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19

Inflammatory and Purpuric Eruptions

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This group of eruptions is composed of lesions of variable morphology and diverse etiology. However, all have erythema as a common feature, a reflection of their inflammatory nature. Several disorders appear to represent hypersensitivity reactions, but for most the etiologic agents are unknown. The differential diagnosis of purpura is extensive in neonates, and includes hematological disorders, infections, trauma, and iatrogenic disorders.

ANNULAR ERYTHEMAS

Annular erythema is a descriptive term that encompasses several entities of unknown etiology characterized by circinate polycyclic lesions that extend peripherally from a central focus.[1,2] Because of subtle differences in clinical features, age of onset, duration of individual lesions, and total duration of the eruptions, a variety of descriptive terms have been coined for these disorders (Table 19-1). For prognostic reasons, it is useful to subdivide annular erythemas into transient and persistent forms.[3] Transient forms include annular erythema of infancy and the less well-established entity erythema gyratum atrophicans transient neonatale. Persistent annular erythemas include erythema annulare centrifugum, familial annular erythema, and erythema gyratum perstans. Other annular erythemas known to be a manifestation of well-defined diseases (e.g. neonatal lupus) or with distinctive clinical or histologic features (e.g. erythema multiforme, erythema chronicum migrans, erythema marginatum rheumaticum, and erythema gyratum repens) are not considered under this heading.

Annular Erythema of Infancy

Annular erythema of infancy is a benign disease of early infancy characterized by urticarial papules that enlarge peripherally, forming 2–3 cm rings or arcs with firm, raised, cord-like or urticarial borders.[4–6] Adjacent lesions become confluent, forming arcuate and polycyclic lesions (Fig. 19-1). Neither vesiculation nor scaling is present at the border. The eruption is asymptomatic. Individual lesions resolve spontaneously without a trace within several days, but new lesions continue to appear in a cyclical fashion until complete resolution within the first year of life. A few cases lasting for years have been described.[7–9]

The cause of annular erythema is unknown, and there are no associated systemic findings. Histologic studies reveal a superficial and deep, dense, perivascular infiltrate of mononuclear cells and eosinophils. No flame figures are observed. The epidermis is normal or mildly spongiotic.

Laboratory studies are normal. Peripheral eosinophilia does not accompany tissue eosinophilia. Immunoglobulin levels, including IgE levels, are normal. The differential diagnosis should include other annular lesions of infancy (see the following discussion). No treatment is warranted because of the self-limited nature of the eruption.

Erythema gyratum atrophicans transiens neonatale is a less well-defined entity,[10] characterized clinically by annular plaques with an erythematous border and an atrophic center. The lesions appear in the newborn period and resolve within the first year of life. Histologic findings include epidermal atrophy and a mild perivascular mononuclear infiltrate. Immunofluorescence studies reveal granular deposits of IgG, C3, and C4 at the dermoepidermal junction and around capillaries. Erythema gyratum atrophicans transiens neonatale possibly represents a variant of neonatal lupus erythematosus.[11]

Erythema Annulare Centrifugum

Erythema annulare centrifugum is a more persistent type of annular erythema that usually affects adults,[12] but may also occur in children and rarely in newborns.[3,13–16] The lesions are clinically somewhat similar to those of annular erythema of infancy, but scaling or vesiculation is seen at the border. The scales lag behind the advancing border, which, in contrast to annular erythema of infancy, is not indurated. Individual lesions resolve spontaneously after a few weeks, but new plaques continue to develop for years, or may be a lifelong condition. There is no associated pruritus.

Erythema gyratum perstans falls within the spectrum of erythema annulare centrifugum.[16–18] Some authors defend the distinctness of erythema gyratum perstans and consider distinctive features of this disorder to be its early onset, a duration of more than 15 years, the presence of slight to severe pruritus, and especially the presence of vesiculation.[16]

Erythema annulare centrifugum is thought to represent a hypersensitivity reaction to several trigger factors, including infectious agents (*Candida*,[19,20] Epstein–Barr virus,[14] and *Ascaris*[21]), drugs or foods,[22,23] and neoplasia, especially in adults. Intradermal injection of candidin or trichophytin may reproduce the clinical lesions.[13,24]

TABLE 19-1 Annular erythemas

	Age of onset	Clinical features	Duration of individual lesions	Duration of eruption	Healing	Histopathology
Transient Forms						
Annular erythema of infancy[4]	Early infancy	Annular plaques No scaling or vesiculation	Days	Transient (5–6 wk; cyclic course)	No residual lesions	Perivascular infiltrate of eosinophils
Persistent Forms						
Erythema annulare centrifugum[11]	Adulthood, newborn period possible	Mild scaling may be seen at borders	Weeks	Persistent (months or years, with new lesions developing continuously)	Residual hyperpigmentation	Superficial and deep perivascular cuff of lymphocytes
Familial annular erythema[22]	Early infancy to puberty Autosomal dominant	Possible vesiculation or scaling Geographic tongue may be associated Pruritus	Days	Persistent (lifelong, short remissions)	Transient hyperpigmentation	Superficial perivascular cuff of lymphocytes Spongiosis and parakeratosis
Erythema gyratum perstans[12]	Early infancy	Scaling, constant Vesiculation possible Central atrophy	Weeks	Persistent (lifelong)	Transient hyperpigmentation	Perivascular cuff of lymphocytes Spongiosis and parakeratosis

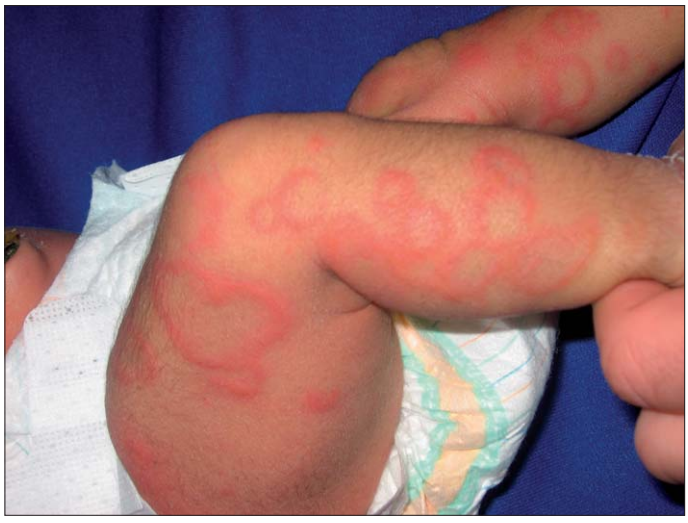


FIG. 19-1 Annular erythema of infancy: The eruption was congenital.

Histologic features consist of a dense, superficial, perivascular mononuclear infiltrate. Parakeratosis or epidermal spongiosis may be present. No therapy has been successful in all cases. Treatment agents include oral nystatin,[20] oral amphotericin B,[19] topical antifungals, antihistamines, disodium cromoglycate, and interferon-α.[13]

Familial Annular Erythema

Familial cases of annular erythema with autosomal dominant inheritance have been described.[25,26] The onset is in early infancy. Scaling, vesiculation, and pruritus may be more common than in erythema annular centrifugum. Lesions resolve with residual hyperpigmentation. Chronicity is the rule. Geographic tongue may be associated.[26]

Differential Diagnosis of Annular Erythemas

Differential diagnosis includes other eruptions with ringlike lesions, such as neonatal lupus, erythema multiforme, urticaria, urticarial lesions of pemphigoid, fungal infections, erythema chronicum migrans, and congenital Lyme disease.[7,27,28] Serum antibody determinations (antinuclear, SS-A, and SS-B) are recommended to exclude neonatal lupus.

NEONATAL LUPUS ERYTHEMATOSUS[29–36]

Neonatal lupus erythematosus (NLE) is a disease of newborns caused by maternally transmitted autoantibodies. The major manifestations are dermatologic and cardiac. Skin findings are transient. Cardiac disease, which is responsible for the morbidity and mortality of NLE, begins in utero and affects the cardiac conduction system permanently. Other findings include hepatic and hematologic abnormalities. Mothers of infants with neonatal lupus have anti-Ro/SS-A autoantibodies in 95% of cases. Anti-La/SS-B and anti-U1RNP autoantibodies have also been implicated in the pathogenesis of NLE in a minority of patients.[37,38]

Cutaneous Findings

Fifty per cent of infants with NLE have skin lesions, and congenital heart block is present in about 10%.[29,36] Lesions commonly develop at a few weeks of age but may be apparent at birth, which suggests that ultraviolet (UV) radiation is not essential for the development of skin lesions in NLE.[39] Clinically, skin lesions are analogous to those of subacute cutaneous lupus in its two variants: papulosquamous and annular. Papulosquamous lesions are more common and are

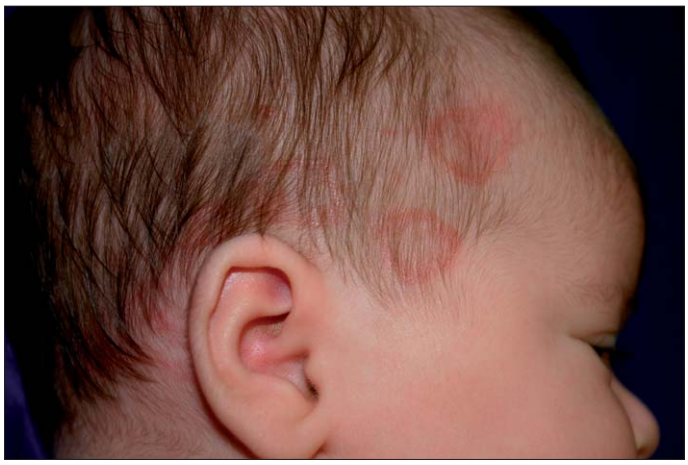


FIG. 19-2 Annular scaly plaques of neonatal lupus erythematosus resembling tinea corporis.

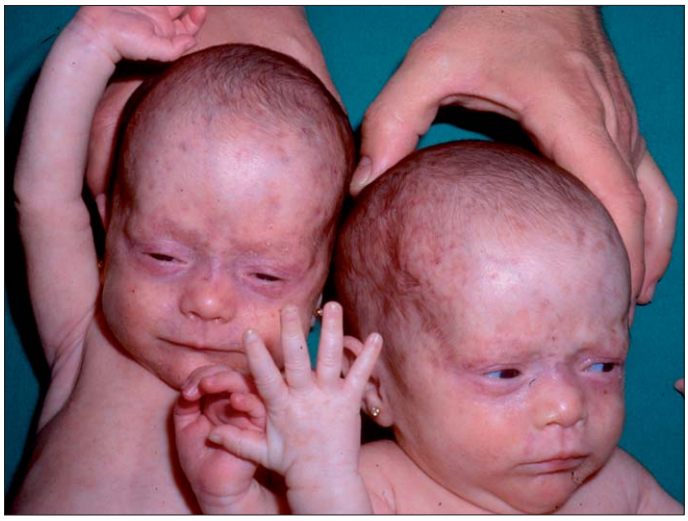


FIG. 19-3 Atrophic plaques and raccoon eyes on the faces of twins with neonatal lupus.

characterized by erythematous, nonindurated scaly plaques (Fig. 19-2). Sometimes the skin lesions have an atrophic appearance (Fig. 19-3). Ulcerations may be present.[40] In contrast to discoid lupus, scarring and follicular plugging are absent. The annular variant, which occurs almost exclusively in Japan, consists of annular, more inflammatory plaques.[41] Lupus profundus and generalized poikiloderma with erosions and patchy alopecia are rare manifestations.[42,43]

NLE lesions may be widespread but are most common on the face and scalp, predominantly affecting the periorbital and malar areas and often causing a 'raccoon eyes' appearance (Figs 19-3 and 19-4). The eruption is frequently precipitated or aggravated by sun exposure. Sun exposure is not strictly required, however, as the lesions may occur in sun-protected areas such as the diaper region, palms, and soles.[39,44,45] Skin lesions are transient and cease to appear around the age of 6 months, after the disappearance of maternal antibodies. Transient hypopigmentation and epidermal atrophy may result (Fig. 19-5).[36] Telangiectasia is a more permanent sequela. Telangiectasia also may be an initial sign of NLE, occurring without preceding identifiable inflammatory lesions; features of cutis marmorata telangiectatica congenita have been observed.[35,46] A case of NLE with a serological profile consistent with drug-induced lupus has been described in a newborn whose mother was treated with α-interferon during pregnancy.[47]

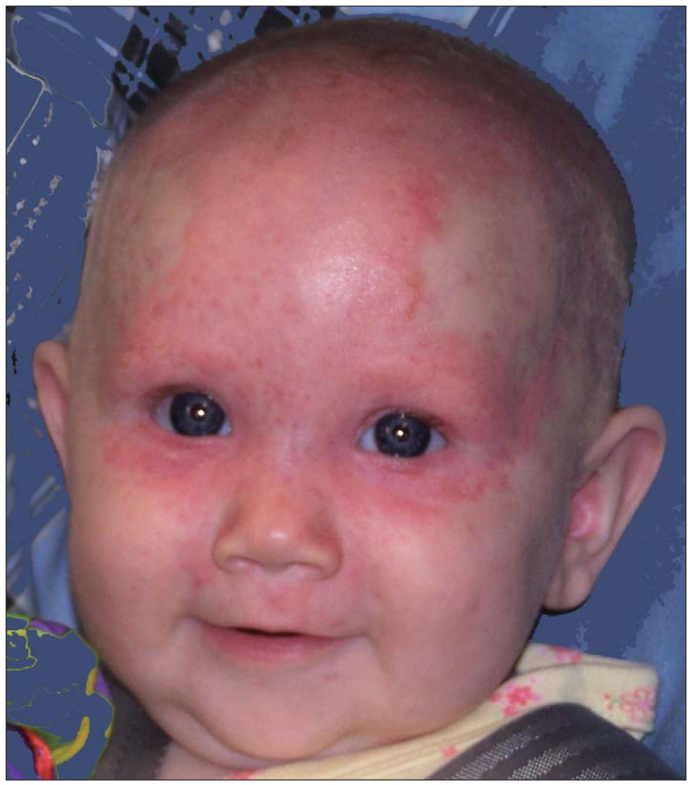


FIG. 19-4 'Raccoon eyes' and prominent facial erytnema in an infant with neonatal lupus (courtesy of Dr. Joseph Lam).

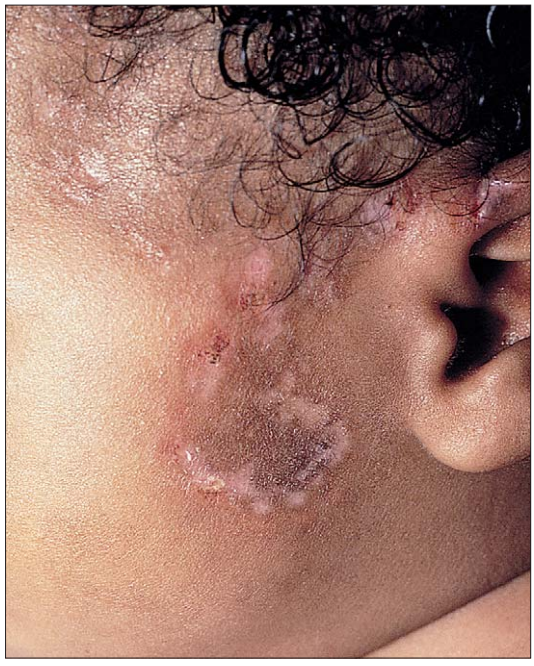


FIG. 19-5 Atrophy and pigmentary changes in an infant with neonatal lupus erythematosus. This boy also had congenital A-V block.

Extracutaneous Findings

The most significant manifestation is isolated complete congenital heart block. More than 90% of such cases are due to

NLE. Most patients have third-degree block, but progression from a second-degree block has been reported.[48] Heart block can often be detected as early as 20 weeks of gestation.

Transient liver disease, manifesting as hepatomegaly (with a picture of cholestasis) or elevation of liver enzymes,[35,49–51] and thrombocytopenia or other isolated cytopenias, may occur.[52] Petechiae and purpura have been described as presenting signs of NLE.[53] Less common findings include thrombosis associated with anticardiolipin antibodies, hypocalcemia, spastic paraparesis, pneumonitis, and transient myasthenia gravis.[54–56] Central nervous system (CNS) involvement has been reported in 10 of 11 consecutive infants with NLE, in the form of ultrasound and CT scan abnormalities which did not result in clinical neurological manifestations.[57] Such CNS involvement in NLE is probably a transient phenomenon.

Between 30% and 50% of mothers of infants with NLE have a connective tissue disease, most commonly SLE or Sjögren syndrome. Most, however, are asymptomatic. The risk for developing overt connective tissue disease in these mothers is highly debated, with estimates ranging from 2% to more than 70%.[36,58–63]

Etiology and Pathogenesis

It is universally agreed that placentally transmitted maternal IgG autoantibodies are necessary for the pathogenesis of NLE, but not sufficient.[64] The most commonly implicated autoantibodies have been anti-Ro/SS-A and anti-La/SS-B. More than 95% of NLE infants have anti-Ro antibody, and 60–80% have anti-La antibodies. A small subset of affected infants do not have detectable anti-Ro or anti-La antibodies, but instead have anti-U1RNP.[37,38] Mothers with high titers of anti-Ro and anti-La antibodies are at greater risk of delivering an infant with NLE. Despite initial observations based on immunoblot or ELISA testing that anti-52 kDa Ro antibodies conferred a higher risk of NLE than anti-60 kDa Ro antibodies, more precise testing with line immunoassay has revealed that antibodies to 60 kDa Ro are significantly more sensitive than antibodies to 52 kDa Ro and 48 kDa La.[65] Furthermore, comparing mothers of children with NLE with rash alone or with congenital heart block, there is no significant difference in the prevalence of any of the three antibodies between the two groups.[65] However, significantly more symptomatic mothers of children with congenital heart block have anti-La antibodies than do disease-matched mothers with unaffected children.[65] Moreover, the mean level of anti-La seems to be higher in mothers of infants with congenital heart block than in mothers of children with cutaneous NLE.[66]

It is not clear why only less than 5% of mothers with anti-Ro and anti-La antibodies give birth to affected children and why mothers of affected infants are often asymptomatic despite having the same antibodies. Furthermore, fraternal twins are often discordant for NLE, and NLE does not occur in every pregnancy. Genetic factors may be important for the development of NLE in children with maternal lupus antibodies. A link has been suggested between NLE rash and the allele HLA-DRB1*03, as well as a -308A polymorphism in the TNF-α gene.[34] Alternatively, maternal and/or sibling microchimerism may play an additional role, as levels of microchimerism have been reported to correlate with NLE disease activity.[67]

Laboratory Tests and Histopathology

Serologic studies for autoantibodies in the mother and infant demonstrate anti-Ro, anti-La, and/or anti-U1RNP antibodies. Anti-nDNA, anticardiolipin antibodies, antinuclear antibody, and rheumatoid factor may also be present. Anti-Sm antibody, highly specific for systemic lupus erythematosus, is not found in NLE. The maternal antibody titer is usually higher than the infant titer, which may even be negative if only immunodiffusion techniques are used. More sensitive methods, such as ELISA, immunoblotting, or line immunoassay, should be used in such instances. Skin biopsy, which is usually not necessary for diagnosis, shows changes characteristic of lupus erythematosus, that is, epidermal atrophy and vacuolization of the basal layer with a sparse lymphohistiocytic infiltrate at the dermoepidermal junction and in a periappendageal distribution. In many instances, histopathological features in children with NLE rash are subtle. Direct immunofluorescence is positive in 50% of cases, demonstrating granular deposits of IgG, C3, and IgM at the dermoepidermal junction. Histopathologic examination of the heart shows replacement of the atrioventricular node by fibrosis or fatty tissue. Endomyocardial fibroelastosis and patent ductus arteriosus may also be seen,[68,69] as well as deposits of IgG and complement.[70]

Differential Diagnosis

The differential diagnosis includes congenital rubella, cytomegalovirus infection, annular erythema of infancy, tinea corporis, and seborrheic dermatitis. Congenital syphilis should also be considered, but mucosal lesions are not a feature of NLE. False positive serologic tests for syphilis may occur in NLE. Telangiectasia and photosensitivity may suggest Bloom syndrome or Rothmund–Thomson syndrome. Serologic studies for autoantibodies in both infant and mother help to confirm the diagnosis. Skin biopsy for histologic and direct immunofluorescence studies is seldom necessary.

Course, Management, Treatment, and Prognosis

Neonates with suspected NLE should receive a complete physical examination, electrocardiogram, complete blood count with platelet count, and liver function tests (Box 19-1).

Skin lesions are transient. Treatment of skin disease consists of sun protection and the application of topical steroids. Pulsed dye laser therapy may be considered for residual telangiectasia. Congenital heart block is permanent. Half of newborns with complete congenital heart block require implantation of a pacemaker in the neonatal period.[32,61,71] The average

Box 19-1 Recommended evaluation of children with neonatal lupus erythematosus

- Clinical skin examination
- Complete clinical examination
- Skin biopsy (if clinical diagnosis not achieved)
- Full blood count (including platelets)
- Coagulation screen (including lupus anticoagulant and antiphospholipid antibodies)
- Serum chemistry (including liver function test)
- Autoantibody screening: antinuclear antibodies, anti-Ro, anti-La, anti-RNP
- Electrocardiogram and echocardiogram. Referral to pediatric cardiologist
- CNS ultrasound. Consider brain CT scan or MRI if clinical examination abnormal

mortality from complete congenital heart block in the neonatal period is 15%; another 10–20% die of pacemaker complications.[27,32] Late-onset cardiomyopathy may develop in a few infants.[72–74]

For mothers with anti-Ro or anti-La antibodies, the risk of delivering an infant with NLE is 1–20%, depending on whether they have asymptomatic or symptomatic SLE.[29,32] The risk of recurrence of congenital heart block in subsequent pregnancies may be as high as 25%.[61] Such pregnancies should be closely monitored, with repeated fetal echocardiograms.[75] If signs of intrauterine congestive heart failure are detected dexamethasone or plasmapheresis, or both, have been given.[32,76–79]

Although NLE is usually self-limited, SLE or other rheumatologic/autoimmune diseases may develop later in life in a small subset of patients.[62,80,81] The exact risk is unknown.

DRUG ERUPTIONS[82–85]

Cutaneous drug reactions are extremely rare in the neonatal period because the ability to generate a drug-induced immune response appears to be lower in infants.[86–88] Furthermore, most drug reactions require time for sensitization, which may range from 1 to 4 weeks or more, as well as re-exposure to the causative drug. Finally, newborns and young infants are less exposed to drugs than adults. Cutaneous adverse reactions to drugs may be classified according to the clinical characteristics of the eruption (Box 19-2). Whenever a suspect eruption is observed, a detailed history of medications should be obtained, including drugs administered to the mother, which may be present in breast milk. Morbilliform (Fig. 19-6) or maculopapular eruptions (Fig. 19-7) are the most frequent type of drug reaction in neonates, and antibiotics are commonly implicated (Fig. 19-8). Distinguishing a drug eruption from a viral exanthem is often difficult.

Box 19-2 Clinical patterns of cutaneous drug reactions

Maculopapular
Urticarial
Serum sickness–like
Hypersensitivity syndrome
Erythema multiforme
Toxic epidermal necrolysis
Fixed drug
Purpuric
Vasculitic
Lichenoid
Photo induced

EMLA cream, a local anesthetic that may be used with great frequency in neonatal units, has been noted to produce a localized purpuric eruption.[89,90] This type of reaction is seen preferentially in neonates, and subsequent applications of the cream do not always reproduce the purpuric lesions. Methemoglobinemia is another complication of EMLA use in this age group.[90] EMLA cream should therefore be used with caution in infants who are taking methemoglobin-inducing medications such as sulfonamides, acetaminophen, nitroglycerin, nitroprusside, and phenytoin, and particularly in those with a history of methemoglobinemia.

Vancomycin, an antibiotic frequently administered to premature newborn infants for *Staphylococcus epidermidis* nosocomial infections, may produce shock and rash in newborns

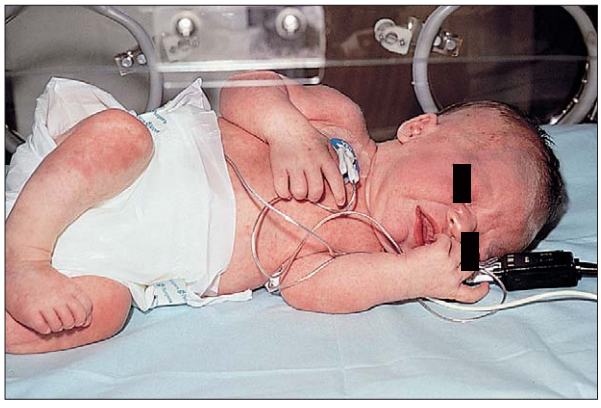


FIG. 19-6 Drug eruption resulting from procainamide.

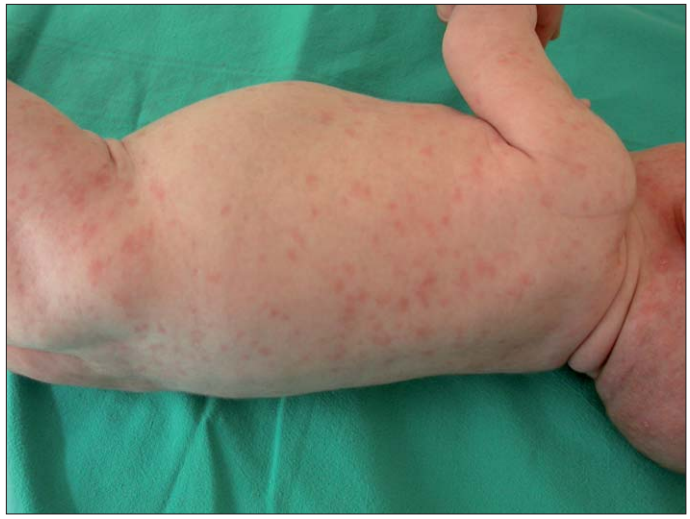


FIG. 19-7 Maculopapular eruption caused by diazoxide.

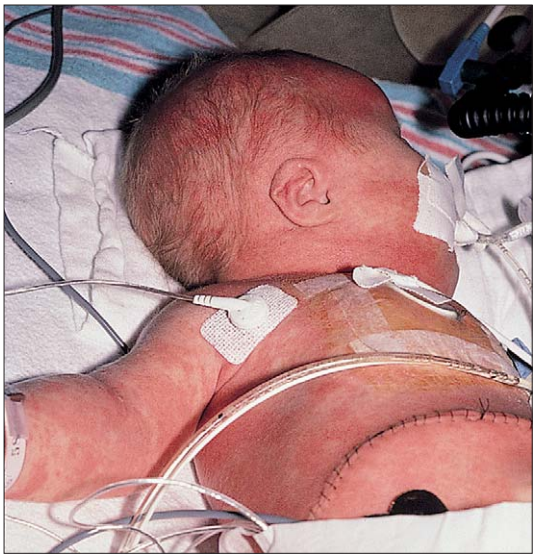


FIG. 19-8 Extensive erythematous eruption caused by a systemic antibiotic.

(red-baby syndrome).[91–93] This reaction is characterized by the appearance of an intense, macular, erythematous eruption on the neck, face, and upper trunk shortly after the infusion is completed. It may be accompanied by hypotension and shock. The reaction resolves rapidly in a matter of hours. It is frequently associated with rapid infusion; however, lengthening the infusion to more than 1 hour does not completely eliminate the risk.[92]

Newborns with AIDS have an increased susceptibility to drug reactions.[94,95] Reactions to trimethroprim/sulfamethoxazole in patients with HIV infections can be severe and life-threatening.[96]

Fixed drug reactions of the scrotum and penis, with erythema and edema resulting from hydroxyzine hydrochloride, have been described in early infancy.[97] However, hydroxyzine hydrochloride is administered infrequently in the neonatal period because of the risk of antimuscarinic effects, such as restlessness and excitation.

Serum sickness-like reaction is a type of drug reaction that occurs predominantly in children and has been reported in infants 5 months of age. [98] It is characterized by fever, an urticarial eruption, and arthralgias. Lymphadenopathy may be present. In contrast to true serum sickness, there are no immune complexes, vasculitis, or renal impairment. The most commonly implicated drug has been cefaclor.[98–100] This type of reaction may be seen in infants with an unknown or presumably viral etiology (Fig. 19-9)

Hypersensitivity syndrome reaction is a serious drug reaction characterized by fever, skin rash, lymphadenopathy, and internal organ involvement, especially of the liver.[101,102] The most commonly implicated drugs are anticonvulsants, and therefore it is not rare in children. A fatal case in a 3-month-old infant has been reported, as well as a case in a premature infant.[103,104]

Toxic epidermal necrolysis (TEN) is extremely rare in newborns. Cases of TEN in newborns have been related to antibiotics and phenobarbital.[105] All cases described so far proved fatal.

Vegetant bromoderma is a reaction to bromides characterized by coalescing papules and pustules which form vegetant inflammatory or pseudotumoral lesions. It usually affects the scalp, face, and legs. Most cases of vegetant bromoderma have been described in infants after the ingestion of syrups and solutions containing bromide, which has sedative and expectorant properties, or the spasmolytic agent scopolamine bromide.[106] The eruption ceases after withdrawal of bromide. The risk of systemic intoxication, known as bromism, makes it advisable to avoid bromide use in newborns and infants.

Other anectodal reports of toxicoderma in very young infants or newborns have been described, such as a papular eruption from G-CSF for collection of stem cells (Fig. 19-10),[107] a lichenoid reaction to ursodeoxycholic acid for neonatal hepatitis,[108] and a maculopapular rash from diazoxide used for neonatal hyperglycemia (see Fig. 19-7).

URTICARIA

Urticaria (hives) occurs frequently in childhood but is uncommon in children younger than 6 months and even rarer in the neonatal period.[82,109–117] Urticaria is usually sporadic; however, familial forms with autosomal dominant inheritance have been described for many of the physical urticarias, such as dermographism, heat urticaria, cold urticaria, and vibratory urticaria.

Urticaria can be divided into acute (lasting less than 6 weeks) and chronic (lasting more than 6 weeks) types. Nevertheless, this arbitrary division has prognostic and etiopathogenic significance. In infants, chronic urticaria is very rare.[111,118] Physical urticarias represent a special subgroup of urticaria in which wheals are elicited by different types of physical stimuli.[119] These include dermographism, cold, pressure, cholinergic, aquagenic, vibratory, and solar urticaria.

Cutaneous Findings

Urticaria is characterized by transient edematous pruritic wheals (Fig. 19-11). By definition, individual lesions last less than 24 hours. Hives may occur on the skin and mucous membranes. Angioedema or giant urticaria is a closely related entity in which there is swelling of the deep subcutaneous tissues and diffuse swelling of the eyelids, genitalia, lips, and tongue. It may be seen alone, or more often in association with 'common' urticaria. Urticaria in children has certain characteristic features. The hives tend to coalesce, forming bizarre polycyclic, serpiginous, or annular shapes (figurative urticaria, Fig. 19-12; or annular urticaria, Fig. 19-13), and may become hemorrhagic.[109,112] Edema is often pronounced

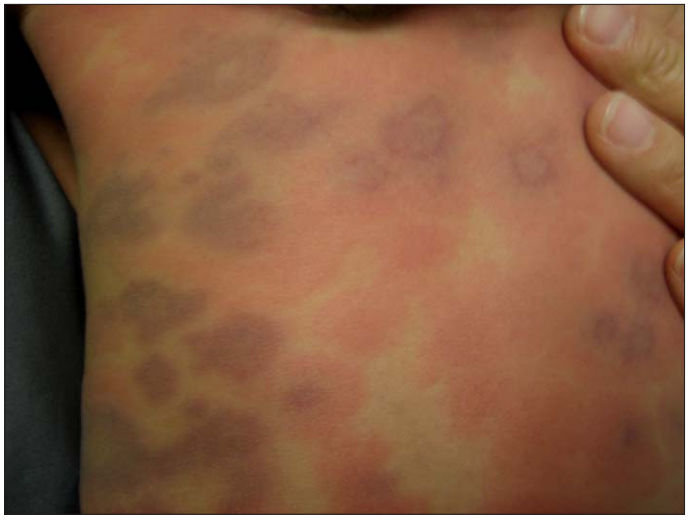


FIG. 19-9 Infant with serum sickness-like eruption.

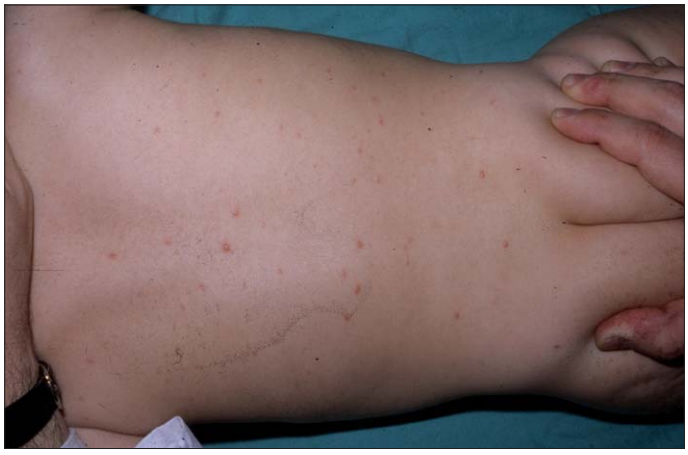


FIG. 19-10 Papulopustular eruption due to G-CSF.

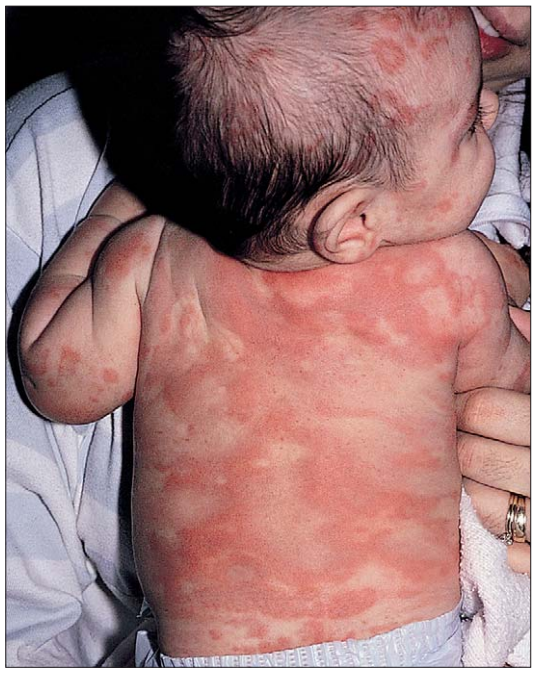


FIG. 19-11 Generalized urticaria following DPT and polio immunizations.

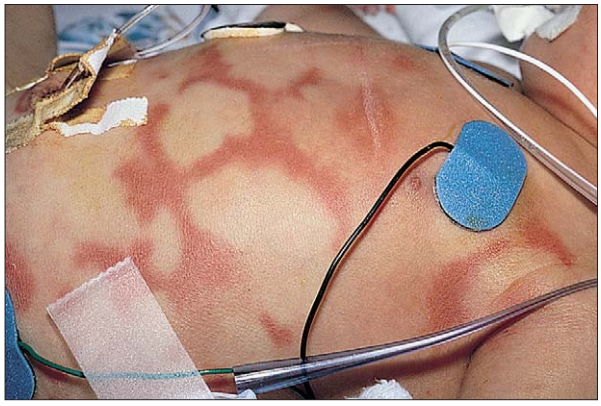


FIG. 19-12 Polycyclic lesions of urticaria associated with prostaglandin E_2 infusion.

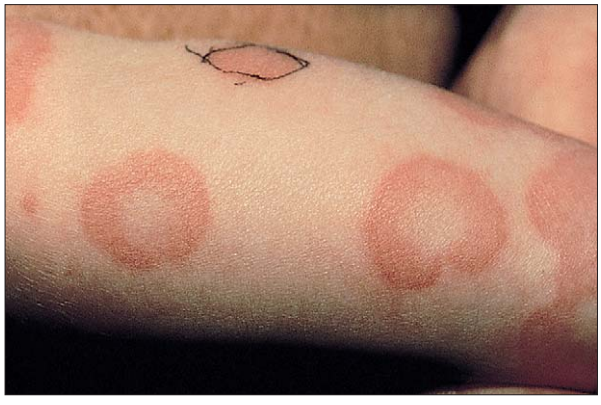


FIG. 19-13 Annular urticaria of unknown etiology.

and painful. These features confer a dramatic appearance to the eruption. in children the itching may be absent. Urticaria may be more common and recurrent in atopic patients.[112,115]

Extracutaneous Findings

Acute urticaria may be accompanied by signs of anaphylactic shock. In cases of angioedema, abdominal pain, diarrhea, vomiting, respiratory compromise, and joint pain may occur.

Etiology and Pathogenesis[82,113]

Urticaria develops as a result of an increased permeability of capillaries and small venules, which leads to leakage of fluid into the extravascular space. Mast cell activation and subsequent mediator release are responsible for these changes. Histamine is the best-known mediator. Many triggers (secretagogues) initiate mast cell degranulation through receptors on mast cell membranes, either via an IgE-dependent mechanism or through complement activation (immunologic secretagogues) or by acting directly without the need for receptors (nonimmunologic secretagogues).

The most common provocative agents in children are drugs, foods, and infections, which account for 40% of the cases of acute urticaria.[112,115,117] Antipyretics (primarily aspirin) and antibiotics (amoxicillin, macrolides, and oral cephalosporins) are the most frequently incriminated drugs. Food-related urticaria is associated with atopy.[112] Cow's milk allergy is one of the main causes of urticaria in infants, being present in 6–35% of cases of cow's milk intolerance.[116,120,121]

Diagnosis

The diagnosis of urticaria is made on clinical grounds. Histopathologic examination of a skin biopsy specimen shows vascular dilation, edema, and a perivascular inflammatory infiltrate composed of lymphohistiocytic cells, polymorphonuclear cells, and more specifically eosinophils. Neutrophils may predominate.

Laboratory tests are not usually necessary for the evaluation of acute urticaria. IgE levels can be elevated in some patients. An exhaustive search for an underlying cause not elicited by history alone is not warranted. An erythrocyte sedimentation rate may suffice as a screening test in cases of chronic urticaria because it is usually elevated in diseases associated with chronic urticaria (e.g. collagen vascular diseases). In 10–15% of patients no cause is identified. Intradermal skin tests to discover suspected allergens are not reliable.

Differential Diagnosis

Urticaria in infants is often misdiagnosed as erythema multiforme, acute hemorrhagic edema, annular erythema of infancy, or Kawasaki disease. In an infant with urticaria and dermographism the possibility of diffuse cutaneous mastocytosis without visible cutaneous lesions should also be considered.[122] NOMID/CINCA (see below) should be considered in young infant with urticaria. The predominance of neutrophils in skin biopsies of children with NOMID may help in the differential diagnosis, although it is not 100% specific. In case of doubt, genetic testic for NOMID is now available.

Course, Management, Treatment, and Prognosis

Despite its alarming symptoms, urticaria in early infancy is usually benign. Exceptions are chronic infantile neurological cutaneous and articular syndrome (CINCA) (see below) and

the inherited physical urticarias, which may have a lifelong course. If medication is required, antihistamines such as diphenhydramine or hydroxyzine are the mainstay of therapy. However, newborns have an increased susceptibility to antimuscarinic side effects, such as central nervous system (CNS) excitation causing convulsions. Systemic corticosteroids should be reserved for cases of intractable urticaria.

Familial Physical Urticarias

Autosomal dominant variants have been described for many of the physical urticarias. Although rare, these familial cases begin early in life, even immediately after birth, and have a lifelong course, usually with increased severity. The exact pathogenic mechanism for many of the physical urticarias is unknown.

Familial cold urticaria (FCU) is an autosomal dominant disorder characterized by the development of burning wheals, and frequently pain and swelling of joints, stiffness, chills, and even fever after exposure to cold, especially in combination with damp and windy weather.[123–126] The skin lesions appear on exposed areas and generalize afterwards. Leukocytosis may be present during the attacks. The reaction may be delayed for up to 6 hours after cold challenge. In contrast to acquired cold urticaria, the reaction cannot be elicited by an ice cube test: rather, the patient must be subjected to cold environmental temperatures or cold water immersion. On skin biopsy a neutrophilic infiltrate predominates. The symptoms tend to improve with age. Responses to H_1 and H_2 blockers and ketotifen are poor. Stanozolol has been of limited benefit.[127] FCU has also been described along with amyloidosis and deafness as Muckle–Wells syndrome (MWS).[128] It has been recently demonstrated that both FCU and MWS are due to mutations in the *CIAS1* (cryopyrin) gene: in fact they are the same disorder and may share exactly the same genetic mutation.[129] FCU and MWS are also allelic diseases with CINCA syndrome (see below), which is also due to *CIAS1* gene mutations.[130]

Familial dermographism (autosomal dominant) has been described in a single large family.[131] In neonates dermographism can also be a manifestation of 'silent' diffuse cutaneous mastocytosis.[122,132] Vibratory urticaria is an autosomal dominant physical urticaria in which wheals develop after repetitive vibratory stimulation or stretching.[133,134] The need for repetitive trauma differentiates it from dermographism. Familial aquagenic urticaria and familial heat urticaria usually have onset in childhood.[135–137]

CHRONIC INFANTILE NEUROLOGICAL CUTANEOUS AND ARTICULAR SYNDROME (CINCA)[138–141]

CINCA syndrome, also known as neonatal onset multisystemic inflammatory disease (NOMID), is a chronic systemic inflammatory disease of neonatal onset characterized by skin rash, arthropathy, and CNS manifestations. Cutaneous findings are the presenting signs. The disease follows a chronic course with acute febrile exacerbations, lymph node enlargement, and hepatosplenomegaly. Two-thirds of patients are born prematurely.

Cutaneous Findings

A skin eruption is usually the first manifestation of the disease and is present at birth or develops during the first 6 months of life. It is characterized by generalized, evanescent, urticarial macules and papules that migrate over the course of a single day and wax and wane in intensity (Fig. 19-14). The rash is persistent, although recrudescence of the skin lesions is noted at flare-ups. The lesions may be pruritic, especially after sun exposure, but are usually asymptomatic.[140,141] Geographic tongue and oral ulcers have been noted in a single patient.[141]

Extracutaneous Findings

Symmetric or asymmetric arthropathy is another constant finding and is severe in half of patients. It is often absent in the first few weeks of life, but usually develops during the first year.[140,142] The severity of the arthropathy correlates with an early onset of joint symptoms. The knees are most frequently affected, followed by the ankles and feet, elbows, wrists, and hands. Joint swelling and pain are more severe during febrile flare-ups. On palpation, a bony consistency is characteristic as a result of epiphyseal and growth cartilage involvement and overgrowth of the patellae. Joint contractures and severe deformities result.

Neurologic signs and symptoms such as headache, vomiting, and seizures develop at a variable age. Intellectual impairment is also common. Both spasticity and hypotonia have been described. Eye involvement is an inconstant finding. Papilledema with or without optic nerve atrophy is the most common feature. Other ocular manifestations include uveitis, keratitis, conjunctivitis, and chorioretinitis.[143] These changes may lead to complete blindness in adulthood. Progressive sensorineural hearing loss and hoarseness are also common.

Affected children have a characteristic phenotype. There is progressive growth retardation and increased head circumference with frontal bossing. Fontanel closure is retarded. Icterus may be present in the neonatal period, especially in patients with severe arthropathy.[140]

Etiology and Pathogenesis

Mutations in the *CIAS1* gene have been identified in 60% of patients with CINCA syndrome.[144,145] *CIAS1* encodes a protein called cryopyrin, which is involved in the regulation of apoptosis and the inflammatory signaling pathway.[145] It is proposed that familial cold urticaria and CINCA represent extreme groups of the same disease, defined by the magnitude of phenotypic expression.[145] Considerable clinical overlapping exists between these disorders.

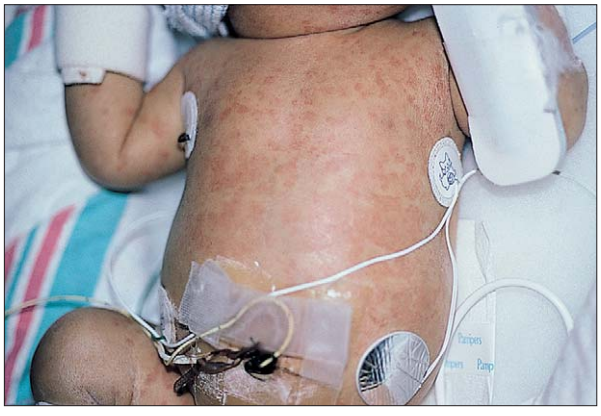


FIG. 19-14 Neonatal onset multisystemic inflammatory disease.

Laboratory Tests, Radiologic Findings, and Histopathology

Nonspecific findings typical of a chronic inflammatory process include microcytic anemia; leukocytosis with high neutrophil and eosinophil counts, elevated platelet counts, sedimentation rates, and acute-phase reactants; and polyclonal hyperglobulinemia G, A, or M. Rheumatoid factor and antinuclear antibodies are usually absent. Liver enzymes may be mildly elevated. CSF examination shows pleocytosis and high protein levels.

Radiologic studies of the affected joints show irregularly enlarged, bizarre, spiculated epiphyses with a grossly coarsened trabecular appearance.[140,142] There is periosteal new bone formation, and growth cartilage abnormalities are frequent. With time, there is bowing deformity of long bones and shortening of diaphyseal length. CT scans of the head have demonstrated hydrocephalus and cerebral atrophy.

Histopathologic examination of the skin reveals interstitial and perivascular neutrophilia.[141,142] Neutrophilic eccrine hidradenitis has been described.[141] Biopsies of lymph nodes, liver, and synovium show nonspecific signs of chronic inflammation.

Differential Diagnosis

NOMID must be differentiated from systemic onset juvenile arthritis. The main differences are its neonatal onset, persistent rash, the short duration of bouts of fever, absence of morning stiffness, and central nervous system involvement. The arthropathy is more deforming, and the radiographic findings of enlarged and disorganized epiphyses are distinctive. In addition, the response to NSAIDs is poor. Urticaria should also be considered and the predominance of eosinophils in skin biopsy may be a relative clue.

Course, Management, Treatment, and Prognosis

The disease follows a chronic course with acute febrile exacerbations. Occasionally it causes death in the first or second decade. Nonsteroidal anti-inflammatory drugs may be effective for pain relief but do not alter the course of the disease. Prednisone has been palliative in doses ranging from 0.5 to 2.0 mg/kg/day.[142] Chlorambucil and penicillamine have been tried, with limited success.[146,147] Thalidomide has shown beneficial effects in a single patient.[148] Other choices include methotrexate, the recombinant human IL-1 receptor antagonist anakinra,[149–152] and the anti-TNF-α agent etanercept.[153]

ERYTHEMA MULTIFORME

Erythema multiforme (EM) is an acute, self-limited disorder of skin and mucous membranes.[154–156] It has been considered a spectrum of disorders, designated EM minor, consisting of skin involvement only or of both the skin and the mouth, and as EM major (Stevens–Johnson syndrome; SJS), which involves at least two mucous membranes with variable cutaneous lesions. Some authors include toxic epidermal necrolysis within this spectrum as a severe form of SJS. Recent evidence suggests that EM and SJS have distinct clinical features and different precipitating factors, so perhaps the terms EM major and EM minor are best avoided.[157,158] EM is a common disease in children[155] but extremely unusual in the neonatal period.[94,155,159–162] Toxic epidermal necrolysis is discussed in Chapter 10.

Cutaneous Findings

The prototypic lesion of EM is a 1–3 cm erythematous, edematous papule that develops a dusky vesicular, purpuric, or necrotic center. A raised edematous ring of pallor surrounded by an erythematous outer ring is often present. These concentric color changes produce the typical target, or iris, lesion. In many cases only two zones are seen, with a single ring around the central papule (atypical target lesions). The lesions are distributed symmetrically and acrally on the extensor surface of the extremities. They may extend to the trunk, flexural surfaces, palms, and soles. In children, lesions on the face and ears are common, but are rare on the scalp[163] (Fig. 19-15).

In SJS, the lesions are more centrally located, predominating on the trunk. The targets are atypical and are usually flat. Individual lesions tend to coalesce in large patches. Areas of epidermal detachment may occur, but usually affect less than 10% of the body surface area. Mucosal lesions occur frequently in EM and are requisite for a diagnosis of SJS. Mucous membrane involvement is characterized by erythema or blisters that rapidly evolve to confluent erosions with pseudomembrane formation. The oral mucosa and conjunctiva are most commonly involved, but genital, anal, pharyngeal, and upper respiratory tract involvement may be seen. The number of mucous membranes involved has been considered one of the main distinguishing features of EM and SJS.

Extracutaneous Findings

Mild, nonspecific, prodromal symptoms of cough, rhinitis, and low-grade fever are occasionally present in EM. Fever, arthralgias, and prostration are common in SJS.

Etiology and Pathogenesis

EM has been considered a hypersensitivity phenomenon to multiple precipitating factors such as infectious agents or drugs. Three etiologic factors have been well documented: herpes simplex for erythema multiforme, and *Mycoplasma* infections and drugs for SJS. Herpes simplex (HSV-1 or HSV-2) is considered to be responsible for more than 80% of EM in children, even if clinical infection is inapparent.[164] HSV-associated EM follows the lesions of herpes by 1–3 weeks and is often recurrent. However, not every episode of recurrent herpes is followed by EM. HSV-specific DNA has been detected by polymerase chain reaction and in situ hybridization in lesional skin from a large number of children with EM, whether 'idiopathic' or clearly HSV related.[164]

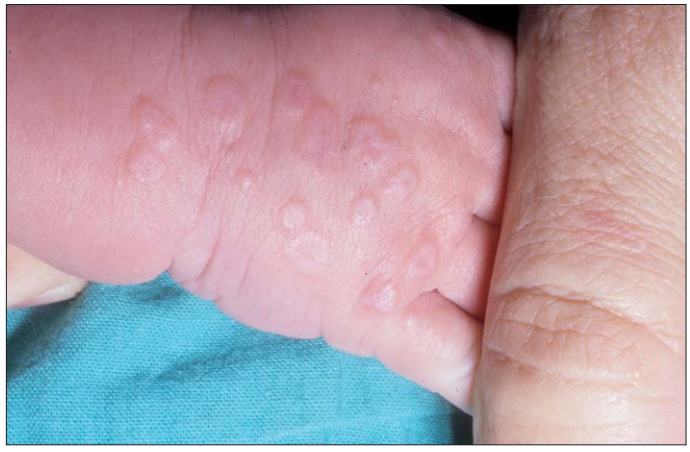


FIG. 19-15 Target lesions of erythema multiforme in a newborn.

Cow's milk intolerance has been described as a cause of erythema multiforme in a neonate.[159] Drugs are the most common cause of SJS. Sulfonamides, phenylbutazone, diphenylhydantoin, and penicillin derivatives are most frequently implicated.[163] Vaccinations were the only known possible causative agents in a newborn and two infants with erythema multiforme.[162,165]

Laboratory Tests and Histopathology

In cases of extensive involvement an elevated sedimentation rate, leukocytosis, and mild elevation of transaminases may be seen. Electrolyte imbalance and hypoproteinemia may be encountered in SJS. Eosinophilia may be seen in drug-related cases.

Histopathologic examination of early lesions reveals a lymphocytic band-like infiltrate at the dermoepidermal junction, with exocytosis and individual necrotic keratinocytes in close proximity to lymphocytes ('satellite cell necrosis'). There is vacuolization of the basal layer with focal cleft formation at the dermoepidermal junction. The upper dermis is edematous. Over time, more extensive confluent necrosis of the epidermis supervenes, resulting in subepidermal blister formation. In EM a lichenoid infiltrate predominates, whereas in SJS epidermal necrosis predominates.

Differential Diagnosis

In typical cases EM or SJS is rarely confused with other entities. Urticarial vasculitis may be considered in some cases. Kawasaki disease may produce target-like lesions; however, associated findings should allow differentiation. Serum sickness-like reactions often associated with the use of Cefaclor or other antibiotics, or even without any known etiology, can also produce targetoid lesions (see Fig. 19-9).

Course, Management, Treatment, and Prognosis

Erythema multiforme is usually self-limited. Individual lesions heal in 1–2 weeks, with residual hyperpigmentation. Conservative supportive care is the preferred form of treatment. Possible underlying causes should be sought. Treatment of underlying infection and discontinuation of nonessential drugs are indicated. Corticosteroids are unnecessary and may even worsen a concurrent infection.[166,167] In HSV-associated EM, early intervention or even prophylactic treatment with oral aciclovir may be beneficial.[168]

SJS has a less favorable prognosis, with a mortality rate of 5–15% if left untreated. The use of corticosteroids in SJS is more controversial.[166,167,169,170] No controlled study has proved their efficacy, and in some studies patients treated with corticosteroids have had a worse prognosis.[171] Corticosteroids may predispose to secondary infection while suppressing the signs of sepsis. Supportive care is extremely important.

SWEET SYNDROME

Sweet syndrome, or acute febrile neutrophilic dermatosis, is a benign disease characterized by tender, raised erythematous plaques, fever, peripheral leukocytosis, histologic findings of a dense dermal infiltrate of polymorphonuclear leukocytes, and a rapid response to systemic corticosteroids.[172–176] Only a few pediatric cases have been reported,[177–190] the youngest being 5 weeks of age.[180] Two brothers with Sweet syndrome starting at 2 weeks of life have been reported.[188]

Cutaneous Findings

The lesions of Sweet syndrome have an acute, explosive onset and are characterized by indurated, tender, erythematous plaques or nodules that vary in size from 0.5 to 4 cm (Fig. 19-16). Tiny pustules may appear at a later stage. The borders may be raised, mammillated, or even vesicular. Some of the lesions may show central clearing, forming annular or gyrate plaques (Fig. 19-17). The lesions are usually multiple and distributed over the face and extremities or, more rarely, the trunk. Without treatment, they tend to heal spontaneously

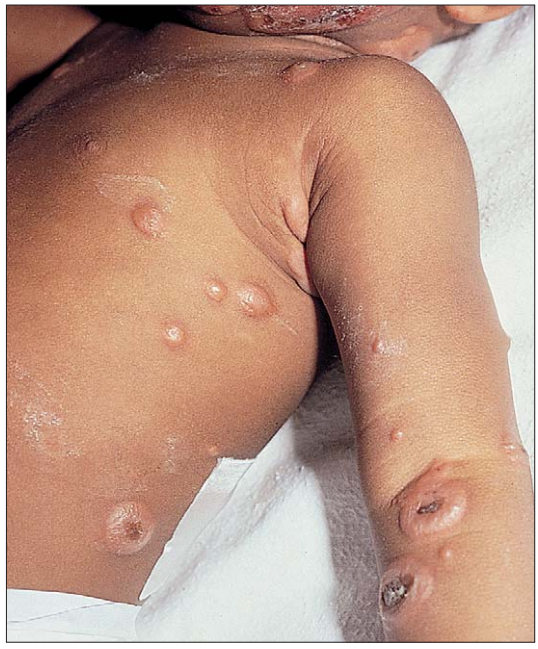


FIG. 19-16 Nodular lesions of Sweet syndrome with central crusting.

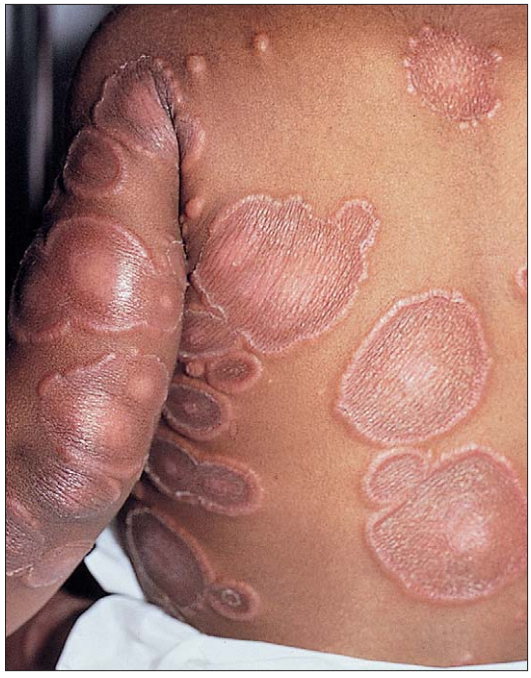


FIG. 19-17 Progression of lesions of Sweet syndrome in the same patient as in Figure 19-16. Plaques and nodules have flattened and are clearing centrally.

within a few months. In some patients, especially children, the lesions heal with areas of secondary cutis laxa, also known as Marshall syndrome.[179,189,191]

Extracutaneous Findings

A high, spiking fever is characteristic but may be absent in up to 50% of patients.[176] Arthralgias or asymmetric arthritis may be associated, and conjunctivitis or iridocyclitis may be seen in one-third of patients.[176] Renal involvement manifesting as proteinuria or hematuria, as well as lung involvement with infiltrates visible on chest radiographs, has also been described. Central nervous system involvement may occur in rare instances and manifest as headaches, convulsions, or disturbance of consciousness. Cerebrospinal fluid pleocytosis with lymphocyte predominance is usually found in such cases.[192]

Etiology and Pathogenesis

The pathogenesis is unknown. Many of the patients reported have had a preceding respiratory tract infection or elevated antistreptolysin O titers.[176] Ten per cent of the cases have been seen in the setting of a variety of hematologic malignancies, particularly acute myeloid and myelomonocytic leukemias.[193] Sweet syndrome has also been associated with solid tumors, inflammatory bowel disease, connective tissue diseases, and chronic granulomatous disease, or it may occur as an adverse reaction to drugs,[194–196] particularly granulocyte colony-stimulating factor[197] or after vaccination.[198] Because of these associations and the rapid response to systemic corticosteroids, Sweet syndrome is thought to represent a hypersensitivity reaction to infectious agents or tumoral antigens.

Laboratory Tests and Histopathology

An elevated erythrocyte sedimentation rate and peripheral leukocytosis are frequent accompanying abnormalities. Eosinophilia, microcytic anemia, mild elevation of liver enzymes, and urinalysis abnormalities may be present occasionally. Antineutrophil cytoplasmic antibodies have been detected in some cases.[176] α_1-Antitrypsin deficiency has been documented in one case of Marshall syndrome.[191]

The histopathologic findings are diagnostic.[173] There is a dense perivascular infiltrate composed almost entirely of neutrophils. The dermis appears edematous, and subepidermal blisters may form. Spongiosis, exocytosis, and intraepidermal vesiculation may be seen. There is endothelial swelling and nuclear dust, but true vasculitis is characteristically absent.

Differential Diagnosis

The lesions of Sweet syndrome may initially resemble those of EM or acute hemorrhagic edema. Lesions on the lower extremities may resemble those of erythema nodosum, but lesions more characteristic of Sweet syndrome are usually present in other locations.

Course, Management, Treatment, and Prognosis

Sweet syndrome is a benign disease but may be a marker of malignancy. If left untreated it resolves spontaneously over weeks to months. Recurrences are common. Marshall syndrome may have a poorer prognosis, with the development of elastolysis in the lungs or cardiovascular involvement.

Oral corticosteroids are the treatment of choice and usually elicit a prompt response.[199] Potassium iodide administration has been successful in a few cases,[200] as have colchicine,[201] dapsone,[202] clofazimine,[189] and intravenous immunoglobulin.[184]

KAWASAKI DISEASE

Kawasaki disease is an acute systemic vasculitis involving small and medium-sized muscular arteries, especially the coronary arteries, of young children. In the past, many cases were called infantile polyarteritis nodosa. The disease is characterized by fever lasting at least 5 days, nonpurulent conjunctivitis, a polymorphous exanthem, erythema and swelling of the hands and feet, inflammatory changes of the lips and oral cavity, and acute nonpurulent cervical adenopathy.[203–206] Coronary artery aneurysms or ectasia develop in 15–25% of untreated children and may lead to ischemic heart disease or sudden death.

Kawasaki disease occurs predominantly in children under 5 and has a peak incidence between 9 and 11 months.[207–209] It is infrequent before 6 months of age, although it has been reported in patients less than 2 weeks of age [210–212] Boys are affected 1.5 times as often as girls. Kawasaki disease is an endemic disease with epidemic and geographic clustering. There is seasonal predominance in late winter and spring, although this may differ in different countries.[213,214] It is most common in Japan, with an annual incidence of 112 cases per 100 000 children under 5, and is steadily increasing.[215,216] Familial cases in household contacts have been described.[217] The recurrence rate is 3%, with some patients having two or more recurrences.

Cutaneous Findings[205,218]

The skin is involved in 99% of patients. The first sign often consists of diffuse erythema and painful induration of the hands and feet. Between 1 and 3 weeks after disease onset the eruption characteristically begins to desquamate beneath the distal nail plates, and peeling may extend to involve the entire palm and sole. Horizontal depressions in the nail plates (Beau's lines) usually result.

A polymorphous exanthem on the trunk and proximal extremities usually appears within 5 days of onset of fever (Fig. 19-18). It is a nonspecific, diffuse maculopapular or

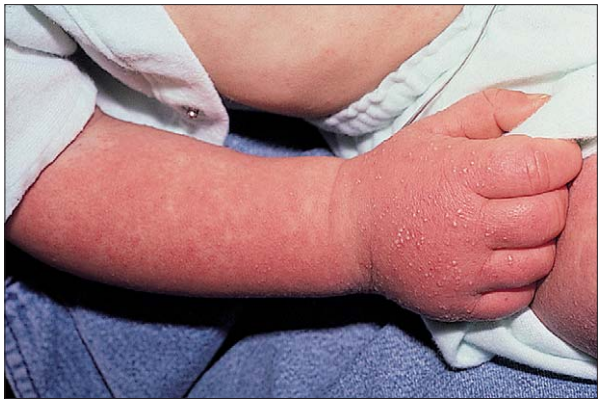


FIG. 19-18 Morbiliform eruption in an infant with Kawasaki disease.

morbilliform eruption, but may be urticarial, scarlatiniform, targetoid, or even pustular. Bullous or vesicular eruptions have not been described. The rash is usually in the perineum, which is a distinctive feature at this early stage, and it desquamates within 48 hours, preceding finger-tip and toe-tip desquamation[219] (Fig. 19-19). Plaque-type, guttate, and pustular psoriasis have been described, either during the acute or the convalescent phase of the disease, which supports a superantigen-mediated etiology.[220–223]

Changes in the lips and oral mucosa include erythema, swelling and fissuring of the lips, strawberry tongue, and erythema of the oropharynx. Oral ulcerations and pharyngeal exudates are not seen.

Intermittent acrocyanosis has been observed in infants younger than 6 months of age,[209] as well as peripheral gangrene.[224] Inflammatory changes with necrosis at the site of a previous BCG inoculation have been reported.[225–228]

Extracutaneous Findings[205,206,218,229]

Prolonged fever for at least 5 days is the cardinal and initial feature of the disease. It begins abruptly and is high, with peak temperatures generally >39°C (102°F) and in many cases >40°C (104°F), with several spikes each day (remittent fever). In the absence of appropriate therapy, fever persists for a mean of 11 days, but it may continue for 3–4 weeks and, rarely, even longer.

Bilateral nonexudative conjunctival injection, involving mainly the bulbar conjunctivae, begins shortly after disease onset and may already be resolved at time of first consultation. Anterior uveitis is frequently noted on slit-lamp examination but is rarely symptomatic.

Cervical lymphadenopathy is the least common diagnostic sign, with a prevalence of approximately 65%. It is usually unilateral, and confined to the anterior cervical triangle. The lymph nodes are often firm, nonfluctuant, and only slightly tender.

Cardiac conditions are the main cause of long-term morbidity and mortality. The pericardium, myocardium, endocardium, and coronary arteries may all be involved. Myocarditis may manifest in the acute phase, and arrhythmias due to ischemia, congestive heart failure, and valvular involvement, usually mitral, may occur. Occasionally there may low cardiac output syndrome or shock. Cardiac auscultation of the infant or child with Kawasaki disease in the acute phase often reveals a hyperdynamic precordium, tachycardia, a gallop rhythm, and an innocent flow murmur. A pansystolic regurgitant murmur may be heard in children with significant mitral regurgitation. Electrocardiography may show arrhythmia, prolonged PR interval, or nonspecific ST and T-wave changes. Pericardial effusion may be detected by an echocardiogram in 30% of patients. Without treatment, coronary artery aneurysms develop in 20% and are most commonly detected 10 days to 4 weeks after onset. Risk factors for the development of coronary aneurysms include age younger than 1 year, male gender, fever for more than 2 weeks, recurrent fever, and delayed treatment. Aneurysms may also develop in systemic medium-sized arteries and result in peripheral gangrene.[224]

Polyarticular arthritis and arthralgias may occur in the first weeks of the illness. It affects small as well as large joints. Irritability is usually prominent. Lethargy and other signs of aseptic meningitis may be present. Abdominal symptoms such as vomiting, diarrhea, and pain are common. In rare instances acute abdominal pain, mimicking a surgical abdomen, may herald the onset of the disease. Mild hepatitis occurs frequently, as does acute distension of the gallbladder (hydrops).

Transient unilateral peripheral facial nerve palsy occurs rarely. Respiratory symptoms due to pulmonary nodules, infiltrates, or pleural effusion may also be observed.[230–232] Rare findings include testicular swelling, hemophagocytic syndrome,[233] and transient high-frequency sensorineural hearing loss (20–35 dB).[234]

Etiology and Pathogenesis[235–237]

Epidemiologic and clinical data suggest that Kawasaki disease has features of infectious disease in an immunologically susceptible host and of an immune-mediated vasculitis. Many etiologic agents, ranging from bacteria such as *Propionibacterium*, *Staphylococcus*, *Streptocuccus*, *Chlamydia* and *Yersinia* to viruses such as Epstein–Barr, parvovirus, adenoviruses, retroviruses, and a novel human coronavirus, have been linked to Kawasaki disease in different geographic outbreaks, but none has been consistently demonstrated.[235] Much of the continuing debate in the literature concerns whether Kawasaki disease is caused by a superantigen or a conventional antigen.[235,237] Evidence of a superantigen-mediated disease process includes the identification of superantigen-producing organisms, isolation of bacterial superantigens, or finding the hallmark of superantigen activation in affected children, such as selective expansion of Vβ2 and Vβ8 T-cell receptor families. However, the immune response in Kawasaki disease is oligoclonal (antigen driven, i.e. similar to a response to a conventional antigen) rather than polyclonal (as found typically in superantigen-driven responses), and immunoglobulin A (IgA) plasma cells play a central role.[235,237]

Regardless of the cause, evidence points to a generalized immune activation with production of various proinflammatory cytokines and endothelial cell activation which lead to coronary artery alteration.[238–241] The most studied cytokine has been TNF-α, which is usually elevated in children with Kawasaki disease. Enzymes, including matrix metalloproteinases that are capable of damaging arterial wall integrity, may also be important in the development of aneurysmal dilatation. Various chemotactins that attract neutrophils and monocytes to coronary arteries may also play an important role.[242]

Host genetic determinants play a role in both susceptibility and coronary artery outcome in Kawasaki disease.[243] The

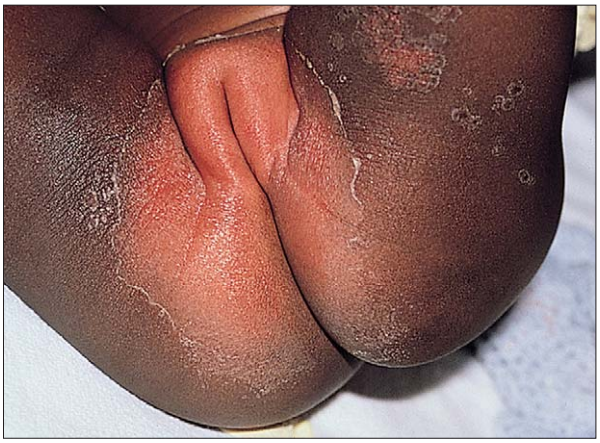


FIG. 19-19 Early perineal desquamative eruption of Kawasaki disease.

incidence rate in siblings is 10 times the population incidence.[217,244,245] The risk of occurrence in twins is higher than in ordinary siblings. Parents who had Kawasaki disease in childhood are more likely to have affected children, and children with recurrent disease.[246]

Laboratory Tests and Histopathology

In the acute phase, laboratory studies show leukocytosis (>15 000/mm^3) with a left shift, normochromic normocytic anemia, increased sedimentation rate and other acute-phase reactants, depressed albumin, and elevated IgM and IgE levels. The degree of elevation of ESR and C-reactive protein may show discrepancy, and both should be measured. Furthermore, elevation of ESR can be caused by IVIG therapy and therefore can not be the sole determinant of the degree of inflammatory activity.[218] Plasma lipids are altered in the acute stage, with depressed plasma cholesterol and HDL.[247,248] There may be mild elevation of transaminases and polyclonal hypergammaglobulinemia. In the subacute stage, in the second and third weeks of illness, there is a marked and almost universal thrombocytosis, which returns to normal in 4–8 weeks. Thrombocytopenia is rarely seen in the acute stage and may be a sign of disseminated intravascular coagulation. Antineutrophil cytoplasmic antibodies may be detectable as a nonspecific epiphenomenon. There may be sterile pyuria with mild proteinuria. Cerebrospinal fluid shows a mononuclear pleocytosis with normal protein and glucose levels. Skin biopsy findings are not specific. There is edema in the papillary dermis, with a mild perivascular mononuclear cell infiltrate. Vasculitis of medium and large arteries is observed.

Diagnosis[218]

There is no single diagnostic test for Kawasaki disease and therefore clinical criteria have been established to guide treatment decisions (Box 19-3). The classic diagnosis has been based on the presence of 5 days of fever and four of the five principal clinical features. Clinical features usually appear sequentially and are not all present at a single point in time, therefore watchful waiting is sometimes necessary before a diagnosis can be made. To avoid holding treatment until more than four clinical criteria are met, and the recognition that many patients with 'incomplete' Kawasaki still develop coronary artery disease, one may diagnose and treat Kawasaki on day 4 of illness in the presence of four principal criteria.[230,249] Also, the diagnosis can be made in patients with fever for 5 days and fewer than four principal features when coronary artery disease is detected by two-dimensional echocardiography (2DE) or coronary angiography. Kawasaki disease should be considered in the differential diagnosis of a young child, specially under 1 year of age, with unexplained fever for 5 days that is associated with any of the principal clinical features of this disease, or even in the presence of other clinical and laboratory findings that are not classic criteria but which are commonly encountered in this disease (Box 19-3).[218] For example, an elevated CRP or ESR and elevated platelet count after 7 days of illness are uncommon in viral infections but are universally seen in children with Kawasaki disease. Echocardiography may be useful in evaluating 'incomplete Kawasaki disease' and should be considered in any infant under 6 months with fever of more than 7 days' duration, laboratory evidence of systemic inflammation, and no other explanation for the febrile illness.[218] Although aneurysms rarely form before day 10 of illness there may be signs of coronary arteritis, decreased contractibility, mitral regurgitation, and pericardial effusion. With all these considerations a new algorithm has been proposed to help in deciding which patient with incomplete Kawasaki disease should undergo echocardiography or receive IVIG treatment (Fig. 19-20).[218]

Box 19-3 Classic diagnostic criteria for Kawasaki disease*

1. Fever of 5 days' duration and at least four of the following:**
2. Changes in the extremities: Erythema of palms, soles; edema of hands, feet; periungual peeling of fingers, toes.
3. Polymorphous exanthem
4. Bilateral conjunctival injection without exudation
5. Changes in the lips and oral cavity: fissuring, strawberry tongue, difuse injection of the oral or pharyngeal mucosa
6. Cervical lymphadenopathy of at least 1.5 cm in diameter.
7. Exclusion of other diseases with similar findings

**Patients with fever of at least 5 days and < four principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by 2DE or angiography.*
***Patients with four principal criteria can be diagnosed on day 4 of fever.*

Other clinical/laboratory findings in Kawasaki disease

- Other clinical and laboratory findings
  - Cardiovascular findings
    - Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
    - Coronary artery abnormalities
    - Aneurysms of medium-sized noncoronary arteries
    - Raynaud's phenomenon
    - Peripheral gangrene
  - Musculoskeletal system
    - Arthritis, arthralgia
  - Gastrointestinal tract
    - Diarrhea, vomiting, abdominal pain
    - Hepatic dysfunction
    - Hydrops of gallbladder
  - Central nervous system
    - Extreme irritability
    - Aseptic meningitis
    - Sensorineural hearing loss
  - Genitourinary system
    - Urethritis/meatitis
  - Other findings
    - Erythema, induration at BCG inoculation site
    - Anterior uveitis (mild)
    - Desquamating rash in groin
- Laboratory findings in acute Kawasaki disease
  - Leukocytosis with neutrophilia and immature forms
  - Elevated ESR
  - Elevated CRP
  - Anemia
  - Abnormal plasma lipids
  - Hypoalbuminemia
  - Hyponatremia
  - Thrombocytosis after week 1§
  - Sterile pyuria
  - Elevated serum transaminases
  - Elevated serum gamma glutamyl transpeptidase
  - Pleocytosis of cerebrospinal fluid
  - Leukocytosis in synovial fluid

Modified from Pediatrics 2004; 114: 1708–1133.

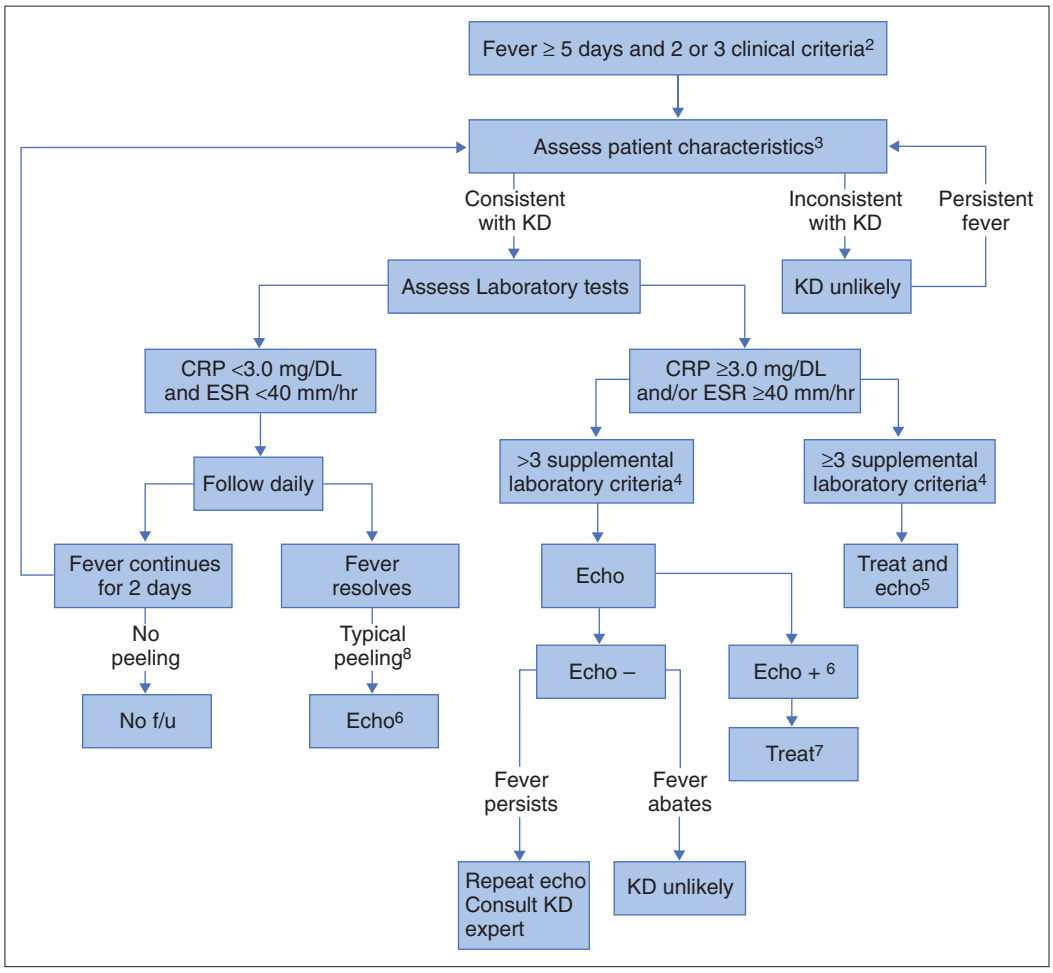


FIG. 19-20 Evaluation of suspected incomplete Kawasaki disease. (1) In the absence of gold standard for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed. (2) Infants ≤6 months old on day ≥7 of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram, even if the infants have no clinical criteria. (3) Patient characteristics suggesting Kawasaki disease are listed in Box 19-3. Characteristics suggesting disease other than Kawasaki disease include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, or generalized adenopathy. Consider alternative diagnoses. (4) Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after 7 days ≥450 000/mm^3, white blood cell count ≥15 000/mm^3, and urine ≥10 white blood cells/high-power field. (5) Can treat before performing echocardiogram. (6) Echocardiogram is considered positive for purposes of this algorithm if any of 3 conditions are met: *z* score of LAD or RCA ≥2.5, coronary arteries meet Japanese Ministry of Health criteria for aneurysms, or ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased LV function, mitral regurgitation, pericardial effusion, or *z* scores in LAD or RCA of 2–2.5. (7) If the echocardiogram is positive, treatment should be given to children within 10 days of fever onset and those beyond day 10 with clinical and laboratory sings (CRP, ESR) of ongoing inflammation. (8) Typical peeling begins under nail bed of fingers and then toes.

Sometimes Kawasaki disease may be 'atypical,' presenting at onset with clinical features that are not generally seen, such as acute abdominal pain, renal impairment, meningeal irritation, pneumonia, or retropharyngeal abscess.

Differential Diagnosis

Many diseases mimic Kawasaki disease, including viral infections, streptococcal infection, juvenile rheumatoid arthritis, erythema multiforme, staphylococcal scalded skin syndrome, toxic shock syndrome, drug hypersensitivity reactions, Rocky Mountain spotted fever, leptospirosis, mercury hypersensitivity reaction (acrodynia), and bacterial cervical adenitis. Low white blood cell count, lymphocytosis and low platelet count may be useful in suggesting a viral infection instead of Kawasaki disease.

Course, Management, Treatment, and Prognosis

The morbidity and mortality of Kawasaki disease depend primarily on coronary artery lesions.[250–254] Coronary artery aneurysms or ectasia develop in 15–25% of untreated children and may lead to ischemic heart disease or sudden death. With early treatment the risk is reduced to around 5–12%.[215,216] Small aneurysms resolve completely within the first 2 years after disease onset in 30–60% of these patients.[255] However, coronary aneurysms, especially if giant (>8 mm), may persist and be complicated by thrombotic occlusion or the development of stenosis at the outlet of the aneurysm. Stenotic lesions as well as early coronary atherosclerosis may develop gradually over several years, so long-term follow-up is warranted.[252,253,256,257]

Several scoring systems have been developed to predict risk for coronary artery aneurisms.[258] The Harada score is one that is used in Japan.[259]

Because the major sequelae of Kawasaki disease are related to coronary artery systems, cardiac imaging is critical in the evaluation of all patients with suspected Kawasaki disease, and serial echocardiograms are recommended. Echocardiography should focus on coronary artery visualization and measurement, but also on left ventricle contractibility, valve function, the presence of pericardial effusion, and measurement of the aortic root.[260] An initial examination should be performed as soon as the diagnosis is suspected and is useful as a baseline for follow-up. Thereafter, for uncomplicated cases it should be repeated at 2 weeks and at 6–8 weeks after disease onset.[218] For those who develop coronary artery aneurysms or other cardiac abnormalities more frequent evaluation is recommended. Other noninvasive imaging modalities, such as MRI, MRA, and ultrafast CT, as well as cardiac stress testing, are being evaluated in the management of Kawasaki disease. Until the aneurysm resolves a stress test may be needed to guide recommendations for physical activity and the need for angiography.

Treatment in the acute phase of the disease is directed to reducing inflammation in the coronary artery wall and preventing coronary thrombosis, whereas long-term therapy in individuals who develop coronary aneurysms is aimed at preventing myocardial ischemia or infarction. Intravenous γ-globulin (IVIG) combined with high-dose aspirin is the treatment of choice in the acute phase of the disease.[229] Aspirin alone does not appear to reduce the frequency of the development of coronary abnormalities, but together with IVIG it has an additive anti-inflammatory effect. In the acute stage aspirin is given in doses of 80–100 mg/kg divided into four. The duration of high-dose aspirin varies in different centers. In many institutions the dose is reduced after the child has been afebrile for 48–72 hours. Others continue until day 14 of illness and >48–72 hours after fever cessation. Following this acute phase low-dose aspirin (3–5 mg/kg) is given as an antiplatelet agent until there is no evidence of coronary changes at 6–8 weeks from disease onset. For patients who develop coronary abnormalities, low-dose aspirin is continued until regression of coronary artery aneurysms, but some clinicians continue indefinitely. Ibuprofen should be avoided in children taking aspirin for its antiplatelet effect because it antagonizes platelet inhibition.

IVIG has been shown to reduce the incidence of coronary artery aneurisms from 20% to 3–4%.[261–264] A single dose of 2 mg/kg has been shown to be superior than lower doses for 4 consecutive days.[261,262] IVIG should be started early, within 10 days of disease onset and preferably within 7 days. Treatment before day 5 does not appear to prevent cardiac sequelae and may be associated with an increased need for IVIG retreatment.[265,266] Treatment after day 10 should be considered if there are still signs of ongoing inflammation (elevated ESR or CRP) or persistent fever.[267] Not all patients respond to a single dose of IVIG and may have persistent or recrudescent fever 36 hours after completion of the initial treatment, and require a second dose. It has been observed that those children who received IVIG very early in the illness are more prone to require a second infusion. Vaccination with live or other vaccines should be deferred for at least 11 months after high-dose IVIG treatment, both to ensure correct immunization and to avoid flares of Kawasaki disease.[268]

The usefulness of steroids in combination with IVIG in the initial therapy of Kawasaki disease is not well established. Steroids shorten the duration of fever and lower ESR and CRP, but do not seem to influence the coronary outcome.[269,270] Steroids have also been used for IVIG treatment failures, but their role in preventing or reversing coronary anomalies is uncertain. It has been recommended to restrict their use in children who have persistent fever after two infusions of IVIG.[218] The most common regimen is intravenous pulse methylprednisolone, 30 mg/kg for 1–3 days.

Because of its inhibition of TNF-α messenger RNA transcription, pentoxifylline may have a theoretical benefit in the initial treatment of Kawasaki disease, although there are only small clinical trials reported.[271] The role of TNF-α antagonists such as infliximab; abciximab, a platelet glycoprotein IIb/IIa receptor inhibitor; plasma exchange; and cytotoxic agents for patients with refractory Kawasaki disease, remains uncertain.[218,272]

ACUTE HEMORRHAGIC EDEMA

Acute hemorrhagic edema (AHE), purpura en cockade, or Finkelstein disease, is an acute, benign leukocytoclastic vasculitis of limited skin involvement occurring in children under 2 years of age.[273–280] AHE has been considered an infantile variant of Henoch–Schönlein purpura; however, because of clinical and prognostic differences it is sometimes regarded as a separate entity.

Cutaneous Findings

The disease is characterized by the abrupt onset of fever; tender edema of the face, eyelids, ears, scrotum, and acral extremities; and ecchymotic purpura on the face and extremities. The trunk is usually spared. Individual lesions often have a darker center and expand centrifugally, giving them a cockade or target-like configuration. Lesions range in size from 0.5 to 4.0 cm and may become confluent, forming polycyclic, annular plaques (Fig. 19-21). Necrotic[279,281] and bullous lesions may be seen.[279,282] Petechiae in the mucous membranes have also been described.[283]

Extracutaneous Findings

Except for fever, there are no associated manifestations. In many patients there is a preceding upper respiratory tract infection. The dramatic cutaneous findings contrast with the general wellbeing of the patient.

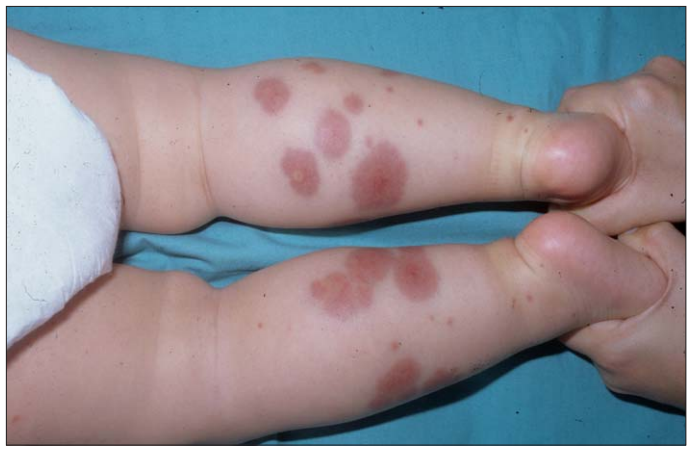


FIG. 19-21 Acute hemorrhagic edema.

Etiology and Pathogenesis

The cause of AHE is unknown. It is thought to represent an immune complex-mediated disease precipitated by a preceding infection, particularly an upper respiratory tract infection, drug intake, or immunization. Staphylococci and *Streptococcus* spp. and viruses (adenoviruses, rotavirus) have been implicated most commonly.

Laboratory Tests and Histopathology

Leukocytosis (both lymphocytic and granulocytic), thrombocytosis, eosinophilia, and an elevated ESR may be present. Urinalysis, tests for occult blood in the stool, immunoglobulin, and complement levels are usually normal or negative. Circulating immunocomplexes may occasionally be found.[282]

Histopathologic examination of skin biopsy specimens demonstrates a small vessel leukocytoclastic vasculitis. Direct immunofluorescence shows deposition of C3 and fibrinogen in the vessel wall. IgM, IgG, IgA, and IgE deposition has also been noted in up to one-third of cases.[282,284–286]

Differential Diagnosis

The differential diagnosis includes Henoch–Schönlein purpura, child abuse, meningococcemia and other infectious purpuras, erythema multiforme, Kawasaki disease, and Sweet syndrome.[273,283] Distinction from Henoch–Schönlein purpura may be impossible[280] (Table 19-2). Perivascular deposits of IgA are not useful for differentiation because they may be present in both entities.

Course, Management, and Prognosis

The prognosis is excellent. The eruption resolves spontaneously without sequelae in 1–3 weeks. Treatment with corticosteroids is not necessary and may lead to complications and worsen the prognosis.[284] Exacerbations may be observed during the clinical evolution, with new crops of lesions and fever,[281,285] but true recurrences weeks or months after the first episode are rare.[280,283] There has been a single report of a fatal ileoileal intussusception in an infant with cutaneous lesions otherwise typical for AHE.[281]

TABLE 19-2 Differential diagnosis between acute hemorrhagic edema and Henoch–Schönlein purpura

	Acute hemorrhagic edema	Henoch–Schönlein purpura
Onset	Acute and dramatic	Less dramatic
Age	2 m–2years	>2 years
Sex	Male predominance	Male predominance
Location	Face, ears, extremities	Lower extremities, buttocks
Morphology	Large medallion-like purpura Facial edema	Palpable purpura Edema of lower extremities
Course	No recurrences	Frequent relapses
Histopathology	Leukocytoclastic vasculitis	Leukocytoclastic vasculitis
Immunodeposits	Variable IgA, IgM, C3	IgA
Systemic involvement	No	Renal, gastrointestinal, joint, CNS

THE PORPHYRIAS[287–295]

The porphyrias are a group of diseases characterized by abnormalities of porphyrin–heme metabolism. Each type results from deficient activity of one of the enzymes of the heme biosynthetic pathway, which leads to an accumulation of heme precursors within plasma, red blood cells, urine, and feces.[295] The genes for these enzymes have been characterized.[287,289,295] Porphyrias are mainly inherited in an autosomal dominant manner with incomplete penetrance, but autosomal recessive and more complex patterns of inheritance are also possible. Porphyrias are classified as hepatic or erythropoietic, according to the organ site in which the underlying defect of heme synthesis is predominantly expressed (see Table 19-3). Cutaneous manifestations in porphyrias may be classified as acute photosensitivity with burning pain, edema, and erythema shortly after sun exposure, or delayed photosensitivity manifesting as skin fragility, subepidermal blisters, milia, disorders of pigmentation, and sclerodermoid signs. Hepatic porphyrias usually manifest acute neurovisceral attacks and delayed photosensitivity, and rarely present before puberty except from the homozygous variants. Elevated porphyrins may be detected in the stool or urine. Erythropoietic porphyrias are characterized by acute cutaneous photosensitivity from early childhood. The more delayed photosensitivity, although less characteristic of this type of porphyria, may be also present.[293] Erythrocyte and plasma porphyrin levels are elevated in erythropoietic porphyrias.

Photosensitivity in porphyrias is maximum for ultraviolet wavelengths between 400 and 410 nm ('Soret band'), the spectrum of maximum absorption of porphyrins.

The pathophysiologic mechanisms involved in the cutaneous manifestations of the porphyrias are multiple and involve the creation of reactive oxygen specimens.[296–298]

Childhood porphyrias are relative uncommon and their exact incidence is unknown. Only those porphyrias manifesting early in infancy are reviewed here.

Congenital Erythropoietic Porphyria

Congenital erythropoietic porphyria (CEP), also called Günther disease, is a rare autosomal recessive disorder caused by deficient activity of uroporphyrinogen III (UROGEN III) synthase which leads to nonenzymatic conversion of hydroxymethylbilane to uroporphyrinogen I, a nonphysiologic substrate that is converted to coproporphyrinogen I; these porphyrinogen I isomers are then oxidized to uroporphyrin I (URO-I) and coproporphyrin I (COPRO-I), which are phototoxic compounds. Elevated levels of URO-I and COPRO-I in erythrocytes result in massive hemolysis, and the released porphyrins accumulate in peripheral blood, skin, bone, and teeth and are excreted in large amounts in the urine and feces.

Cutaneous Findings[292,299,300]

CEP presents with severe photosensitivity from birth or early infancy with formation of vesicles and bullae on areas exposed to sun, phototherapy devices, or even ambient lighting.[301] There is also marked skin fragility. As a result of the phototoxic injury and the increased skin fragility, there are severe mutilations, mainly of the fingers, hands, and face, particularly the nose and ears, but also in sun-protected areas. Hypertrichosis of the face and extremities, scarring alopecia of the scalp and eyebrows, and pigmentary changes (hyperpig-

TABLE 19-3 Classification of the porphyrias, enzymatic defect, porphyrin profile, and age of onset

Tissue origin	Type	Enzyme deficiency	Porphyrin profile				Age of onset
			Erythrocyte	Plasma	Urine	Stool	
Erythropoietic	Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase	URO-I, COPRO-I, PROTO	URO-I, COPRO-I, PROTO	URO-I > COPRO-I	COPRO-I	Birth, infancy
	Erythropoietic protoporphyria (EPP)	Ferrochelatase	PROTO	PROTO	Normal	PROTO	Infancy, early childhood
Hepatic	Acute intermittent porphyria (AIP)	Porphobilinogen deaminase	Normal	Normal	ALA, PBG	Normal	After puberty, no cutaneous manifestations
	Variegate porphyria (VP)	Protoporphyrinogen oxidase	Normal	COPRO, PROTO	COPRO > URO	PROTO > COPRO	Second decade, homozygous variant at birth, infancy, or early childhood
	Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase	Normal	COPRO	COPRO	COPRO	After puberty, homozygous variant (harderoporphyria) at birth, infancy, or early childhood
	Porphyria cutanea tarda (PCT)	Uroporphyrinogen decarboxylase	Normal	URO	URO-I > III	ISOCOPRO	Third of fourth decade
	ALA dehydratase porphyria	ALA dehydratase	PROTO	ALA, COPRO, PROTO	ALA, COPRO, URO	COPRO, PROTO	Any age, no cutaneous manifestations
Hepatoerythropoietic	Hepatoerythropoietic porphyria (HEP)	Uroporphyrinogen decarboxylase	Zn-PROTO	URO	URO-(I and III)	ISOCOPRO	Early infancy

ALA, *5-aminolevulinate;* COPRO, *coproporphyrin;* ISOCOPRO, *isocoproporphyrin;* PBG, *porphobilinogen;* PROTO, *protoporphyrin;* URO, *uroporphyrin.*

mentation and hypopigmentation) are also common. Over time, severe facial mutilation results, with destruction of nasal and auricular cartilages, ectropion, and eclabium, as well as shortening and contraction of the fingers. Milder phenotypes may have onset later in childhood.[302]

Extracutaneous Findings

The accumulation of porphyrins in deciduous and permanent teeth produces red discoloration (erythrodontia) and reddish fluorescence on Wood's light examination, which is pathognomonic. The urine is also reddish, which causes pink discoloration of the diapers that fluoresces – an early bed-side diagnostic sign. Porphyrins accumulate in the amniotic fluid and brownish amniotic fluid may be observed. Severe hemolytic anemia and secondary splenomegaly occur. Anemia may be so severe as to lead to hydrops fetalis and death in utero. Patients with late-onset disease may not develop hemolytic anemia but only thrombocytopenia and myelodysplasia. Ocular changes include ectropion, photophobia, and keratoconjunctivitis.[303] Other manifestations include osteodystrophy with increased bone fragility, and porphyrin-rich gallstones.

Genetics

The gene for UROGEN III synthase is localized on chromosome 10. Several mutations have been identified,[304] and different mutations correlate with the level of residual enzyme activity and hence with disease severity and genotypes.[302,305,306]

Laboratory Tests and Histopathology

Histologic examination of skin biopsy specimens from blisters reveals subepidermal cleavage (within the lamina lucida) and minimal inflammatory infiltrate. Perivascular accumulation of PAS-positive, diastase-resistant, homogeneous hyaline material (porphyrins) may be seen, which is best viewed with fluorescence microscopy. See Table 19-3 for porphyrin excretion profile. Measurement of URO III synthase activity is available. Prenatal diagnosis from amniotic fluid is possible by either measurement of uroproporphyrin I or direct gene mutation analysis.[307–310]

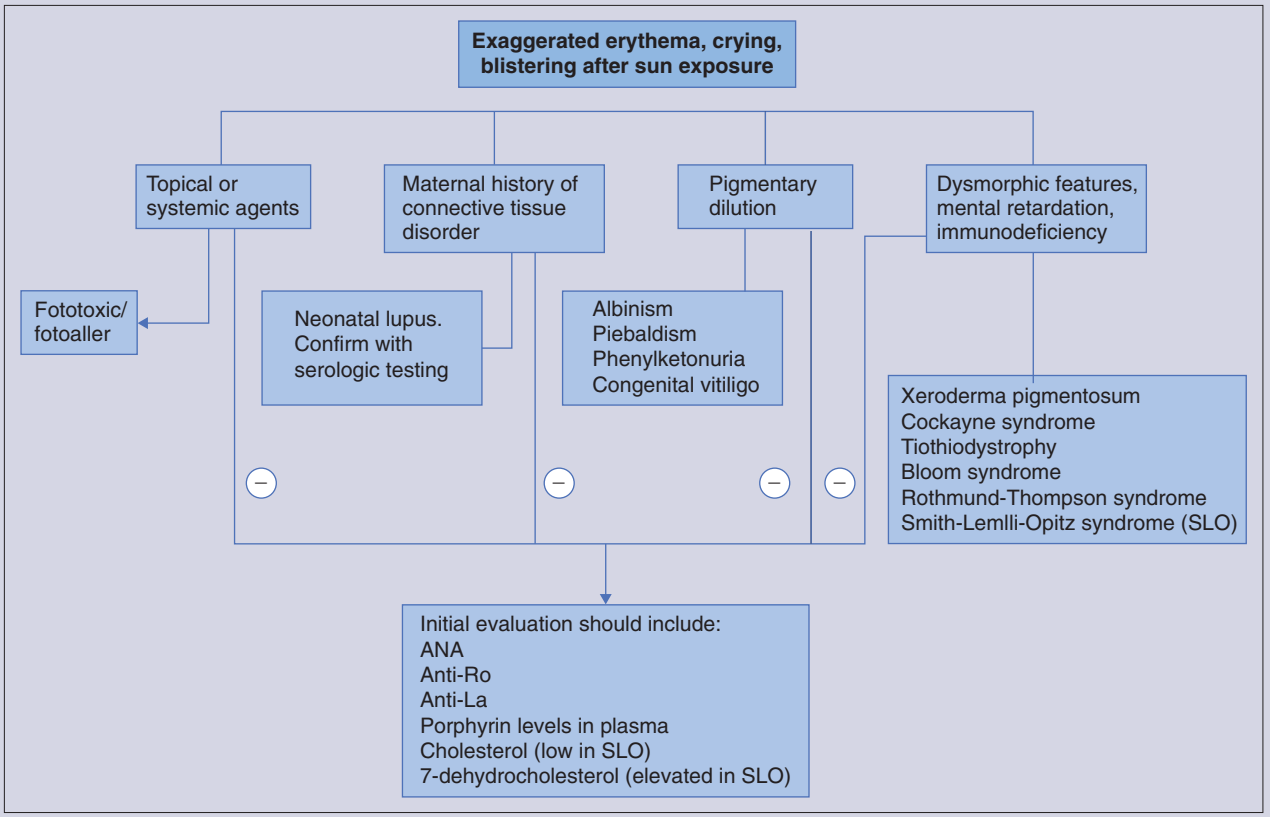
Differential Diagnosis

Other photosensitivity diseases presenting early in life (Box 19-4) or diseases manifesting with blisters, such as epidermolysis bullosa and bullous pemphigoid, should be considered. Determination of porphyrins is diagnostic and allows differentiation from other porphyrias presenting early in life with photosensitivity.

Prognosis

The clinical severity of CEP is highly variable, ranging from hydrops fetalis, hepatosplenomegaly, and severe anemia in utero to adult-onset disease with only cutaneous manifestations.[311] In most cases, however, patients survive well into adulthood, albeit with severe mutilations or major disfigurement.

Box 19-4 Causes of photosensitivity in neonates



Treatment[312]

Protection from sun exposure is essential. Chemical sunscreens do not achieve good protection against Soret band radiation, so protective clothing and physical sunblocks are necessary. Long-wavelength, UV-absorbing films are encouraged on car windows and windows at home. Children with the severe phenotypes and severe hemolysis benefit from repeated erythrocyte transfusions and hydroxyurea to suppress erythropoiesis. Hematocrits should be maintained above 32%, with appropriate iron chelation. The efficacy or repeated erythrocyte transfusion may decrease at puberty. Subsequent splenectomy is often needed to control hemolytic anemia.[313,314] Activated charcoal,[315–318] and β-carotene[319,320] have been used, with inconsistent results. Bone marrow transplantation or stem cells from cord blood offer the possibility of correcting enzyme activity.[321–325] Replacement gene therapy has been accomplished in vitro.[326,327]

Erythropoietic Protoporphyria[287,298,328]

Erythropoietic protoporphyria (EPP) is the most common form of cutaneous porphyria apart from porphyria cutanea tarda (PCT). EPP is caused by deficient activity of ferrochelatase, leading to the accumulation of protoporphyrin in erythrocytes, plasma, and feces. Clinical symptoms typically begin in infancy or early childhood, with a peak incidence between 2 and 4 years of age. EPP is usually inherited as an autosomal dominant condition, but most individuals who are heterozygous for the inherited mutations are asymptomatic, because of half-normal ferrochelatase activity[329] For protoporphyrin to accumulate sufficiently to cause photosensitivity, a reduction of enzymatic activity to below a critical threshold of about 35% of normal is required. Some families may have autosomal recessive inheritance.[329–331]

Cutaneous Manifestations

Clinical manifestations are those of an acute phototoxic reaction, which triggers an episode of crying within minutes of sunlight exposure due to burning pain or stinging sensations on exposed areas (the face and the dorsal aspect of hands). Some patients are photosensitive to fluorescent lighting.[328] Erythema, edema, and urticarial lesions occur, but vesicles and bullae are rare (Fig. 19-22). Fine petechiae may occur on sun-exposed areas after prolonged exposure. Some patients have only subjective symptoms.[328] With chronic exposure there is characteristic thickening and wrinkling of the knuckle pads, furrowing around the mouth (pseudorhagades), and shallow elliptical scars on the nose, cheeks, and forehead.

Hemolytic anemia is absent, but in some patients a mild hypochromic, microcytic anemia may occur. Protoporphyrin-rich gallstones may develop in childhood. Fatal liver failure resulting from the progressive accumulation of protoporphyrin in hepatocytes is a possible outcome in about 2.5% of patients, altering the prognosis for an otherwise clinically benign disorder. Recessive inheritance may predispose to severe liver disease.[329,332]

Genetics

The gene for ferrochelatase is localized on chromosome 18. Over 70 mutations in this gene have been identified in EPP

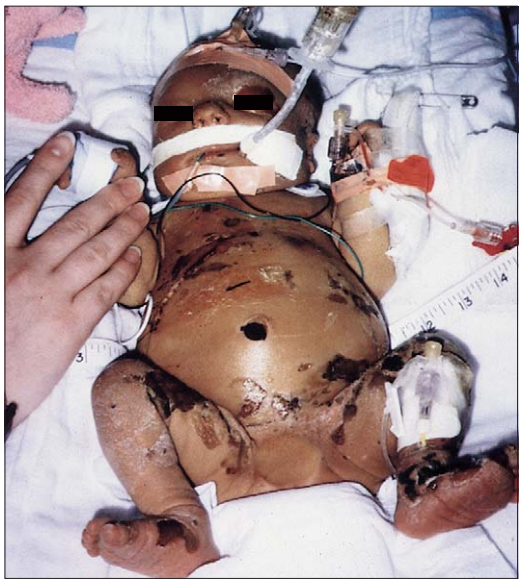


FIG. 19-22 Porphyria. (Courtesy of Henry Lim and Tor Schwayder.)

families.[329,333] In most symptomatic patients inheritance of a second mutation is needed in order to reduce the enzymatic activity to a critical threshold where clinical symptoms are caused. Autosomal recessive inheritance has been demonstrated in 3% of patients with EPP.[329]

Laboratory tests and Histopathology

Histopathologic examination of skin biopsy specimens of sun-exposed areas shows marked concentric deposits of a hyaline material around dermal blood vessels. This material is PAS positive and diastase resistant.

Patients with EPP should undergo frequent liver function tests, and those with persistent abnormalities should have a liver biopsy. Children with high erythrocyte protoporphyrins should have periodic determination of blood, urinary, and fecal porphyrins because increased excretion of copropophyrins, high erythrocyte protoporphyrins and reduced excretion of faecal protoporhyrins can predict liver failure.[334]

Diagnosis

The diagnosis of EPP is established by detecting elevated levels of protoporphyrin in erythrocytes, plasma, and feces. In addition, fecal and erythrocyte coproporphyrins may be increased. A rapid microfluorometric assay for free erythrocyte protoporphyrins and examination of a blood smear for fluorescent erythrocytes may also be used as screening tests.[335] The differential diagnosis includes other types of porphyria, but causes of immediate photosensitivity such as PMLE or solar urticaria do not occur in infants.

Treatment

The mainstay of treatment for erythropoietic protoporphyria is sun avoidance and the use of physical sunscreens.[336,337] Topical dihydroxyacetone may be helpful in some patients by producing brown pigment.[287] Oral administration of β-carotene (30–90 mg/day for children) has been shown in uncontrolled studies to increase tolerance to sun exposure because it quenches the formation of free radicals.[334,338,339] Narrowband ultraviolet B phototherapy has been proposed, as this wavelength does not cause photosensitivity.[340] Desensitization with PUVA therapy has also been used. Oral iron, intravenous hematin, transfusion therapy, and a high-carbohydrate diet have been used to prevent protoporphyrin accumulation in the liver by reducing protoporphyrin production, but their efficacy is unproven.[334] Cholestyramine or activated charcoal have been used to interrupt the enterohepatic circulation of protoporphirins.[341] Avoidance of alcohol and drugs that interfere with hepatic excretory function is also essential. Liver transplantation has been performed in a few patients with liver failure, although the enzymatic defect is not thereby corrected and hence the long-term outcome is poor.[342–345] Modification of the lighting in the operating room is necessary to avoid photoxicity to exposed organs.

Hepatoerythropoietic Porphyria

Hepatoerythropoietic porphyria (HEP) is an extremely rare disorder caused by a marked deficiency of uroporphyrinogen decarboxylase due to a homozygous state.[346–349] Clinical manifestations begin in infancy, or more commonly in early childhood, and resemble both porphyria cutanea tarda and Günter disease. The disease usually presents with darkening of the urine and delayed-type cutaneous photosensitivity, with vesicles, skin fragility, milia, and scarring. With time, hypertrichosis, sclerodermoid changes, and mutilation similar to the manifestations of Günter disease become apparent. Anemia, hepatosplenomegaly, and abnormalities of liver function of varying degrees may also occur, but are less common than in congenital erythropoietic porphyria. The porphyrin excr etion pattern resembles that of porphyria cutanea tarda (PCT), with elevated urinary uroporphyrins and 7-carboxylated porphyrins, and a smaller elevation of coproporphyrins, 6- and 5-carboxylated porphyrins. Increased isocoproporphyrins in feces are characteristic. Unlike in PCT, erythrocyte proto is increased.

Treatment is directed to sun protection. Hypertrichosis in hepatoerythropoietic porphyria has been treated successfully with high-intensity pulses of noncoherent light.[350]

Other Porphyrias

Homozygous Porphyrias

Other porphyrias with onset of symptoms in infancy or early childhood include homozygous variants of aminolevulinate dehydratase (ALAD) deficiency, homozygous coproporphyria (harderoporphyria), homozygous variegate porphyria, and homozygous acute intermittent porphyria.[351]

ALAD deficiency porphyria is rare (fewer than 10 patients reported) and usually manifests later in childhood or adulthood, but neonatal onset has been reported.[352] Clinical manifestations from birth are recurrent attacks of pain, vomiting, hyponatremia, and symptoms of polyneuropathy affecting motor functions, including respiration. Raised levels of 5-aminolevulinic acid and coproporphyrin in urine are found. Very low erythrocyte aminolevulinate dehydratase activity is diagnostic. Liver transplantation in patients with neonatal onset has little effect.[353]

In harderoporphyria, neonatal jaundice, hemolytic anemia, and hepatosplenomegaly dominate the clinical picture.[354–357] Blisters may occur during phototherapy for neonatal jaundice. Diagnosis depends on detecting very low coproporphyrinogen oxidase activity, elevated coproporphyrin in urine, markedly

elevated harderoporphyrin and coproporphyrin in feces, and zinc protoporphyrin in erythrocytes.

Homozygous variegate porphyria may present shortly after birth with marked photosensitivity or, more commonly, with erosions, blisters, and milia following minor trauma in sun-exposed areas.[358–360] Acute attacks are absent, but mental and growth retardation, seizures, nystagmus, and clinodactyly have been described.

Homozygous variant of acute intermittent porphyria may present early in life with ataxia, mental retardation, convulsions, cataracts, and hepatosplenomegaly, but acute attacks typical of acute intermittent porphyria do not occur in these children.[361–364] There are no cutaneous manifestations. Markedly increased porphobilinogen and ALAD in urine are found and are responsible for the orange urine.

TRANSIENT PORPHYRINEMIAS[365–368]

Transient increases in porphyrin levels have been described in neonates with hemolytic disease of the newborn and in a neonate with severe liver failure due to tyrosinemia type 1.[368] These infants develop erythema, violaceous discoloration, purpura, erosions, and blisters in areas exposed to phototherapy, with sharp demarcation at photoprotected sites. Sensitivity to sunlight may occur.

Elevated levels of plasma/urine porphyrins (mainly coproporphyrin) and/or erythrocyte protoporphyrin are found, which normalize spontaneously during the first few months. The cause of transient porphyrinemia is unclear but is probably due to cholestasis. Other factors likely to be involved include blood transfusions and drug use.

PURPURA IN THE NEWBORN

Purpura in the neonate is almost always an emergency and should prompt an immediate search for an underlying disorder. Apart from trauma, purpura in the newborn may be due to coagulation defects, platelet abnormalities, or infections (see Box 19-5). Extramedullary erythropoiesis also causes purpuric lesions by a different mechanism.

In the evaluation of a neonate with purpura it is important to obtain a maternal and familial history of bleeding diathesis and thromboembolic phenomena, drug intake, and symptoms of infectious diseases. A general physical examination and workup for sepsis is warranted. Laboratory studies should include hemoglobin and hematocrit values, platelet count, white blood count, coagulation studies, and TORCH serologies.

DERMAL ERYTHROPOIESIS (BLUEBERRY MUFFIN BABY)

Persistence of the erythropoietic activity of fetal dermal mesenchyme into the newborn period produces a characteristic purpuric eruption for which the term blueberry muffin baby was coined. The eruption, first observed in newborns with congenital rubella (Fig. 19-23), may be the result of other intrauterine infections (Fig. 19-24) and hematologic dyscrasias.[369–371] A blueberry muffin-like eruption may also represent metastatic infiltration of the dermis by congenital malignancies, without true extramedullary erythropoiesis (Fig. 19-25).

Cutaneous Findings

The cutaneous lesions of blueberry muffin babies consist of dark blue or magenta, nonblanchable, round to oval papules

Box 19-5 Differential diagnosis of neonatal purpura

1. Extramedullary erythropoiesis (blueberry muffin baby)
2. Coagulation defects
   - Protein C and S deficiency (neonatal purpura fulminans)
   - Hemorrhagic disease of the newborn
   - Hereditary clotting factor deficiencies
3. Platelet abnormalities
   a. Immune platelet destruction
      - Alloimmune neonatal thrombocytopenia
      - Maternal autoimmune thrombocytopenia (ITP, lupus)
      - Drug-related immune thrombocytopenia

   b. Primary platelet production/function defects
      - Thrombocytopenia with absent radii syndrome
      - Wiskott-Aldrich syndrome
      - Fanconi anemia
      - Congenital megakaryocytic thrombocytopenia
      - X-linked recessive thrombocytopenia
      - Other hereditary thrombocytopenias
      - Giant platelet syndromes (Bernard-Soulier, May-Hegglin)
      - Trisomy 13 or 18
      - Alport syndrome variants
      - Gray platelet syndrome
      - Glanzmann thrombasthenia

   c. Kasabach-Merritt syndrome*
4. Infections†
   - Congenital (TORCH)
   - Sepsis
   - HIV
   - Parvovirus B19
5. Trauma
6. Purpuric phototherapy-induced eruption

Modified from Baselga E, Drolet BA, Esterly NB. J Am Acad Dermatol 1997;37:673–705.
**Both thrombocytopenia and consumption coagulopathy are involved in the pathogenesis.*
†Infection may cause purpura by several mechanisms.

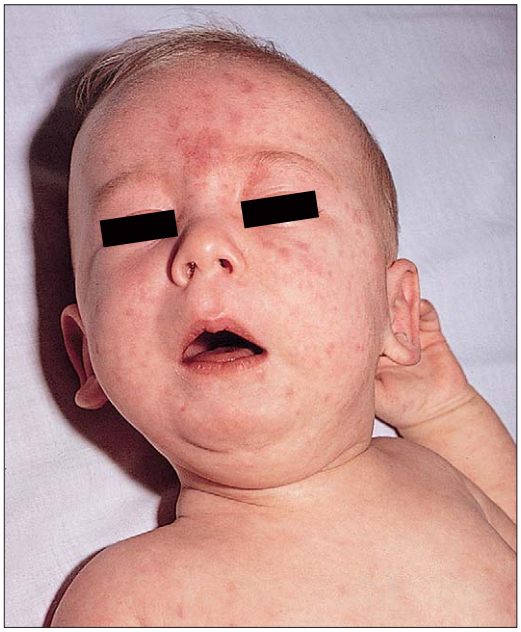


FIG. 19-23 Infant with congenital rubella and 'blueberry muffin' lesions.

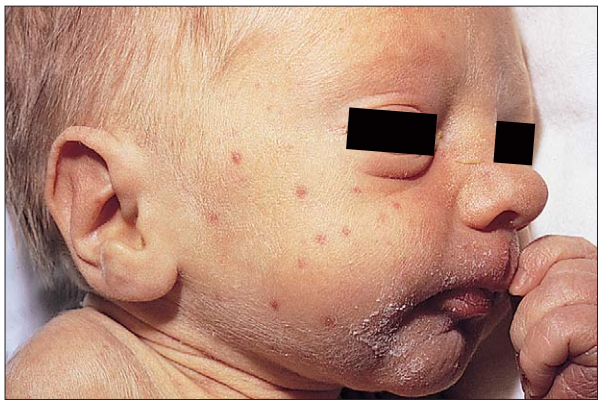


FIG. 19-24 'Blueberry muffin' lesions associated with cytomegalic inclusion disease.

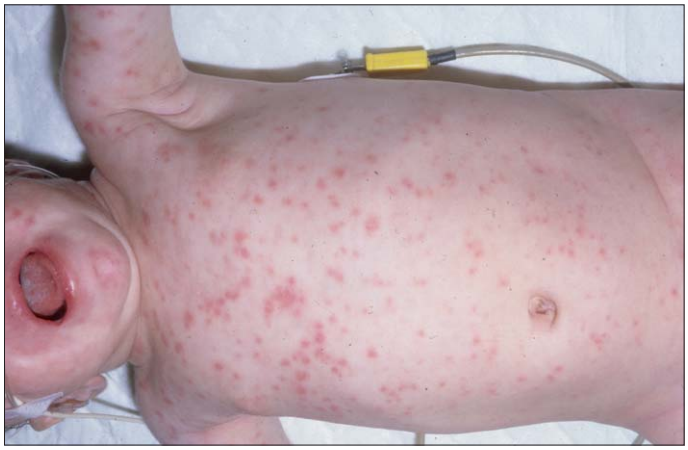


FIG. 19-25 Infiltration of the skin by leukemia cutis producing a blueberry muffin appearance.

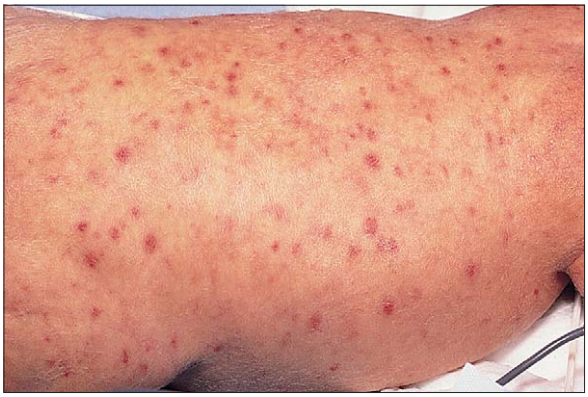


FIG. 19-26 Lesions of dermal erythropoiesis in an infant with Rh incompatibility due to RhoGAM failure.

ranging in size from 1 to 7 mm and have a generalized distribution, with emphasis on the head, neck, and trunk (Fig. 19-26). The papules are firm to palpation, with an infiltrative quality that distinguishes them from petechiae and purpura, which often coexist in the same patient. These lesions evolve into dark purple to brown macules and involute spontaneously within 2–6 weeks.[273] Blueberry muffin lesions caused by infiltrative processes are usually larger, more nodular, less hemorrhagic, fewer in number, and firmer to palpation.

Extracutaneous Findings

Accompanying abnormalities vary with the underlying cause.

Etiology and Pathogenesis

In the prevaccination era rubella was the most common cause of dermal erythropoiesis, but now congenital cytomegalovirus (CMV) infection is the major cause.[369,370] Dermal erythropoiesis has been associated with other intrauterine infections, such as Coxsackie B2[369] and parvovirus B19,[372] as well as hematologic dyscrasias such as Rh incompatibility (Fig. 19-24),[373,374] maternofetal ABO incompatibility,[369] spherocytosis,[375] and the twin transfusion syndrome[210,216] (Box 19-6). In rare instances it may occur in otherwise healthy newborns.[369,376]

Laboratory Tests and Histopathology

Histopathologic examination demonstrates poorly circumscribed collections of nucleated and nonnucleated red blood cells, predominantly confined to the reticular dermis and extending to the subcutaneous tissue.[369–371] Occasionally a few myeloid precursors may be interspersed.

Laboratory findings depend on the underlying cause. In the evaluation of a blueberry muffin baby the following tests are indicated: peripheral blood count, hemoglobin level, TORCH serologies, viral cultures, and a Coombs' test. Skin biopsy is not always necessary for diagnosis, but may be helpful if an infiltrative process is suspected.

Differential Diagnosis

The differential diagnosis includes other causes of neonatal purpura, such as coagulation defects, platelet abnormalities, and infections.[273] Neoplastic diseases that produce infiltrative metastases in the neonatal period, such as neuroblastomas,[377–379] rhabdomyosarcomas,[380] myelogenous leukemias,[381–383] and Langerhans' cell histiocytosis, especially the congenital self-healing reticulohistiocytosis variant (Hashimoto–Pritzker),[384,385] should be considered.

Course, Management, Treatment, and Prognosis

The lesions of true dermal erythropoiesis fade and resolve spontaneously 3–6 weeks after birth. Treatment is directed at the underlying condition.

PROTEINS C AND S DEFICIENCIES (NEONATAL PURPURA FULMINANS)

Neonatal purpura fulminans is a rare condition characterized by massive and progressive hemorrhagic necrosis of the skin accompanied by thrombosis of the cutaneous vasculature in the neonatal period.[386–391] Occasionally larger vessels and other organs are involved. The primary pathologic event is widespread thrombosis, which is responsible for a hematologic picture of disseminated intravascular coagulation (DIC). In neonates, purpura fulminans is usually the result of inherited thrombophilic disorders that are attributable to protein C deficiency, protein S deficiency, or resistance to activated protein C due to factor V mutations.

Cutaneous Findings

Neonatal purpura fulminans manifests 2–12 hours after birth. In rare instances, delayed onset of up to 6–10 months of age has been described.[392] Cutaneous lesions consist of extensive

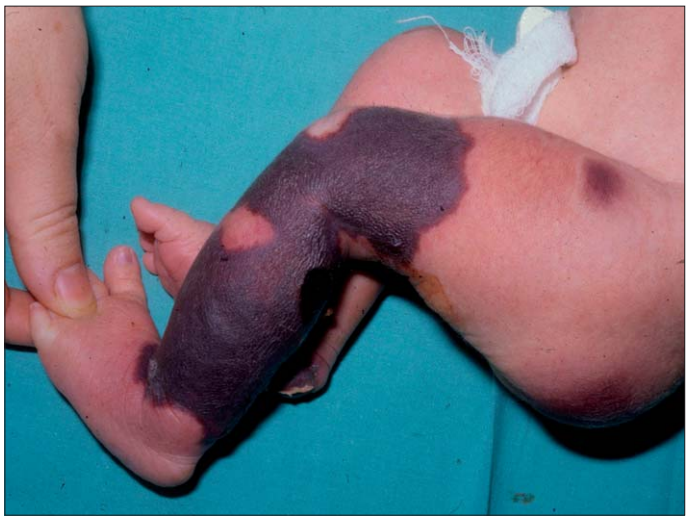


FIG. 19-27 Neonatal purpura fulminans due to protein C deficiency.

ecchymoses in a diffuse and often symmetric distribution that rapidly evolve into hemorrhagic bullae and purple-black necrotic skin lesions, which ultimately form a thick eschar (Fig. 19-27). The initial ecchymotic areas are sharply defined from the surrounding skin and usually have a red, advancing inflammatory rim. They are most common at sites of trauma or pressure, the buttocks, extremities, trunk, and scalp. Mucous membranes may rarely be involved.[393] If treatment is instituted in the first 1–3 hours, before necrosis ensues, the initial lesions may be reversible.[390]

Extracutaneous Findings

Other organs may be affected by the microvascular thrombosis, most commonly the CNS and eye, but also the kidney and gastrointestinal tract. Cavernous sinus involvement, which may occur in utero, can result in hydrocephalus, seizures, intracerebral hemorrhage, and mental retardation.[388,394,395] Microphthalmia, cataracts, and blindness due to vitreous or retinal hemorrhage may be seen.[388,389] Deep venous thrombosis and pulmonary embolism have also been described.[394]

Etiology and Pathogenesis

Purpura fulminans in the neonatal period is almost always caused by inherited thrombophilic states such as homozygous protein C and S deficiency or resistance to activated protein C. Severe bacterial infection associated with DIC can also induce purpura fulminans in the neonate, although it is more common in infancy or early childhood.[396,397] Proteins C and S are vitamin K-dependent glycoproteins with antithrombotic properties.[398,399]

Protein C deficiency is an autosomal dominant disease with incomplete penetrance.[399] Homozygous or compound heterozygous patients have a severe clinical phenotype and usually present with neonatal purpura fulminans, although they may be asymptomatic or present later in life with recurrent thrombosis.[400,401]

Protein S deficiency is also transmitted as an autosomal dominant trait with incomplete penetrance.[399] Homozygous patients may develop neonatal purpura fulminans, although the risk is lower than in patients with homozygous protein C deficiency.[387,402]

Neonatal purpura fulminans may also be caused by activated protein C resistance due to a mutation in the factor V gene.[393,403] Resistance to activated protein C may coexist with protein S and protein C deficiencies, becoming an additional genetic risk factor for purpura fulminans or thromboembolic complications, and explaining in part the incomplete clinical penetrance of inherited thrombophilic disorders.[404]

Laboratory Tests and Histopathology

Blood coagulation studies demonstrate evidence of DIC, including prolonged prothrombin and partial thromboplastin times, increased fibrin split products, reduced fibrinogen, and reduced platelets. Microangiopathic hemolytic anemia may occur.

Biopsy of the early skin lesions demonstrates occlusion of dermal blood vessels by microthrombi. Hemorrhage and dermal necrosis are present in the more advanced stages. Necrosis of the overlying epidermis with subepidermal hemorrhagic bullae occurs in later phases. Secondary fibrinoid necrosis of dermal vessel walls may be present in the necrotic areas, but primary vasculitis is absent.[390,405]

A definitive diagnosis of protein C and S deficiency is established by measurements of protein C and S levels.[399] Protein C deficiencies can be identified by immunoenzymatic assays measuring the actual concentration of the protein in plasma, and two functional assays measuring the enzymatic activity and the anticoagulant activity. These tests distinguish two types of protein C deficiency. In type I, which is the most common, reduced synthesis of the normal protein leads to a low plasma concentration in all three assays. In type II, a qualitative deficiency, levels are normal but functional assays are abnormal. For protein S deficiency, functional and immunoenzymatic assays are available, and both the free form and the inactive form that circulates bound to C4b-binding protein have to be measured.[399] Type I deficiency is characterized by low total and free protein S, type II by normal free protein S and low activity, and type III by low free protein levels with normal total levels.

Interpreting the results of the assays may be difficult because protein C and S levels are physiologically reduced in the neonatal period, and may be undetectable in sick newborns with liver disease, respiratory distress syndrome, DIC, or sepsis.[389,390,396,397,406] A complete sepsis workup is therefore recommended in any case of neonatal purpura fulminans. Serial determination of protein levels in patients and other family members is necessary to exclude a transient deficiency and confirm true congenital deficiency.

Differential Diagnosis

The cutaneous lesions of purpura fulminans are very characteristic and rarely mistaken for any other condition. Other causes of purpuric eruptions in the newborn may be considered (see Box 19-6).

Course, Management, Treatment, and Prognosis

Without treatment, neonatal purpura fulminans is often fatal. If the diagnosis is suspected, therapy should be initiated immediately without waiting for the results of protein C and S measurements. Prompt treatment may completely reverse early skin lesions. Initial therapy consists of the administration of fresh frozen plasma (10–15 mL/kg/12 h) or prothrombin complex concentrate, sources of protein C, protein S, and activated protein C.[389,390] A protein C concentrate has been developed that has the advantage of avoiding blood volume overload and does not carry the risk of transmission of viral

Box 19-6 Differential diagnosis of blueberry muffin lesions

Dermal erythropoiesis
- Congenital infection
  - Rubella
  - Cytomegalovirus
  - Parvovirus B19
  - Coxsackievirus B2
- Hemolytic disease of the newborn
  - Rh incompatibility
  - Blood group incompatibility
- Hereditary spherocytosis
- Twin transfusion syndrome

Neoplastic-infiltrative diseases
- Neuroblastoma
- Rhabdomyosarcoma
- Langerhans cell histiocytosis

Congenital leukemia

Modified from Baselga E, Drolet BA, Esterly NB. J Am Acad Dermatol 1997;37:673–705.

diseases.[407,408] Protein S concentrate is not yet available for clinical use. Replacement therapy should be continued until all lesions have healed, usually after 4–8 weeks. Long-term treatment involves careful administration of oral anticoagulants, starting at very low doses and with protective replacement therapy to avoid coumarin-induced skin necrosis. Experience with long-term treatment using protein C infusions is limited. There are few case reports of a successful liver transplant for homozygous protein C deficiency.[409,410]

PURPURIC PHOTOTHERAPY-INDUCED ERUPTION

This benign, transient purpura in transfused neonates who undergo phototherapy is characterized by raspberry-colored, nonblanching lesions at exposed sites, sparing sites that are protected from lights (e.g. leads and temperature probes).[206,208] The eruption develops after 1–4 days of phototherapy and clears spontaneously after discontinuation of light therapy. Histologically there is extravasation of red blood cells in the dermis without epidermal damage. The pathogenesis of this disease is unknown, although transient porphyrinemia has been detected in some patients.[367,411] The purpuric nature of the eruption and the absence of 'sunburn cells' differentiate this eruption from 'sunburn' caused by exposure to UVA from fluorescent lamps.[412] Congenital erythropoietic porphyria and transient elevated porphyrin levels in neonates with hemolytic disease may also cause photosensitivity.[411] Drug-induced phototoxicity in neonates who have received photosensitizing chemicals such as fluorescein dye, furosemide or methylene-blue must be considered.[413–416]

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