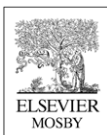




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## Skin Signs of Systemic Disease in Childhood

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### EDITORIAL COMMENT

Many of us were drawn to the specialty of dermatology by the excitement of recognizing key dermatologic features that led to the diagnoses of important systemic disorders. Although there is significant overlap between the skin signs of systemic disease in children and adults, there are several conditions in which important distinctions exist in the characteristic clinical presentation. Our author, Dr. Amy Gilliam, has special experience and expertise in pediatric rheumatologic disorders. In an interesting case-based format, Dr. Gilliam provides a comprehensive overview of the clinical findings in several rheumatologic conditions that are more specific to children in contrast to their adult counterparts. Furthermore, she provides an update on diagnosis and management of several uniquely pediatric disorders including neonatal lupus erythematosus, childhood vasculitides (Kawasaki disease, Henoch Schonlein Purpura, acute hemorrhagic edema of infancy) and the more recently described neonatal-onset multisystem inflammatory disorder (NOMID) syndrome. This article provides clinically relevant information that may aid the clinician in the accurate and prompt recognition of these challenging diseases. Timely diagnosis will hopefully result in more effective therapy as well as prevention of disease-related complications that may ultimately improve the outcomes in these complex patients.

*Amy Jo Nopper, MD*

**T**he diagnostic criteria for many systemic disorders in both adults and children include at least one skin finding, and the skin may be the first of several organs affected by these conditions. Early recognition of subtle cutaneous signs of systemic illness in childhood can help to prevent adverse outcomes through earlier initiation of appropriate treatment. Although adults and children are affected by many of the same systemic conditions, there are some dermatologic features of these illnesses that are unique to the pediatric population. In this review, several cases of children presenting with cutaneous features of systemic disease will be discussed.

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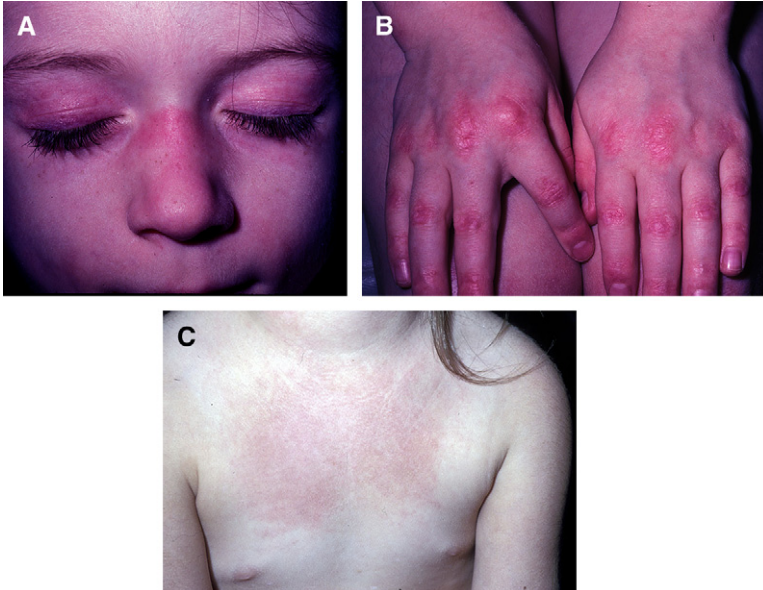
## CASE 1

A 7-year-old girl presents with erythematous, ill-defined, and slightly scaly patches and plaques on her face, dorsal hands, and chest (Fig. 1A–C). Her parents complain that she is “tired all of the time,” and is having trouble doing things she used to be able to do. In fact, her teacher at school has complained about her ability to participate in physical education lately.

## JUVENILE DERMATOMYOSITIS

This case demonstrates several of the classic skin findings that can be seen in acute juvenile dermatomyositis (JDM). Much like in adulthood, the rash of dermatomyositis in childhood can be mistaken for atopic dermatitis or an acute allergic reaction. However, because of its characteristic distribution and associated symptoms, the dermatologist should be able to recognize the dermatologic features of JDM and evaluate further for systemic involvement.

JDM is a rare multisystem autoimmune disease characterized by vascular inflammation that primarily affects muscle and skin. Two to four children per million per year are affected by JDM [1], and it occurs most often in children between the ages of 2 and 15. The diagnostic criteria for JDM are depicted in Box 1, and are quite similar to those for adult dermatomyositis. Although the



**Fig. 1.** (A) Case 1: erythema of the eyelids and central face in a young girl presenting with fatigue. (Courtesy of Ilona J. Frieden, MD, San Francisco, CA.) (B) Case 1: erythema and eczematous lesions overlying the metacarpophalangeal and interphalangeal joints of a young girl presenting with fatigue. (Courtesy of Ilona J. Frieden, MD, San Francisco, CA.) (C) Case 1: erythema of the chest in a young girl presenting with fatigue. (Courtesy of Ilona J. Frieden, MD, San Francisco, CA.)

**Box 1: Diagnostic criteria for juvenile dermatomyositis***Characteristic Rash*

Symmetric proximal muscle weakness

Elevated muscle enzymes (CPK, aldolase, lactate dehydrogenase, and transaminases)

Inflammatory myopathy based on characteristic histopathology

Inflammatory myopathy based on characteristic: EMG changes

Definite JDM: rash + 3/4 criteria; probable JDM: rash + 2/4 criteria; possible JDM: rash + 1/4 criteria

criteria for muscle disease have not officially been altered, most pediatric rheumatologists obtain a T2-weighted MRI in lieu of the confirmatory muscle biopsy or electromyogram (EMG), given its less-invasive nature. However, when the diagnosis of JDM is unclear, such as in the case of possible mixed connective tissue disease, muscle biopsy is considered the “gold standard” confirmatory test. Cutaneous histopathology is not included in the diagnostic criteria for JDM because it is rather nonspecific and can resemble that seen in lupus erythematosus, as it is characterized by a vacuolar interface dermatitis. However, a skin biopsy may be useful in helping to exclude other diagnostic possibilities such as atopic or contact dermatitis, psoriasis, and drug eruptions.

Although the etiology of JDM is unknown, a number of viral and bacterial pathogens as well as complex autoimmune phenomena have been implicated [2]. An immune-mediated vasculitis appears to be a key event in JDM pathogenesis. One hypothesis suggests that chimerism plays an important role in the pathogenesis in that maternally derived T cells, which normally persist in a state of tolerance or anergy, are activated leading to an antihost inflammatory response such as is seen in the setting of graft-versus-host disease [3]. Although familial incidence of dermatomyositis is exceedingly rare, specific susceptibility alleles have been identified, including the HLA-DQA1\*0501 allele, which is linked to persistent fetal microchimerism, and the tumor necrosis factor- $\alpha$  (TNF $\alpha$ )-308A locus, which is associated with a more chronic disease course and various complications such as calcinosis cutis, partial lipodystrophy, insulin-resistant diabetes, and hyperlipidemia [2].

The skin findings that are considered “classic” or hallmark for dermatomyositis can be seen in both adults and children and include the heliotrope rash (see Fig. 1A), represented by violaceous periorbital edema, erythema, or telangiectasia, which can also be part of a more confluent erythema that involves the entire face. Sometimes, with involvement of the bridge of the nose and malar cheeks, the skin changes may resemble the malar rash of systemic lupus erythematosus. Gottron’s papules/sign (see Fig. 1B), also specific to dermatomyositis in both adults and children, is characterized by scaly, violaceous papules or plaques, most commonly located on the interphalangeal joints but also seen over

other bony prominences such as the metacarpals, elbows, knees, and malleoli. These cutaneous lesions are often mistakenly diagnosed as psoriasis or atopic dermatitis, as the clinical differential diagnosis of Gottron's papules includes these conditions. In some cases, Gottron's papules can present with only subtle erythema in these locations, making a clinical diagnosis more difficult. Also, both adults and children with dermatomyositis often demonstrate evidence of photosensitivity and commonly have the "V-sign" rash, which is characterized by erythema, scaling, and poikiloderma on the upper chest and face (see Fig. 1C). When this photosensitive eruption involves the upper back as well, it is termed the "shawl sign."

In JDM, however, these hallmark findings of dermatomyositis are not often seen on *initial* presentation. As Peloro and colleagues [4] reported, based on a 30-year experience, the majority of JDM patients present with a nonspecific extremity rash and periungual erythema. Also, approximately one third of children with JDM were noted to have pruritus at the time of presentation. This is an often underrecognized symptom that can be a significant problem for both adults and children with dermatomyositis.

Vasculopathic lesions, which result in cutaneous necrosis and ulceration, are reported to be more common in JDM than in adult dermatomyositis, and are associated with a more severe course and worse functional outcome [5]. Although cutaneous necrosis is less common in adults, the occurrence of this finding has been reported to be predictive of the presence of cancer [6]. Unlike in adult dermatomyositis, JDM is not associated with an increased risk for occult malignancy. Although malignancy has been reported in only a handful of children with JDM, it is estimated that 18% to 32% of adults with dermatomyositis have an associated malignancy [7].

Vasculopathic lesions can also lead to dystrophic calcification at the sites of inflammation, resulting in severe, disabling calcinosis cutis, which occurs in up to one third of cases of JDM, but is extremely rare in adult dermatomyositis. This cutaneous calcification presents as painful, hard nodules that can extrude spontaneously through the skin, creating a nidus for infection (Fig. 2). It occurs at sites of trauma (elbows, knees, and buttocks), often beginning 1 to 2 years after disease onset, and can be demonstrated through the use of routine imaging studies, including plain films, CT, and MRI scans. Calcinosis cutis is thought to be related to long-term, uncontrolled inflammation because children who are treated aggressively and early in the disease course are less likely to develop soft tissue calcification [8]. The link between calcification and inflammation has been further defined as both macrophages and certain pro-inflammatory cytokines, namely interleukin (IL)-6, IL-1 $\beta$ , and TNF- $\alpha$ , have been identified in the fluid of a calcium deposit of a patient with JDM [9]. One theory as to why children develop calcification while adults do not relates to the fact that there is often a significant delay in making the diagnosis of JDM in children as compared to adults, in which the diagnosis is made more rapidly.

Lipodystrophy is a rare cutaneous finding that has been reported more frequently in association with JDM compared to adult dermatomyositis [10,11].



**Fig. 2.** Calcinosis cutis of the right elbow in an 11-year-old girl presenting with pain.

The entire clinical syndrome is comprised of generalized or localized partial loss of subcutaneous fat, hypertrichosis, acanthosis nigricans, hepatomegaly, insulin resistant diabetes, and hyperlipidemia. This lipodystrophy, predominantly seen in females, is characterized by progressive, slow, and symmetrical loss of fatty tissue that mainly involves the upper half of the body, often starting on the face and progressing in a cephalocaudal direction. Based on the fact that subtle metabolic abnormalities, such as hypertriglyceridemia and insulin resistance, have occasionally been found to precede the lipodystrophy, some authors recommend that patients with JDM be screened for these metabolic abnormalities during routine follow-up [12]. (See Table 1, which summarizes the cutaneous manifestations seen more commonly in juvenile versus adult dermatomyositis.)

The hallmark extracutaneous feature of JDM is proximal muscle weakness, which can present in younger children as listlessness or easy fatigability.

**Table 1**

Cutaneous manifestations of adult and juvenile dermatomyositis

Common in both adult and juvenile dermatomyositis	More common in juvenile dermatomyositis
Gottron's papules	Vasculopathic lesions (+/-ulceration)
Heliotrope rash	Calcinosis cutis
Periungual erythema, nail-fold telangiectasias, and cuticular overgrowth	Lipodystrophy (+/- hypertrichosis and acanthosis nigricans)
"V sign" rash	
Photosensitivity	
Pruritus	

*Data from Santmyire-Rosenberger B, Dugan EM. Skin involvement in dermatomyositis. Curr Opin Rheumatol 2003;15(6):714-22.*

Children with JDM can also develop muscle pain in addition to the muscle weakness, arthritis, limb edema, and joint contractures due to tenosynovitis [13]. Patients with severe disease can have dysphagia, dysphonia, and evidence of respiratory muscle weakness.

Laboratory evaluations are useful in helping to make the diagnosis of JDM (see Box 1) and in monitoring disease activity. Specifically, aldolase is often used to track disease progression and assess responsiveness to therapy. In both children and adults, autoantibodies to aminoacyl-tRNA synthetases, most commonly anti Jo-1, help to define the “antisynthetase syndrome,” which is associated with debilitating arthritis, interstitial lung disease, and resistance to therapy [5]. In contrast, the presence of autoantibodies to Mi-2, which are directed against a nuclear helicase, predicts a milder course and good response to treatment in both the juvenile and adult forms of dermatomyositis [5].

Although outcomes are improving, approximately two thirds of children with JDM experience a chronic continuous or polycyclic course while the remaining one third have a monocyclic course, defined as disease that goes into permanent remission after 2 years of disease activity [14]. Based on retrospective multicenter data over an 11-year period, Huber and colleagues [14] reported that 35% of JDM patients were still receiving medication for persistent disease activity after a median follow-up of 7 years.

The mainstay of treatment for JDM is corticosteroids. Prior to the introduction of corticosteroids, the mortality rate of JDM was over 30%, while it is currently reported to be less than 2% to 3%. More recently, steroid-sparing agents have been utilized in an attempt to avoid the side effects associated with long-term steroid therapy. Methotrexate has become the steroid-sparing agent of choice due to the fact that pediatric rheumatologists have gained extensive clinical experience with this agent in the treatment of juvenile arthritis and have found low-dose therapy to be safe and effective [15]. The typical treatment regimen for JDM consists of early intervention with high-dose corticosteroids concurrent with the introduction of a steroid-sparing agent such as methotrexate or intravenous immunoglobulin (IVIG). Subsequently, steroids are tapered over weeks to months to the minimum dosage required for adequate disease control or until the disease remits on its own.

At times, the skin disease remains a problem despite achievement of good control of the myositis. Also, there are well-described cases of amyopathic dermatomyositis occurring in childhood as well as in adulthood [16]. These patients exhibit the classic cutaneous findings of dermatomyositis in the absence of clinical, laboratory, or histologic evidence of myositis. For cases with recalcitrant skin disease and/or amyopathic dermatomyositis, therapeutic measures such as oral hydroxychloroquine, topical steroids/immunomodulators, and avid sun protection are often employed.

## CASE 2

An 11-year-old female presents with a 6-month history of fixed mottling on her legs, with less prominent involvement of her arms (Fig. 3). These skin changes



**Fig. 3.** Case 2: fixed lacy, reticulate mottling on the legs of an 11-year-old girl.

are more pronounced when she is cold but do not fade completely when she warms up. She has no other complaints, including joint pain, unexplained fever, or other skin alterations.

This case illustrates an example of livedo reticularis (LR) in a young girl. LR is a skin vasculopathy represented by violaceous, reticulate, net-like patterns in the skin most often located on the legs, but that can also affect the upper trunk and arms. True or “fixed” LR, also called “livedo racemosa,” does not change or disappear with changes in ambient temperature, and LR can be either primary or secondary in nature. *Primary* or *idiopathic* LR is a diagnosis of exclusion, while *secondary* LR is often related to hypercoagulable states and autoimmune conditions. Therefore, the presence of LR, especially when extensive such as in this case, should alert the clinician to investigate for associated disease because the pathogenesis may be related to vaso-occlusive microthrombotic vascular events or inflammatory phenomena, either immune complex mediated or that which is associated with antinuclear cytoplasmic antibody.

The hypercoagulable disorder that is most frequently associated with LR is the antiphospholipid syndrome (APS), an autoimmune disorder, which is strictly defined as the presence of either vascular thrombosis or recurrent fetal loss and elevated titers of antiphospholipid antibodies, namely the lupus anticoagulant or beta-2-glycoprotein I-dependent anticardiolipin. Therefore, a diagnosis of APS requires the presence of both clinical and laboratory criteria. However, these criteria are often not applicable to children because the pediatric population does not experience fetal loss and rarely develops vascular thrombosis. Therefore, other features, such as a history of migraines and/or seizures, should be considered suggestive of this condition in childhood if other features of APS are present based on history, laboratory evaluation, and physical examination. Livedo is the primary cutaneous manifestation of APS and occurs in 25% of patients [17]. The presence of LR in the setting of APS is highly associated with arterial thrombotic events, manifested by migraines, seizures, cardiac valve thickening and vegetations, and cerebral or ocular ischemic arterial events [17,18]. Other hypercoagulable conditions that can present with LR include protein C and S deficiency, antithrombin III deficiency, cold agglutininemia, cryoglobulinemia, cryofibrinogenemia, polycythemia vera, and essential thrombocythemia.

LR can also be a manifestation of autoimmune conditions, namely lupus erythematosus and polyarteritis nodosa. In childhood, polyarteritis nodosa is



quite rare. However, lupus erythematosus is the most common connective tissue disease of childhood. Lupus erythematosus includes several subtypes: systemic lupus, subacute cutaneous lupus, chronic cutaneous (or discoid lupus), and neonatal lupus. Although subacute cutaneous lupus is exceedingly rare in childhood, systemic lupus erythematosus (SLE) is the most frequent pediatric presentation of lupus.

## LUPUS ERYTHEMATOSUS IN CHILDHOOD

Although the majority of cases of SLE occur in adult women, 15% to 20% of cases present in the first 2 decades of life [19]. Males and females are equally affected until puberty, after which the female to male ratio becomes 9:1. Diagnostic criteria are depicted in Box 2, and are the same as those used for adults. Adults and children with SLE share a similar clinical presentation and immunologic findings. However, systemic sequelae of SLE are more severe in the pediatric population, as childhood cases of SLE demonstrate a higher prevalence of end-organ involvement and a more aggressive clinical course. For instance, lupus nephritis, accelerated atherosclerosis, neuropsychiatric complications, and restrictive lung disease occur with higher frequency in childhood versus adult SLE [19].

As mentioned, the skin findings seen in children with SLE are similar to those observed in adults. Approximately 50% of children with SLE have a malar rash [20], which can vary from mild flushing to more sharply demarcated areas of erythema, edema, and scaling over the bridge of the nose and malar cheeks. Classically, the malar rash of SLE spares the nasolabial folds, and it occurs in a photosensitive distribution. Children with SLE can also have a more generalized polymorphous rash on the trunk. In most cases, this rash is maculopapular and can resemble a drug eruption. Other cutaneous findings include oral ulcerations, which are usually asymptomatic but can be painful and are more commonly seen on the palate and buccal mucosa rather than on the tongue or gingiva. Finally, a patchy or diffuse alopecia, vasculitic skin lesions, LR(as described), and Raynaud's phenomenon can be observed in children with SLE.

Discoid skin lesions may also occur in the setting of childhood SLE, and occasionally they present in a linear configuration following the lines of Blaschko (Fig. 4). Presentation with this linear form of cutaneous lupus appears to be more common in children [21] but skin-only, chronic cutaneous lupus or discoid lupus erythematosus (DLE) is rare in the pediatric population. When DLE occurs in childhood, a high proportion of patients may go on to develop SLE. As reported by Moises-Alfaro and colleagues [22], in a series of 27 pediatric cases of DLE, 26% (seven cases) developed SLE during a mean follow-up of 36 months. A family history of rheumatic disease was the major risk factor that was found to be associated with progression to SLE in these patients.

The most common extracutaneous feature of children presenting with SLE is fever, which is usually low-grade and persistent over many weeks. Compared to adults, children also more commonly develop a nondestructive arthritis.

Laboratory findings for childhood SLE are similar to those in adults. Antidouble stranded DNA (dsDNA), anti-Smith, and anti-U1 RNP antibodies are

**Box 2: American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus***Arthritis*

Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion

*Malar rash**Discoid rash**Photosensitivity**Oral ulcers**Renal disorder*

(a) Persistent proteinuria  $>0.5$  g/d or  $>3+$

OR

(b) Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed

*Neurologic disorder*

(a) Seizures—in the absence of offending drugs or known metabolic derangements

OR

(b) Psychosis—in the absence of offending drugs or known metabolic derangements

*Hematologic disorder*

(a) Hemolytic anemia—with reticulocytosis

OR

(b) Leukopenia— $<4000$ /mm on two or more occasions

OR

(c) Lymphopenia— $<1500$ /mm on two or more occasions

OR

(d) Thrombocytopenia—less than 100,000/mm in the absence of offending drugs

*Abnormal ANA titer**Immunologic disorder*

(a) Anti-DNA: antibody to native DNA in abnormal titer

OR

(b) Anti-Sm: presence of antibody to Sm nuclear antigen

OR

(c) Positive finding of antiphospholipid antibodies based on<sup>a</sup>:

1. an abnormal serum level of IgG or IgM anticardiolipin antibodies

2. a positive test result for lupus anticoagulant using a standard method

3. a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test

#### Serositis

- (a) Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion
- OR
- (b) Pericarditis—documented by ECG or rub or evidence of pericardial effusion

At least 4 of 11 of the criteria must be satisfied. They may develop all at once or individually over any period of observation

°These criteria were originally devised in 1982, and the immunologic disorder criterion (highlighted) was revised in 1997.

Data from Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1997;40:1725; and Feletar M, Ibanez D, Urowitz MB, et al. The impact of the 1997 update of the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus: what has been changed? *Arthritis Rheum* 2003;48(7):2067–9.

used as specific diagnostic markers, and levels of anti-dsDNA antibodies correlate with disease activity. More recently, antibodies to ribosomal P protein (anti-P) have been shown to be more prevalent in childhood-onset SLE (42%) compared to adult-onset SLE (7–8%), and the presence of both anti-P and anti-dsDNA antibodies has been linked to a higher incidence of nephritis and poorer prognosis [23].

Extracutaneous complications of juvenile-onset SLE include renal, cardiac, hematologic, neuropsychiatric, pulmonary, and musculoskeletal problems. Therefore, treatment can vary depending on the extent and nature of visceral involvement. Mild disease can be managed with sun protection/sun avoidance,



**Fig. 4.** Discoid lesion of lupus erythematosus on the right cheek of a 13-year-old girl, presenting in a linear configuration following the lines of Blaschko.

high-dose nonsteroidal anti-inflammatory agents, and topical steroids/immunomodulators for treatment of skin lesions. Moderate cutaneous disease is often managed with antimalarial agents such as hydroxychloroquine at a dose of up to 6 mg/kg/d [24].

As with JDM, corticosteroids are first-line therapy for severe, potentially debilitating disease, and steroid-sparing agents are introduced early on to minimize the amount of corticosteroid required to achieve remission. Steroid-sparing agents used in the setting of childhood SLE include azathioprine, methotrexate, mycophenolate mofetil, and cyclosporine. Intravenous cyclophosphamide has been the standard of care for the treatment of lupus glomerulonephritis in the past. However, its use is limited by potentially toxic effects, including bone marrow suppression, hemorrhagic cystitis, opportunistic infections, malignancy, and gonadal toxicity. Clearly, the possibility of premature gonadal failure is likely to be of much greater concern when treating pediatric versus adult patients, although this is not absolute. Recently, Ginzler and colleagues [25] demonstrated that induction therapy with mycophenolate mofetil was superior to intravenous cyclophosphamide in inducing complete remission of lupus nephritis in 140 adult patients. More studies are needed as the experience with mycophenolate mofetil in childhood is currently limited to small case series for this indication [26,27]. However, this data holds promise for the future availability of safer immunosuppressive therapies for children with SLE.

Other issues that are more relevant to juvenile versus adult SLE include the fact that children with SLE have an increased risk for osteoporosis and osteopenia, which is attributed to a combination of treatment with corticosteroids, chronic disease-related factors, and limited sun exposure. Because childhood and adolescence are critical periods for the accumulation of bone mass compared to healthy peers, children with SLE do not reach an equivalent peak bone mass [28]. Also, premature cardiovascular disease and accelerated atherosclerosis are now being recognized as significant problems in juvenile SLE and are thought to be multifactorial in origin [19]. Possible factors include vascular injury due to ongoing inflammation and treatment-related factors such as steroid-induced hypertension and obesity [29]. Atherosclerosis beginning in childhood has profound implications in terms of morbidity and mortality for these patients given that they have a lifetime ahead of them.

Neonatal lupus erythematosus (NLE) is a distinct pediatric subset of lupus erythematosus. It is an acquired autoimmune disorder, characterized by maternal autoantibodies against RNA protein complexes (Ro/SSA, La/SSB, and U1 RNP) that cross the placenta and lead to the clinical manifestations of NLE, which include cutaneous, cardiac, hematologic, and hepatic manifestations [30,31].

The cutaneous lesions occur in approximately half of NLE infants and are usually characterized by erythematous, often scaly, annular plaques on sun-exposed areas such as the head and neck, particularly on the scalp, malar, and periorbital regions (Fig. 5A). Less common presentations can include the presence of cutaneous atrophy and erosions (as depicted in Fig. 5B.) The eruption can occur at birth, but more commonly appears within the first 8 weeks of



**Fig. 5.** (A) Erythematous, scaling annular plaques on the scalp of a 3-week-old infant with neonatal lupus erythematosus. [Courtesy of Ilona J. Frieden, MD, San Francisco, CA.] (B) Erosive lesions in a periorbital or "raccoon eyes" distribution of a newborn with neonatal lupus erythematosus.

life, after exposure to ultraviolet (UV) light, including after phototherapy for hyperbilirubinemia [32]. By 3 to 6 months of age, the cutaneous lesions resolve but may leave residual hyperpigmentation, telangiectases, and/or mild atrophy. The resolution of the skin rash parallels the disappearance of the maternal autoantibodies from the infant's serum by 5 months of age.

Irreversible congenital heart block is the most-feared extracutaneous manifestation of NLE, and the exact mechanism by which maternal antibodies initiate and perpetuate inflammation, causing scarring, fibrosis, and calcification in and around the atrioventricular node, is not yet defined. However, the development of congenital heart block is highly associated with a specific antibody profile to 52-kD SSA/Ro, which may become a useful tool for identifying pregnant anti-SSA/Ro-SSB/La-positive women at risk of delivering a baby with congenital heart block [33]. Congenital heart block usually presents in utero with early detection around 18 to 24 weeks of gestation. Heart block is irreversible, requiring pacemaker in two thirds of infants and associated with mortality rates of 15% to 30% percent [31].

Neonates with NLE may also present with petechiae or purpura secondary to thrombocytopenia, which occurs in 10% to 20% of cases. A transient hemolytic anemia and leukopenia can occur as can hepatomegaly with jaundice, due to passive congestion associated with heart failure or secondary to extramedullary hematopoiesis.

Treatment is usually unnecessary if the course is not complicated by congenital heart block or other organ involvement as this form of lupus erythematosus resolves spontaneously. Recommended management of the cutaneous lesions of NLE includes sun avoidance and the use of low potency topical corticosteroids.

### CASE 3

A 16-year-old female with a long-standing history of polyarticular rheumatoid factor positive juvenile rheumatoid arthritis (JRA) presents with a 6-month

history of painful nodules on her elbows and hands. Her JRA has been complicated by Felty syndrome and a history of labial pyoderma gangrenosum (PG), and she takes multiple immunosuppressive medications, including corticosteroids, etanercept, and azathioprine. Her physical examination is notable for slightly tender erythematous papules and dermal nodules located symmetrically on her elbows, palms, dorsal hands, and overlying the proximal interphalangeal joints. Some have central crusts or umbilication (Fig. 6).

### NEUTROPHILIC DISORDERS PRESENTING IN CHILDHOOD

This case demonstrates an example of palisaded neutrophilic and granulomatous dermatitis (PNGD) in childhood, which is a form of leukocytoclastic vasculitis that occurs in patients with lupus erythematosus, rheumatoid arthritis, and other diseases that generate immune complexes. Other names for this condition include Churg-Strauss granuloma, cutaneous extravascular necrotizing granuloma, rheumatoid papules, superficial ulcerating rheumatoid necrobiosis, and interstitial granulomatous dermatitis with arthritis. It was originally described by Churg and Strauss, in 1951, as a manifestation of allergic granulomatosis. Since then, it has been reported by several other authors in association with underlying systemic disease. In 1994, Chu, Connolly, and Leboit proposed the term “palisaded neutrophilic and granulomatous dermatitis of immune complex disease” to represent these symmetrical papular lesions seen on extremities of patients with autoimmune disorders that generate immune complexes [34].

Classic clinical features include symmetrically distributed tender papulonodules that can be skin colored or violaceous. They typically demonstrate central crusting or umbilication and affect elbows and digits (Fig. 6).

Histopathologic examination of early lesions reveals small-vessel leukocytoclastic vasculitis and dermal neutrophilic infiltrates that lead to degeneration of collagen and a granulomatous reaction in the injured dermis. Unlike in rheumatoid nodules, the neutrophilic infiltrates of these lesions are located in the



**Fig. 6.** Case 3: tender erythematous papules and dermal nodules, with central crusts or umbilication, located symmetrically on the elbows of 16-year-old female with juvenile rheumatoid arthritis.

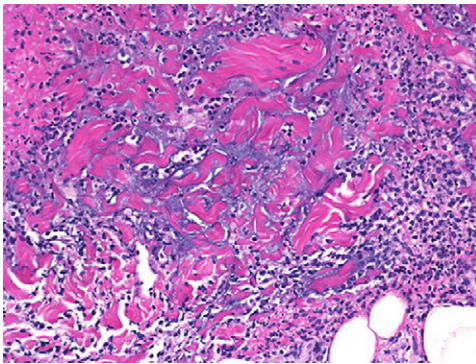
dermis rather than in the subcutis. Mature lesions show histiocytes palisaded around foci of dermal necrobiosis and evidence of fibrosis with neutrophilic debris (Fig. 7). Direct immunofluorescence reveals immune complex deposition.

PNGD is typically self-limited, with lesions lasting for up to 2 years. The course of lesions can parallel that of the underlying systemic disease, and exacerbation may occur with tapering of immunosuppression. Patients with PNGD are often already on immunomodulatory therapy due to their underlying condition. However, treatment for persistent and problematic lesions includes the addition of dapsone [35] and corticosteroids as well as other immunosuppressive therapies.

Other neutrophilic dermatoses that occur in childhood include Sweet's syndrome and pyoderma gangrenosum. PG is an ulcerative neutrophilic disorder that is rare in childhood, with approximately 4% of cases occurring in infants and children. Compared to PG in adults, pediatric cases of PG are frequently a manifestation of a systemic disease, the most common being ulcerative colitis [36]. Other conditions associated with PG in childhood include other inflammatory bowel disease (Crohns), JRA, hematologic malignancy, hepatitis, SLE, HIV infection, and Type II diabetes mellitus [13,37].

Childhood PG presents in a similar fashion as it does in adults, often beginning with a small painful pustule that evolves to form a necrotic plaque with violaceous undermined borders healing with a cribiform scar. In adults and older children, the lower extremities are most often affected. However, in infants, a genital or perineal distribution is more common [36,38]. Lesions on the head and face are rare in adults but have been reported in children [36].

If an underlying condition has not already been diagnosed, the workup in children with PG should include a complete blood count, erythrocyte sedimentation rate (ESR), electrolyte panel with glucose, liver function tests, and an antinuclear antibody. Pathologic specimens should be obtained for fungal and bacterial cultures as well as routine histopathology should the diagnosis of PG be in question. Also, a thorough history, physical examination, and



**Fig. 7.** Characteristic histopathologic findings in PNGD: a palisaded granuloma around leukocytoclastic debris, fibrin, and altered collagen.

review of systems should be performed, with careful attention to the gastrointestinal and musculoskeletal systems, because these are the most likely to be affected.

If PG does not resolve with treatment for the underlying disorder or no associated condition is identified, local care and intralesional steroids may be used. If these fail, treatment with anti-inflammatory and immunosuppressive agents such as corticosteroids, dapsone, cyclosporine, or mycophenolate mofetil is often successful.

Sweet's syndrome, or acute febrile neutrophilic dermatosis, is a rare inflammatory condition of unknown cause characterized by tender, erythematous skin lesions and a dermal infiltrate of mature neutrophils. Often, fevers and peripheral leukocytosis are also present, and therapy with corticosteroids causes dramatic improvement. In adults, Sweet's syndrome is associated with internal malignancy in 10% to 20% of cases, whereas in childhood, Sweet's syndrome is more likely to be postinfectious [39]. However, when the diagnosis of Sweet's syndrome is made in a child, an appropriate workup for systemic illness should be performed, as pediatric cases have been associated with acute myelogenous leukemia, myelodysplastic syndrome, and osteogenic sarcoma. Workup should include a complete history and physical examination, a complete blood count, and examination of the peripheral smear. Persistent leukocytosis, anemia, and/or thrombocytopenia may warrant a bone marrow biopsy [39].

A rare complication of Sweet's syndrome that has been reported in childhood is acquired cutis laxa (also called Marshall's syndrome) [40]. It is hypothesized that the loss of elastic tissue and anetoderma-like skin changes that are observed in this syndrome occur as a result of the release of elastase and other inflammatory mediators from neutrophils, which cause destruction of dermal elastic fibers. It has also been suggested that inherited  $\alpha$ 1-antitrypsin deficiency may be associated with this syndrome of acquired cutis laxa following Sweet's syndrome [40].

#### **CASE 4**

A 2-year-old is referred for severe diaper dermatitis. The rash has failed to respond to lotrimin and a barrier diaper cream; on further history, it becomes evident that the child has been extremely irritable over the past several days with a fever of 101°F. His parents are attributing these symptoms to a viral illness. On examination, the child has erythema and marked desquamation in the perineal area (Fig. 8).

#### **VASCULITIDES OF CHILDHOOD**

Primary vasculitis can present in childhood. In fact, there are two vasculitic conditions, Kawasaki disease (KD) and Henoch-Schönlein purpura, which occur more commonly in the pediatric age group. Other vasculitides, including macroscopic and microscopic polyarteritis nodosa, Wegener's granulomatosis, and Takayasu's arteritis, are rare in children and more frequently seen in adulthood.

Case 4 illustrates a frequently overlooked cutaneous finding of KD, an acute, multisystem self-limited vasculitis of unknown etiology that occurs primarily in





**Fig. 8.** Case 4: Two-year-old male presenting with perineal desquamation, fever, and irritability. (Courtesy of Ilona J. Frieden, MD, San Francisco, CA.)

children and is the leading cause of acquired heart disease in developed countries. Perineal desquamation is a very specific finding in KD, and is often mistaken for a diaper rash. This perineal desquamation is observed in the acute phase of KD, during the first week of symptoms, in contrast to the acral desquamation seen in the convalescent phase, which begins about 10 to 14 days after onset of symptoms.

The other cutaneous manifestations of KD include a polymorphous rash, which can be morbilliform, targetoid, and even micropustular. A more unusual cutaneous finding in KD is reactivation at the site of Bacille Calmette-Guérin (BCG) vaccination. This feature may even serve as a diagnostic tool for “incomplete” KD [41,42], which refers to children who do not meet diagnostic criteria but have persistent fever as well as several of the other characteristic signs of KD. Other cutaneous findings include swollen hands and feet, palmar erythema (often with a sharp demarcation line,) and erythema of the urethral meatus associated with urethritis. In the convalescent phase of KD, acral desquamation can occur, which starts at the fingertips and periungually. Also during the convalescent phase, onset of psoriatic lesions has been reported [43]. This phenomenon is associated with an increase in frequency of coronary complications, suggesting a poor prognosis for this association [44].

Other mucocutaneous findings of KD include conjunctival injection with classic perilimbal sparing. This is not a purulent conjunctivitis, as there is no tearing or exudate, but is simply cytokine mediated vessel dilatation. A slit lamp examination may reveal anterior uveitis. Cracked, red lips (Fig. 9) are another common feature as is the “strawberry tongue,” which is due to the sloughing of the filiform papillae and persistence of the fungiform papillae giving the “strawberry” appearance. Unilateral lymphadenopathy is seen in only a minority of patients, and is a much less specific finding than the other findings discussed previously, such as the perineal desquamation.



**Fig. 9.** Cracked red lips characteristic of acute Kawasaki Disease. (Courtesy of Ilona J. Frieden, MD, San Francisco, CA.)

The etiology of KD is unknown. It is hypothesized that a yet unidentified infectious agent triggers an inappropriate immune response in a genetically susceptible individual. An infectious trigger is suspected due to the fact that the epidemiology of KD is associated with discrete seasonal peaks, geographic clustering, and clinical features suggestive of infection, such as the presence of fever, rash, and adenitis, as well as the fact that the age group affected reflects that in which childhood infections typically occur (ages 6 months to 4 years). Yet, a single infectious agent has not been reliably linked with onset of KD. Recent studies have suggested the possibility that a novel human coronavirus, the “New Haven coronavirus,” is the trigger [45]. However, this hypothesis has since been refuted. Shimizu and colleagues [46] assessed for the presence of this virus in the respiratory tracts of a geographically and ethnically diverse population of patients. They found that only 2% (1 of 48 patients) with acute KD had evidence of infection with the human coronavirus.

Genetic predisposition also seems to play an important role in susceptibility to developing KD as demonstrated by the markedly increased incidence of the disease in Asian versus European populations. Siblings of affected children have a 10-fold to 15-fold higher incidence of KD than the general population (in Japan) [47]. Several researchers are actively seeking to identify specific genetic polymorphisms and susceptibility loci, because identification of these may provide a better understanding of the role specific mediators play in etiopathogenesis of KD, which could in turn improve diagnosis and treatment of this disease.

The former and recently revised diagnostic criteria for KD are outlined in Table 2 [48]. Traditionally, to meet criteria for diagnosis, a child was required to have a fever for at least 5 days. Now, because clinicians are making the diagnosis of KD more rapidly, cases with 4 or even fewer febrile days shortened by early IVIG therapy have been proposed to be equivalent to cases with 5 or more febrile days. The criteria have also been revised, keeping in mind that the presence of cervical lymphadenopathy is less common than the other clinical

**Table 2**

Diagnostic criteria for Kawasaki disease: former criteria and revised criteria

Former criteria	Revised criteria (5/6 of items needed for diagnosis) <sup>a</sup>
Fever $\geq 5$ days + at least four of the following	Fever may be $< 5$ days if shortened by treatment
Polymorphous Exanthem	Bilateral nonpurulent conjunctivitis
Bilateral nonpurulent conjunctivitis	Mucous membrane changes
Mucous membrane changes	Polymorphous exanthem
Nonpurulent cervical lymphadenopathy	Extremity changes
Extremity changes	Acute nonpurulent cervical lymphadenopathy

<sup>a</sup>For cases with coronary artery complication, only 4/6 items are needed for diagnosis.

Data from Ayusawa M, Sonobe T, Uemura S, et al. Kawasaki Disease Research Committee. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr Int* 2005;47:232-4.

findings are (seen in only half of cases.) Therefore, cervical lymphadenopathy has been placed further down on the list, reflecting its lower frequency [48]. “Incomplete” KD should be used to describe patients with fever and at least two of the clinical criteria for KD as well as laboratory data reflecting systemic inflammation such as elevated white blood cell count, ESR, C-reactive protein, and low hemoglobin [49]. Incomplete disease is particularly problematic because it is poorly recognized, causing patients to be at risk for coronary complications. This atypical presentation is more common in young infants less than 3 months of age and older children.

The most-feared complication of KD is the development of coronary artery lesions, which occur in up to 30% of untreated and five percent of treated patients [50]. The timely diagnosis of KD is essential in preventing the coronary artery damage, and treatment that is initiated after 10 days of illness is associated with a higher incidence of coronary complications and poorer outcomes. Approximately 2% of those with coronary artery lesions experience myocardial infarction [51].

The current standard of care for those who meet KD criteria is IVIG, 2 g/kg given over 12 hours, and aspirin, 80 to 100 mg/kg/d divided into four doses. The duration of high-dose aspirin therapy varies from center to center, but most institutions treat with high-dose aspirin until the child has been afebrile for 48 to 72 hours. Then, if there are no coronary complications, the dose is reduced to an antiplatelet dose of 3 to 5 mg/kg/d until the ESR and platelet counts normalize [52]. Some have reported the effectiveness of the addition of steroids and methotrexate to this therapy [53,54]. More recently, Burns and colleagues [55] reported promising results with the use of infliximab for a series of patients with refractory KD who failed to become afebrile with conventional therapy. Most of these patients responded rapidly and completely to a single infusion of infliximab, and no infusion reactions or other major adverse events were reported.

## HENONCH SCHÖNLEIN PURPURA

The most common self-limited, multisystem vasculitis that is seen almost exclusively in childhood is Henoch Schönlein purpura (HSP), which consists of the classic tetrad of nonthrombocytopenic palpable purpura, abdominal pain, arthritis, and nephritis. HSP affects boys slightly more often than girls, with an M:F ratio of approximately 1.8:1 [56]. It typically occurs in children between the ages of 5 and 15 years but rarely can be seen in infancy and adulthood as well.

The characteristic cutaneous feature of HSP is palpable purpura, which is most often located on the lower extremities and buttocks (Fig. 10). However, the purpura can also involve the upper extremities and face occasionally. Purpura is present in almost 100% of cases of HSP at some point during the course of disease. Yet, in approximately one quarter of cases, skin lesions are not observed on initial presentation [56]. Edema is another cutaneous feature of HSP, and scrotal edema can occur in up to 13% to 35% of cases in males due to vasculitis of scrotal blood vessels [56].

The abdominal pain of HSP is most often colicky pain with associated vomiting and/or bloody stools. In a subset of patients, HSP can be complicated by intussusception, which is usually ileoileal in location rather than the more typical ileocolic location. Gastrointestinal symptoms and arthritis may precede the rash of HSP by 1 to 2 weeks, but it is rare for nephritis to precede the skin manifestations. Reports of the incidence of renal involvement in HSP vary and range from 10% to 60%. However, larger clinical studies indicate that renal disease occurs in about half of children with HSP [57]. Most of these children have mild abnormalities such as mild proteinuria and/or microscopic hematuria with normal renal function. Severe nephropathy occurs in up to 7% of childhood cases of HSP [56], whereas the incidence and morbidity of renal involvement is much higher in adults, resulting in a poorer prognosis for adult cases overall.

Most children recover within 3 to 6 weeks, but relapses are not uncommon. Approximately 30% to 40% of children will relapse, often during the first 12 months after onset of disease. Some children will relapse more than once. Poorer prognosis is associated with significant renal involvement, and factors



**Fig. 10.** Palpable purpuric lesions on the lower extremities of a teenaged boy with Henoch Schönlein Purpura.

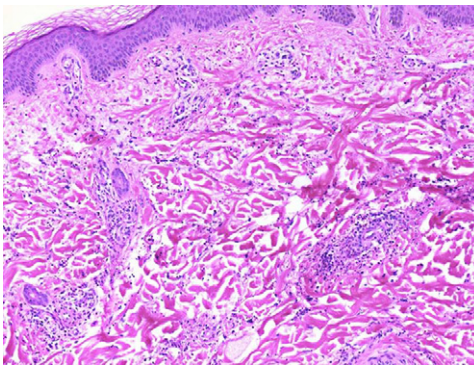
predictive of this include: the presence of severe abdominal pain with gastrointestinal bleeding, persistent purpura for a period longer than 1 month, and older age at onset of disease (over 4 years of age) [57].

The pathogenesis of HSP is unknown. Many antigens, including infections, vaccines, drugs, foods, and insect bites, have been reported to trigger HSP, and the disease is characterized by the deposition of immunoglobulin, immune complexes, and complement components in vessel walls. Histopathology from skin lesions of HSP shows leukocytoclastic vasculitis, characterized by dense infiltrates of neutrophils and nuclear dust around blood vessels, which contain fibrin within their walls (Fig. 11). On direct immunofluorescence, immunoglobulin A (IgA) deposition can be detected in the cutaneous vessel walls in approximately 75% of cases [58]. This presence of IgA is highly suggestive of the diagnosis of HSP as it can also be detected in small-vessel walls of intestinal and renal tissue in the setting of HSP.

Because it is a self-limited disease, treatment for HSP is not always necessary. Supportive care with nonsteroidal anti-inflammatory medications, rest, and pain relief is usually sufficient. However, systemic corticosteroids are also used, and their role in the management of HSP is controversial [59].

### ACUTE HEMORRHAGIC EDEMA OF INFANCY

Among the self-limited cutaneous vasculitides that occur in childhood is also acute hemorrhagic edema of infancy (AHEI), a rare but benign variant of leukocytoclastic vasculitis that occurs in children up to 2 years of age. AHEI is likely along the spectrum of HSP, but because of clinical and prognostic differences, it is sometimes regarded as a separate entity [60]. By definition, there is lack of visceral involvement in AHEI, although this is not absolute, as there are rare reports of systemic involvement, including reported cases of gastrointestinal vasculitis and one case of associated intussusception. Also in the literature



**Fig. 11.** Characteristic histopathologic findings of Henoch Schönlein Purpura: leukocytoclastic vasculitis consisting of neutrophilic infiltrates and nuclear dust around blood vessels, which contain fibrin within their walls.

are cases of transitory renal problems with microscopic hematuria or mild proteinuria associated with AHEI, all with spontaneous recovery [61].

The cutaneous findings in AHEI are quite similar to those seen in HSP except that the distribution of skin lesions differs. In AHEI, there is edema and large purpuric or target-like lesions observed on the face, auricles, scrotum, and extremities, often sparing the trunk (Fig. 12). Occasionally, lesions can develop dusky centers and become necrotic or even bullous. Another factor that distinguishes AHEI from HSP is that although histopathology of AHEI shows leukocytoclastic vasculitis, deposition of IgA in dermal blood vessels is not a constant feature. Deposition of IgA is observed in only 30% of cases of AHEI, whereas deposition of IgM is more common (seen in 80% of cases) [62].

Associated complications in AHEI are rare. Although it is difficult in this age group to discern whether joint pain is present, some sources report associated arthralgias in approximately half of patients [63]. Patients may have elevated ESRs, leukocytosis, thrombocytosis, and eosinophilia, but the remainder of the laboratory workup, including urinalysis and stool for guaiac, are usually within normal limits. AHEI resolves within 2 to 3 weeks without any treatment. However, if the skin manifestations are severe or if there is evidence of articular or cartilage compromise (as with involvement of the auricle), therapy with oral corticosteroids may be instituted.

### CASE 5

A 15-month-old boy is brought for evaluation of a recurrent eruption of urticarial plaques that began early in infancy (Fig. 13). The parents report that the skin lesions appeared when he was a newborn and have waxed and waned



**Fig. 12.** Palpable purpuric and dusky “target-like” skin lesions on the limbs of a 20-month-old with acute hemorrhagic edema of infancy. (Courtesy of Jeffrey L. Sugarman, MD, PhD, Santa Rosa, CA.)



**Fig. 13.** Case 5: 15-month-old boy with a recurrent urticarial eruption that began in the neonatal period. (Courtesy of Ilona J. Frieden, MD, San Francisco, CA.)

since, without any discernable precipitating factor. The eruption does not seem particularly pruritic. On further history, the parents describe recurrent fevers of unknown etiology and that he is “small for his age.”

### **NEONATAL-ONSET MULTISYSTEM INFLAMMATORY DISORDER**

This case illustrates several of the findings associated with neonatal-onset multisystem inflammatory disorder (NOMID), also called chronic infantile neurologic, cutaneous, and articular syndrome, which is a rare, congenital auto-inflammatory disorder that is characterized by chronic, systemic inflammation. The cutaneous findings of NOMID include the above-mentioned recurrent evanescent urticarial eruption that begins in the neonatal period. The skin rash occurs in all patients with NOMID and persists throughout their lives [64,65].

Extracutaneous features of NOMID include recurrent fevers and neutrophilia, joint manifestations, ophthalmologic complications such as uveitis and papilledema, and central nervous system involvement, including chronic aseptic meningitis, cerebral atrophy, developmental delay, and mental retardation. The ophthalmologic and central nervous system involvement is progressive, and often leads to vision and hearing loss. Joint symptoms may range in severity from mild arthralgias to a chronic deforming arthropathy, which can present as symmetric patellar overgrowth and epiphyseal and metaphyseal abnormalities. Patients also often experience growth retardation, likely due to chronic ongoing inflammation. Neutrophils are the predominant inflammatory cell in this disorder, and polymorphonuclear cell infiltrates can be found in multiple target organs, including the skin. Cutaneous histopathology reveals

perivascular neutrophils and sometimes neutrophilic eccrine hidradenitis [64,65].

NOMID is considered to be an *autoinflammatory* disorder rather than an *autoimmune* disorder. Autoinflammatory disorders lack the high-titer autoantibodies and antigen-specific T-cell self-reactivity that is characteristic of the autoimmune disorders [66]. Other conditions that are classified in this category include Familial Cold Autoinflammatory Syndrome and Muckle-Wells syndrome. Mutations in *CIAS1* have been demonstrated in many but not all patients with these conditions and in approximately half of NOMID cases. *CIAS1* is the gene that encodes cryopyrin, which is involved in the regulation of apoptosis and inflammation. Given that cryopyrin is specifically involved in the processing of IL-1 $\beta$ , the therapy for NOMID that has been associated with the greatest success is anakinra, which is an IL-1 receptor antagonist. NOMID patients who have been treated with anakinra have been reported to demonstrate rapid improvement in clinical symptoms and laboratory markers of inflammation [64]. Without proper treatment, however, prognosis is poor, given that this is a genetically inherited condition that does not remit on its own.

## CASE 6

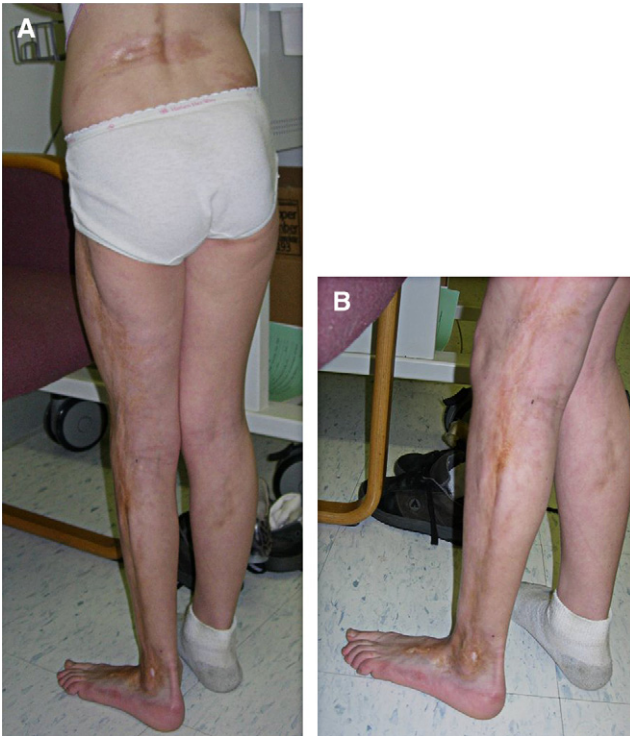
A 9-year-old girl presents with an insidious onset of “bruise-like” lesions appearing along her right leg. Her parents cannot recall when they first noticed the skin changes, but they have been present for at least 1 year and seem to be progressing. She is otherwise healthy, and her family history is negative for autoimmune disease. She denies any difficulty swallowing or respiratory problems. Her only complaint is of occasional bilateral knee and ankle pain. On examination, the child has a linear area of hyperpigmented and sclerotic skin extending from her right lower back and hip, along the lateral aspect of her right leg, onto her right dorsal foot (Fig. 14A and B).

## JUVENILE LOCALIZED SCLERODERMA

This case demonstrates a classic presentation of a child with linear scleroderma, which is a form of juvenile localized scleroderma (JLS). It often takes months to years before patients with localized scleroderma are diagnosed due to the insidious nature of the disease. Also, these patients do *not* present with symptoms of systemic sclerosis, as they are not at risk for developing systemic scleroderma. However, other extracutaneous manifestations can be a feature in JLS.

Overall, scleroderma in adults and children can be subdivided into three distinct entities: localized, limited (or Calcinus cutis, Raynaud’s, esophageal dysfunction, sclerodactyly, and telangiectasia [CREST] syndrome), and systemic scleroderma. These conditions do not overlap, in that patients with one form rarely, if ever, evolve into another form. Systemic sclerosis in childhood is quite uncommon, accounting for less than 3% of all cases of systemic scleroderma, and limited scleroderma is also exceedingly rare. Localized scleroderma is the most common form of scleroderma that is seen in childhood, and the subtype of localized scleroderma that is associated with the greatest morbidity,





**Fig. 14.** (A) Case 6: 9-year-old girl with a linear area of hyperpigmented and sclerotic skin extending from her right lower back and hip, along the lateral aspect of her right leg, onto her right dorsal foot. (B) Case 6: close-up view of the linear depressed band of sclerotic and hyperpigmented tissue on the right leg of a 9-year-old girl.

namely linear scleroderma, is more common in children versus adults. Approximately two thirds of all cases of linear scleroderma are diagnosed before the age of 19 [67–69].

The natural history of localized scleroderma is that it “burns out” after an average of 3 to 5 years. However, when localized scleroderma, especially the linear subtype, involves deep tissues such as the muscle and bone, functional disabilities, and disfigurement can ensue. If linear scleroderma involves the face, it is called *en coup de sabre* when it involves the forehead (Fig. 15) and Parry Romberg Syndrome (PRS) or *progressive hemifacial atrophy* when it involves the lower half of the face (Fig. 16). Facial involvement is particularly problematic not only because it can produce facial deformity, but also because it can also be associated with dental, ophthalmologic, and central nervous system complications.

Zulian and colleagues [70] recently reported that 22% of patients with JLS manifest one or more extracutaneous features, based on the largest cohort analysis to date of 750 patients. The most common extracutaneous finding was arthritis, which was seen in 12% of children with JLS. Of these, most had linear



**Fig. 15.** Linear depression on the forehead of an 11-year-old boy with a previous history of sclerotic skin in that area consistent with *en coup de sabre*.

scleroderma, and 30% were rheumatoid factor positive. Interestingly, the location of the arthritis was *unrelated* to the site of skin involvement in one fourth of these patients.

Neurologic and ophthalmologic involvement are known to be more common in patients with linear scleroderma that involves the face. Neurologic complications can include seizures, facial palsy, and headaches (including migraines). When imaging studies and brain histopathology are performed in these



**Fig. 16.** Five-year-old girl with a 3-year history of progressive hemiatrophy of her right face consistent with Parry Romberg Syndrome.

patients, nonspecific white matter abnormalities, intraparenchymal calcification, chronic localized meningoencephalitis, intracranial vascular malformations, and aneurysms are reported [71]. The most common ophthalmologic complication of facial linear scleroderma is progressive enophthalmous secondary to atrophy of orbital fatty tissue [72], but other reported complications include oculomotor nerve palsy, retinal vasculitis, uveitis, and iridocyclitis.

Monitoring disease activity in localized scleroderma is exceedingly difficult, as there are no consistent markers or serologies available for determining disease activity. Currently, many providers rely on palpation of the skin (the “feel” test) and serial digital Mega Hertz photography, which can be useful in detecting subtle progression of skin lesions. Research using imaging modalities has explored the use of 13-mH ultrasound, which detects the thickness of skin lesions but is more useful in making the diagnosis of localized scleroderma rather than monitoring for disease activity [73]. Infrared thermography appears to be quite promising for this purpose, in that it can successfully detect evidence of disease activity. However, it is limited by high false positive rates for clinically inactive skin lesions on areas such as the face, where there is minimal subcutaneous tissue [74].

Management of JLS depends on the severity of disease and degree of potential for disfigurement or functional disability. For nonfacial, well-localized, plaque-type skin lesions, observation is appropriate with the possible addition of superpotent topical steroids and/or topical calcipotriene, which has been demonstrated to soften skin lesions especially when used under occlusion [75].

Intermediate-level intervention includes the use of oral minocycline, hydroxychloroquine, and UV light. UV light improves skin lesions for both localized and systemic scleroderma patients through several mechanisms. For one, UV upregulates matrix metalloproteinases and collagenase, which promote collagen breakdown. UV also causes depletion of skin-infiltrating T-lymphocytes and pro-inflammatory cytokines. UVA1 is the preferred wavelength for treatment of scleroderma, and has been demonstrated in Europe to be quite efficacious in softening skin lesions [76,77]. This is because, compared to other wavelengths, it penetrates more deeply into the dermis and is less well absorbed by melanin [78]. However, this therapy is not widely available in the United States, and therefore, providers must rely on psoralen plus UVA (PUVA) or UVB, which are less successful in inducing collagenase activity. Encouraging results were reported in a recent study, which demonstrated that although medium-dose UVA1 was significantly more effective in softening skin lesions of localized scleroderma, narrow-band UVB (NB UVB) produced remarkable improvement in skin lesions as well [79]. The fact that NB UVB, like UVA1, penetrates more deeply into the dermis than other wavelengths (such as broadband UVB) further explains the efficacy of this more widely available treatment option for localized scleroderma.

Aggressive management of JLS includes the use of D-Penicillamine, oral calcitriol, and methotrexate in combination with corticosteroids, which is becoming the therapy of choice for most pediatric rheumatologists and pediatric dermatologists for severe, progressive, disfiguring JLS. Uziel and colleagues

[80] published the original case series using methotrexate and pulsed IV methylprednisolone in 10 JLS patients and demonstrated a 90% response rate. Subsequently, further evidence for the efficacy of this regimen in pediatric patients has been reported by two groups in Europe [81,82], and it is now becoming the treatment of choice for patients with severe disease that threatens function or disfigurement.

Other treatment modalities include physical therapy techniques both for improving range of motion of affected limbs as well as stretching exercises for contractures. Finally, for skin lesions that have not demonstrated evidence of disease activity in more than 2 years, plastic surgery reconstructive techniques [83] can be employed to improve the appearance of the “burned out” skin lesions.

## SUMMARY

Several systemic disorders of childhood are characterized by cutaneous stigmata, and these skin signs can serve as important diagnostic clues. Many of the systemic illnesses that are seen in both the pediatric and adult populations often manifest in different ways with respect to their cutaneous features. Also, there are conditions that uniquely present in childhood, such as KD, HSP, acute hemorrhagic edema of infancy, and NOMID. Early recognition of these disorders is important for initiation of appropriate therapy and prevention of adverse outcomes.

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