagnosis as well as with follow-up visits. A high index of suspicion is warranted for patients with presumed progressive or refractory diaper dermatitis or seborrheic dermatitis

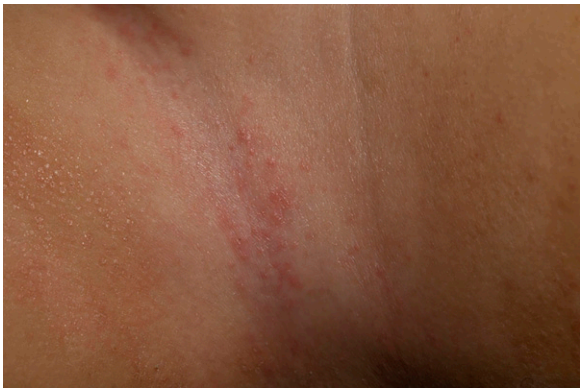

Figure 12. Erythematous to brown crusted papules and papulovesicles seen in Langerhans cell histiocytosis.

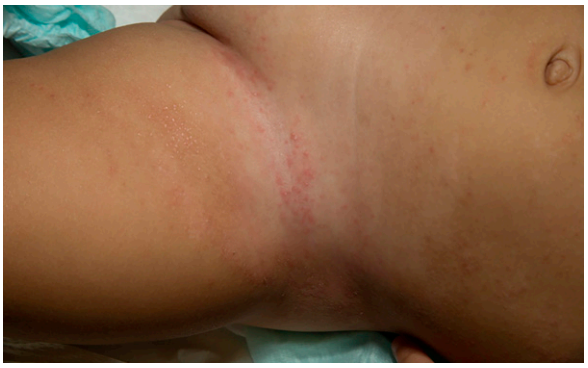

Figure 13. Cutaneous findings commonly erupting in flexural areas of a patient with Langerhans cell histiocytosis.

characteristically exhibiting reddish orange to brown scaly papules, erosions, and petechiae to avoid possible delays in LCH diagnosis. Treatment of cutaneous disease includes topical corticosteroids, nitrogen mustard, imiquimod, phototherapy, and, rarely, systemic immunosuppressive agents. Skin-only LCH has a better prognosis with fewer recurrences compared with multisystem LCH. (136)(138)(145)

Congenital self-healing reticulocytosis, or Hashimoto-Pritzker disease, is a self-healing congenital subtype of cutaneous LCH without systemic involvement. It consists of solitary or multiple skin lesions, characterized by brown to purple ulcerated or eroded papules, pustules, or vesicles without predilection for any specific body site. Subsequently, self-resolution ensues within several weeks, often accompanied by a residual atrophic white scar. Histopathological findings are characteristic of LCH. There is scarce evidence of relapse or progression. Close follow-up is warranted along with exclusion of similar cutaneous lesions in early childhood, such as juvenile xanthogranuloma, Spitz nevus, and mastocytoma. (153)(154)(155)(156)

LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a heterogeneous chronic autoimmune inflammatory disorder with a global incidence of 0.3 to 2.2 per 100,000 children. (157)(158)(159)(160) SLE predominantly affects females, is prevalent after 10 years of age, and frequently involves individuals of Asian, African, Indigenous North American, and Hispanic/Latino ancestry. A severe monogenic form of disease has been described before 5 years of age associated with consanguineous marriages. (161)(162)(163)(164)

Dermatologic manifestations are the first indication of SLE in 23% to 28% of patients. (162)(165) Cutaneous LE can be further subdivided into acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE). (165)(166) Other skin changes associated with LE include Raynaud phenomenon, nail fold telangiectasia, livedo racemosa (irregular, branched, erythematous, or violaceous skin discoloration), erythema multiforme, and urticarial vasculitis.

ACLE is associated with underlying SLE. It manifests as a symmetrical, discrete, localized, erythematous maculopapular rash associated with fine scale over the central portion of the face in a classic butterfly-like distribution (Fig 14), sparing the nasolabial folds. It can become confluent and present with mucosal ulcerations and facial edema. Although less common, ACLE can manifest as a generalized erythematous papular rash involving the trunk (Fig 15), face, and extremities and can resemble a drug eruption, viral exanthem, or even toxic epidermal necrolysis. The rash can be pruritic and bears remarkable accentuation on light exposure. ACLE lasts for days to weeks and can lead to postinflammatory hyperpigmentation or hypopigmentation, particularly in persons of color. Residual scarring and ulcerations are sparse. (165)(167)(168)(169)(170)(171) Histopathology reveals epidermal hyperkeratosis and atrophy, vacuolar interface changes, dermal mucin, and a dense inflammatory infiltrate predominantly composed of mononuclear cells in the perivascular and perifollicular zones along with some deposition at the dermal-epidermal junction. (165)(172) A substantial number of patients develop painless, white plaques with erythema of the buccal mucosa and hard palate along with nasal ulcers, typically of the lower septum. (173) Bullous lesions, including of the oral mucosa, can be found. (174)(175)

Generally, CCLE is categorized into discoid LE (DLE), LE profundus/panniculitis, and chilblain LE (CLE). DLE is the most common form with localized (scalp, face, ears) and disseminated variants, with generalized disease commonly including the palmoplantar surfaces and sparing the inguinal folds. The well-demarcated, coined-shaped patches

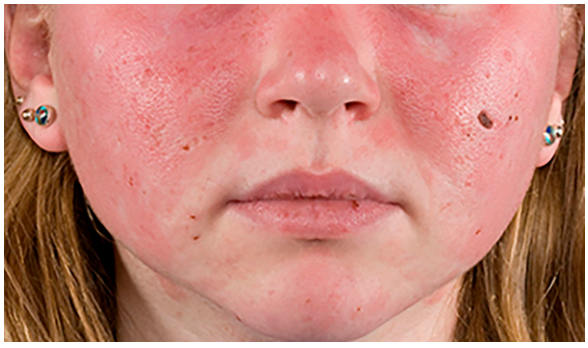

Figure 14. Erythematous rash in a butterfly-like distribution over the central face sparing the nasolabial folds, also called malar rash in lupus erythematosus.

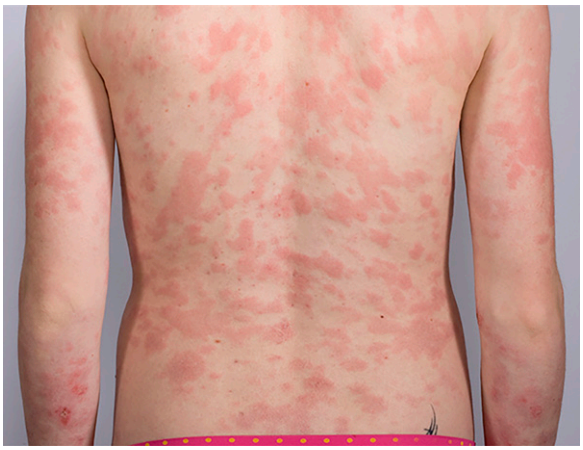

Figure 15. Erythematous rash diffusely distributed over the trunk of a patient with lupus erythematosus.

have overlying scale and distinct keratotic spikes resembling carpet tacks (carpet tack sign). Gradually, dyspigmentation, scarring, and telangiectasias develop. Scalp lesions progress to permanent scarring alopecia without effective treatment. Nail bed dystrophy is also observed with DLE. Disseminated DLE has a higher risk of underlying systemic disease. (170)(171)(176)(177)(178) In children, isolated DLE progresses to SLE in up to 26% of patients. (179) A small number of patients exhibit LE profundus/panniculitis, characterized by indurated nodules, 1 to 3 cm in size over the scalp, proximal extremities, breast, trunk, and buttocks. (180)(181) CLE has the unique appearance of red to purple painful papules over the digits in response to cold. Similarly, these lead to atrophic scars and telangiectasias. Systemic involvement can occur with CLE as well.

SCLE is characterized by an erythematous, maculopapular rash that develops acutely over sun-exposed areas, including the neck, upper chest, upper back, extensor arms, and dorsal hands, sparing the knuckles. Lesions transform into scaly annular/polycyclic or papulosquamous plaques over time. Residual scarring is exceedingly rare; however, some lesions can evolve into distinct areas of hypopigmentation. SCLE is often associated with mild systemic disease, and patients are typically positive for anti-Ro (SSA) antibodies. (167)(171)(182)(183)(184)

Neonatal LE (NLE) is a unique subtype of LE. The condition typically occurs in infants with mothers who have a predisposition for SLE or other connective tissue disease. Up to 85% of neonates with NLE develop cutaneous manifestations, either at birth or within the first few weeks after birth. (185) Periorbital erythema or "raccoon eyes" should prompt evaluation for NLE. Many other cutaneous features have been described, including annular scaly plaques, discoid lesions, atrophic (scarlike) lesions, telangiectasias, and mucosal ulcerations. Sun-exposed sites are commonly affected. NLE is caused by transplacental passage of antibodies, particularly anti-Ro (SSA) and anti-La (SSB) antibodies. The affected infant and mother can also exhibit positive antinuclear antibodies (ANAs), antiphospholipid antibodies, and/or antiribonucleoprotein antibodies. If NLE is suspected, the infant requires a thorough physical examination, CBC count, and liver function tests to evaluate for internal organ involvement. NLE is strongly associated with irreversible congenital heart block, and a thorough cardiac evaluation is warranted. Fortunately, the cutaneous manifestations of NLE clear over 6 to 12 months as maternally transferred antibodies wane. While they are present, these cutaneous lesions can be treated with topical corticosteroids or calcineurin inhibitors, and these lesions can be potentially prevented from occurring through photoprotection. (186)

Diagnosis of SLE is clinical and is supported by positive photoreactivity, positive ANA, ds-DNA antibody, anti-Smith antibody, and/or antiphospholipid antibodies. Biopsy is performed in atypical cases. The direct immunofluorescence test, historically known as the "lupus band test," has uncertain diagnostic value and is not routinely performed. (171) Medications can also trigger SLE, CCLE, and SCLE; therefore, a thorough review of medication history is crucial. Drug-induced LE is often associated with positive ANA, antihistone, and/or anti-ssDNA antibodies. (187)(188) Patients with SLE with or without cutaneous involvement require a long-term, individualized treatment approach focused on photoprotection and use of systemic agents such as hydroxychloroquine, corticosteroids, and immunomodulators (eg, methotrexate, IVIg). Providers must be mindful of the adverse effects of certain medications and aware of the physical appearance consequences of untreated or suboptimally managed skin disease. Involvement of other subspecialists (rheumatology, nephrology) is warranted on a case-by-case basis. Periodic follow-up visits and adequate psychological support is essential for successful, long-term management of SLE, including its cutaneous manifestations. (189)(190)(191)

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared to be causing a pandemic by the World Health Organization on March 11, 2020. (192) Globally, it has affected close to 30 million people, including children of all ages. (193)(194)(195)(196) In April 2020, a novel multisystem inflammatory syndrome in children having a temporal

association to confirmed cases of COVID-19 was first described. (197)(198)(199)(200) This unique clinical entity has been named multisystem inflammatory syndrome in children (MIS-C) by the Centers for Disease Control and Prevention (CDC) and the World Health Organization, whereas in the United Kingdom it is known as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. (198)(201) Its incidence is estimated to be 2 per 100,000 in individuals younger than 21 years. (202) Median age at onset is 8.6 years (range, 3 months to 20 years), with a slight male predominance. Black and Hispanic children tend to be affected more than children of Asian descent. Obesity and asthma are the most common underlying comorbidities. (203)(204)(205)

The exact pathophysiology is unclear. One hypothesis suggests that MIS-C is a postinfectious phenomenon resulting from an exaggerated, abnormal IgG antibody–mediated immune response to SARS-CoV-2 antigen. (201)(203)(206)(207) Another study points toward the potential role of host genetics in triggering this anomalous inflammatory response. (208)

Clinical presentation includes a temperature of at least 100.4°F (≥38.0°C) lasting for an average of 3 to 5 days; gastrointestinal symptoms, including abdominal pain, vomiting, and diarrhea; mucocutaneous inflammation, such as skin rash, conjunctivitis, lip swelling/redness, and swelling of hands and feet; respiratory symptoms, including acute respiratory distress syndrome and pneumonia; renal signs such as with acute kidney injury; hematologic abnormalities, such as anemia, thrombocytopenia, neutrophilia, and lymphopenia; and neurocognitive features, including headache and lethargy. Fever is the presenting complaint in close to 100% of the patient population. (201)(204)(205)(209)

An erythematous, polymorphous rash with mild or absent pruritus, beginning anywhere on the body and commonly distributed over the trunk, extremities, and face has been identified in MIS-C. Several studies have used the terms *generalized eruption, erythroderma, desquamating, macular,* and *maculopapular* to describe this skin rash. It is almost always accompanied by mucocutaneous inflammation, persists throughout the course of MIS-C, and ultimately resolves in conjunction with the other clinical manifestations. There have been no reports of dermatologic manifestations persisting beyond the clinical course of MIS-C. (200)(201)(206)(210)(211)(212) A recent study reported 87% of children aged 0 to 5 years having dermatologic findings in MIS-C compared with 61.5% of those aged 13 to 20 years. (202)

Any clinical suspicion of MIS-C requires both reverse transcription polymerase chain reaction testing and serologic testing for SARS-CoV-2 virus. (200)(204)(205)(213)(214) The CDC has formulated a case definition for MIS-C, which is summarized in Table 2. A persistent decline in left ventricular function (especially the left ventricular systolic function) is noted in 50% to 60% of cases, and 20% to 50% of cases have coronary artery abnormalities, along with elevated troponin and brain natriuretic peptide levels. (201)(209)(215)

MIS-C ranges from mild to severe illness and warrants multidisciplinary care. (216)(217) Any child with severe illness characterized by shock, hemodynamic instability, worsening respiratory status, acute kidney injury, and coagulopathies must be hospitalized. Effective fluid resuscitation with vasopressors is the initial step, followed by antimicrobial therapy for infectious symptoms and immunomodulating agents such as IVIg (patients with moderate to severe illness or meeting criteria for complete or incomplete KD). Glucocorticoids and adjunctive therapy with interleukn-1 inhibitors and interleukn-6 inhibitors are used in shock and fluid-refractory hypotension. The utility of convalescent plasma is uncertain; anticoagulation with low-molecular-weight heparin is recommended in patients at risk for thrombotic complications. (216)(217)(218) Serum troponin and brain natriuretic peptide levels, along with baseline 12-lead electrocardiography and echocardiography, are recommended, with serial echocardiography based on the initial clinical picture and echocardiography findings. (215)

Compared with KD, MIS-C affects older children and adolescents, predominantly impacts black and Hispanic children, has prominent gastrointestinal symptoms, frequently involves left ventricular dysfunction, and causes marked elevation of inflammatory markers such as C-reactive protein. (202) Bacterial sepsis and toxic shock syndrome can be differentiated based on bacterial culture and SARS-CoV-2 test results. (219) Hemophagocytic lymphohistiocytosis and macrophage activation syndrome, also characterized by excessive, aberrant immune responses, have a lower incidence of cardiac and gastrointestinal dysfunction in contrast to MIS-C. (220) The prognosis of MIS-C is uncertain. Despite having similarities with other inflammatory disorders, such as KD, the disease course can be long, can require intensive care interventions, and can also prove fatal in some cases. (201)(209)

Table 2. Outline of a Case Definition of MIS-C by the Centers for Disease Control and Prevention

All of the following criteria must be met for a diagnosis of MIS-C:
1. Any individual aged <21 y; AND
2. Presenting with fever ≥100.4°F (≥38°C) lasting for ≥24 h, or subjective fever lasting for ≥24 h; AND
3. Laboratory evidence of inflammation, including but not limited to elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, interleukin-6, or neutrophils; reduced lymphocytes; and low albumin; AND
4. Evidence of clinically severe illness requiring hospitalization; AND
5. Multisystem (≥2) organ involvement, including dermatologic, cardiac, renal, respiratory, gastrointestinal, hematologic, or neurologic; AND
6. No alternative plausible diagnosis; AND
7. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serologic test, or antigen test; or COVID-19 exposure within 4 weeks before symptoms onset.

Any individual who fulfills these criteria and also meets the criterion of complete or incomplete Kawasaki disease must be reported. MIS-C must also be considered in any pediatric death with evidence of SARS-CoV-2 infection. COVID-19=coronavirus disease 2019, MIS-C=multisystem inflammatory syndrome in children, RT-PCR=reverse transcription polymerase chain reaction, SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
Modified from Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with corona virus disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Published May 14, 2020.

Summary

- Dermatologic manifestations are often an early indicator of systemic diseases and might be the only markers of clinical disease in otherwise asymptomatic patients. (2)(3)
- Common childhood systemic diseases with dermatologic manifestations include acrodermatitis enteropathica, dermatitis herpetiformis, juvenile dermatomyositis, erythema nodosum, Henoch-Schönlein purpura, inflammatory bowel disease, and systemic lupus erythematosus. These disorders can be acquired or congenital with mild to severe clinical presentation and distinct histologic findings. (13)(36)(61)(82)(96)(125)(138)(167)
- Based on research and consensus, diagnosis is clinical, with biopsy warranted in atypical cases, (15)(82)(114) except in Langerhans cell histiocytosis, where a definitive diagnosis is contingent on positive histologic features. (138) Treatment modalities are mainly focused on management of acute flare-ups and chronic underlying disease. Topical treatments are often used, with systemic treatments used as an adjunct or in refractory cases. (41)(44)(78)(96)(132)(142)
- Regular follow-up visits and adequate psychosocial support are critical for successful management of dermatologic manifestations in childhood systemic diseases.

QUALITY IMPROVEMENT PROJECT SUGGESTION

Dermatologic manifestations of systemic diseases in the pediatric population are often underrecognized or misdiagnosed by nondermatologic providers. Delay in definitive diagnosis can result in disease morbidity. (4)(7)

To potentially reduce such obstacles in everyday clinical practice, we suggest careful, mandatory recording of cutaneous findings using available digital photography technology for pediatric patients with systemic diseases. In addition, teledermatology should be used when possible to ensure prompt consultations with a dermatologist. This would likely lead to timely diagnosis and formulation of an appropriate management plan. The importance of teledermatology in skin care has been recognized in this era of the COVID-19 global epidemic, when access to dermatologists is widely limited. (221) This technology could also be used for follow-up care, particularly when dermatologic signs and symptoms change, erupt, or persist. Timely acquisition and careful storage of skin examination images will be instrumental in providing effective patient care and continued education of medical providers.

References for this article can be found at http://pedsinreview.aappublications.org/content/42/12/655.

***To view teaching slides that accompany this article, visit* https://pedsinreview.aappublications.org/content/42/12/655/tab-supplemental.**

Dermatologic Manifestations of Systemic Diseases in Childhood

Fatima I. Quddusi, MD, * Molly J. Youssef, MD, *†
Dawn Marie R. Davis, MD, *†

*Department of Pediatric and Adolescent Medicine, and,
†Department of Dermatology, Mayo Clinic, Rochester, MN

Pediatrics in Review — American Academy of Pediatrics

PIR QUIZ

1. You are evaluating a 6-month-old female infant with erythematous to orange scaly crusted patches located on the face and abdomen. Some of the lesions are vesicular in nature. The mother reports that the patches first appeared around the nostrils, eyes, mouth, and perianal area. She has had a history of chronic diarrhea and failure to thrive. Which of the following laboratory tests is the most appropriate next step in diagnosis of this condition?

   A. Mutation analysis of *ZIP4*.
   B. Serum iron level.
   C. Serum transferrin level.
   D. Serum zinc level.
   E. Skin biopsy.

2. A 16-year-old female, known to your practice, presents to your clinic with e rythematous papules on the extensor surfaces of her elbows during the past few days. She has a medical history of gluten sensitivity. On physical examination you notice, in addition to the skin findings, enamel defects. A perilesional skin biopsy is performed. Which of the following histopathologic findings is most likely to be seen and to confirm the diagnosis in this patient?

   A. Eosinophilic infiltrate and fibrin deposition of the dermal papillae.
   B. IgA antibodies in the tips of dermal papillae and along dermal base immunofluorescence.
   C. Keratinocyte necrosis, cytoplasmic pallor, vacuolization, and confluent parakerato the epidermis.
   D. Lymphohistiocytic infiltration of the dermal adipose tissue.
   E. Neutrophilic infiltration, septal edema, and vasculitis.

3. An 8-year-old boy is brought to the office by his parents for evaluation of a worsening 2 days ago. The patient also has been complaining of generalized joint pain and abdominal pain. On physical examination of the skin, there are palpable purpuric lesions over the lower extremities, non-blanching. Abdominal examination shows a soft, non-tender abdomen with no rebound. Stools are hemoccult negative. Which of the following is the most appropriate next step in management?

   A. Begin corticosteroid therapy.
   B. Begin high dose aspirin therapy.
   C. Monitor urine dipstick, hydration, bed rest, and pain.
   D. Perform a renal biopsy.
   E. Perform a skin biopsy.

4. You are evaluating an 8-month-old female infant with persistent diaper dermatitis for t note some red orange scaly papules with erosions and petechiae. No other physical findings are seen. In discussing the diagnosis with the parents, which of the following statements best describes the characteristic features of this condition?

   A. Diagnosis is confirmed by the presence of BRAF V600E.
   B. Prognosis is good since the condition is limited to skin only.
   C. Skin manifestations are more likely to occur than bone involvement.
   D. Systemic steroids are the recommended initial treatment.
   E. The infant is likely to develop a self-healing form of reticulocytosis.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2021 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit*™, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2023, however, credit will be recorded in the year in which the learner completes the quiz.

2021 *Pediatrics in Review* is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio Program. *Pediatrics in Review* subscribers can claim up to 30 ABP MOC Part 2 points upon passing 30 quizzes (and claiming full credit for each quiz) per year. Subscribers can start claiming MOC credits as early as October 2021. To learn how to claim MOC points, go to: https://www.aappublications.org/content/moc-credit.

5. A 9-year-old boy is brought to the pediatric emergency room in a local hospital with fever of 102°F for the past 4 days, diarrhea, lip swelling and redness, and swelling of hands and feet. He is noted also to have a polymorphous rash distributed over the trunk, extremities, and face. He has tested positive for SARS-CoV-2 virus the week prior. On physical examination, he is hemodynamically stable. Skin examination shows an erythematous polymorphous rash and swollen hands and feet. There is also evidence of conjunctivitis and red lips. In addition to intravenous immunoglobulins, serum troponin, and brain natriuretic peptide (BNP) levels, which of the following is the most appropriate next step in management?

   A. Cardiac catherization.
   B. Echocardiogram.
   C. Renal biopsy.
   D. Skin biopsy.
   E. Systemic corticosteroids.