Clinics in Dermatology (2019) **37**, 213–226

ELSEVIER

Clinics in Dermatology

Viral exanthems in children: A great imitator

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Abstract Viral exanthems are frequent in children and are mostly self-limited. Early recognition and differentiation from other childhood illnesses are important to direct further investigations and treatment initiation. The clinical presentation of viral exanthems in children includes a polymorphic spectrum of skin eruptions ranging from classic viral exanthems to "atypical" presentations that can mimic nonviral diseases; thus, viral exanthems of childhood can be readily diagnosed on clinical grounds, but not rarely do they represent a diagnostic challenge. In this review, we focus on viral diseases in children that may be difficult to diagnose due to their clinical similarities with nonviral diseases, and we offer clues for the differential diagnosis and proper diagnostic testing in such cases.

Introduction

Viral-induced exanthems in childhood account for a significant number of patient visits to pediatric outpatient clinics, as well as for inpatient and emergency room consultations.[1] They are mostly harmless and self-limited in the healthy child but are often a matter of diagnostic difficulty. While some viruses present with characteristic cutaneous or mucosal features that aid in making a prompt diagnosis, the majority of viral exanthems remain nonspecific, and even when a viral disease is suspected, a clear viral etiology cannot be addressed. Viral exanthems may present as a macular, maculopapular, papular, urticarial, or vesicular diffuse cutaneous eruption that is commonly accompanied by prodromal clinical manifestations such as fever and malaise.[2,3] As a result, recognition and differentiation from other severe illnesses during childhood in some cases may be challenging but is often crucial to outline further investigation or to initiate treatment.[4–5]

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https://doi.org/10.1016/j.clindermatol.2019.01.009
0738-081X/

The spectrum of viral causes of exanthems has widened with the emergence of novel viruses and advances in laboratory diagnostic methods[6,7]; furthermore, the declining rate of vaccination in some countries, along with increasing population and universal vector movement, warrant a high level of expertise for the clinical diagnosis of both classic and atypical presentation of viral exanthems to assure prompta diagnosis and establish proper health care measures.[8,9]

This review focuses on common specific viral exanthems in children that commonly mimic nonviral dermatoses, and highlights certain scenarios with unusual presentations of viral diseases that may be misdiagnosed.

Hand, foot, and mouth disease and enteroviral exanthems

Hand, foot, and mouth disease (HFMD) is a highly contagious viral illness typically affecting children younger than 5 years of age. For many years, enterovirus-type 71 and coxsackievirus (CV)-A16 were the most common causes of HFMD

outbreaks worldwide; however, an increasing incidence of HFMDlike disease caused by CV-A6 and CV-A10[10,11] has occurred since 2008, when several outbreaks of HFMD due to these emerging viruses were reported in Asia, America, and Europe. The disease has received noticeable attention due to increasing evidence that the clinical, epidemiologic, and etiologic characteristics of HFMD are currently quite different from those initially thought.[12,13] Classic HFMD is predominantly a localized eruption limited to the oral cavity with vesicles and painful ulcerations after 1 to 2 days of fever onset, followed by the appearance of typical grayish vesicles with surrounding erythema on the palms and soles but also on the buttocks and genital region. Though classic HFMD has quite distinctive clinical features, nonviral diseases, such as erythema multiforme or bullous pemphigoid, can be mimicked. Cases of atypical HFMD are associated with CV-A6 and usually present with a severe and extensive clinical picture.[14,15] This peculiar presentation has been attributed to mutations in various regions of the viral genome.[16]

Several morphologic patterns of atypical HFMD have been proposed. A widespread vesiculobullous and erosive eruption, with perioral, acral, and buttock predilection, may be misdiagnosed as immunoglobulin A linear dermatosis, erythema multiforme, Stevens-Johnson syndrome, mycoplasma-induced euption and mucositis, zinc deficiency, and Langerhans cell histiocytosis (Figure 1). The eczema herpeticum-like eruption (eczema coxsackicum) mainly affects areas involved by eczematous lesions in children with atopic dermatitis and is often confused with bacterial superinfection (Figure 2). A Gianotti-Crosti–like eruption may occur. Rarely, a petechial or purpuric eruption may mimic cutaneous vasculitis or acute, bacterial purpura. Finally, onychomadesis and acral desquamation are late manifestations that can be attributed to other causes such as acute illness, Kawasaki disease, or scarlet fever.[14] These HFMD morphologies are not known to portend a worse prognosis, and the majority of patients are managed in an outpatient setting with supportive care measures showing complete resolution of their clinical manifestations within 7 to 10 days.[14,15,17]

Prompt diagnosis of enteroviral exanthems is usually made on clinical grounds, but other differentials of erosive or bullous disorders in children must be considered, as these portray a different prognosis. Also, a correct diagnosis avoids unnecessary hospitalization, invasive testing, and antibiotic therapy. Complications of enteroviral exanthems are unusual, but meningitis, encephalitis, neurogenic pulmonary edema, and acute heart failure have been described.[18–20]

There is no specific antiviral treatment for enteroviral infections. Acyclovir is not effective, and its use is only indicated for eczema herpeticum caused by the herpes simplex virus (HSV); thus, a differentiation of both diseases is necessary. The definite diagnosis of enteroviral exanthems can be achieved through detection of enterovirus by real-time reverse transcriptase polymerase chain reaction (PCR) from vesicular fluid, but throat swabs and stool samples are also acceptable.[21] Eczema coxsackium may be clinically indistinguishable from eczema herpeticum, and in these cases, HSV testing should be performed to rule out a herpetic infection that needs further treatment with acyclovir.

Gianotti-Crosti syndrome

Several viruses from entirely different groups can cause an immune response leading to a well-characterized exanthematous skin eruption named papular acrodermatitis of childhood or Gianotti-Crosti syndrome (GCS).[22,23] The syndrome was originally described in 1955 by Ferdinando Gianotti (1920-1984) and Agostino Crosti (1896-1988) in Milan, Italy and was found to be associated with hepatitis B infection.[22] Subsequent reports from different countries highlighted further cases associated with the Epstein-Barr virus, cytomegalovirus, coxsackievirus, parvovirus B19, *Human herpesvirus* 6, and parainfluenza virus, among many others; cases after immunization have also been confirmed.[24,25] In a retrospective review of 696 patients with molluscum contagiosum, 5% have been shown to develop a Gianotti-Crosti–like eruption.[26] Taking into account these observations, Gianotti-Crosti syndrome is best regarded as a parainfectious reaction pattern associated with viral infections and immunizations.

The clinical manifestation is characterized by a symmetric eruption of monomorphous small papules or papulovesicles on the cheeks, ears, extensor surface of the arms and legs, and buttocks (Figure 3). Skin lesions are usually firm, erythematous to brown papules of 1 to 5 mm in size and are usually more edematous in young infants.[23] Occasionally, they may become hemorrhagic, purpuric, or even overtly papulovesicular. In the early stage of the disease, patients may present with a transient eruption on the back, chest, or abdomen, and the isomorphic phenomenon (Koebner phenomenon) may be present.[3] Children between 6 months and 14 years may be affected, but most cases occur during early childhood between ages 1 to 6.[2,3] Many patients show prodromal viral clinical manifestations, but the exanthem is rarely accompanied by lymphadenopathy, hepatomegaly, or splenomegaly. The mucosal membranes are typically spared.

The diagnosis of GCS is clinical, but a skin biopsy may be required in difficult cases. Histologic findings are not diagnostically specific but enough to suggest GCS. There is a superficial perivascular lymphocytic infiltrate, mild spongiosis, and prominent focal exocytosis of mononuclear cells into the lower part of the epidermis. This is usually accompanied by some degree of basal vacuolar change and the presence of an infiltrate at the dermoepidermal junction, producing a spongiotic-lichenoid reaction. Papillary edema and extravasation of erythrocytes can be seen, but vasculitis is not a feature.[27,28]

When lesions have a purpuric appearance, they can be misdiagnosed as Henoch-Schönlein purpura (HSP). In HSP, lesions are larger, appear in crops, and usually affect older children with joint tenderness and visceral involvement. In infants and young children, acute hemorrhagic edema (AHE) can be considered due to the characteristic trunk sparing in

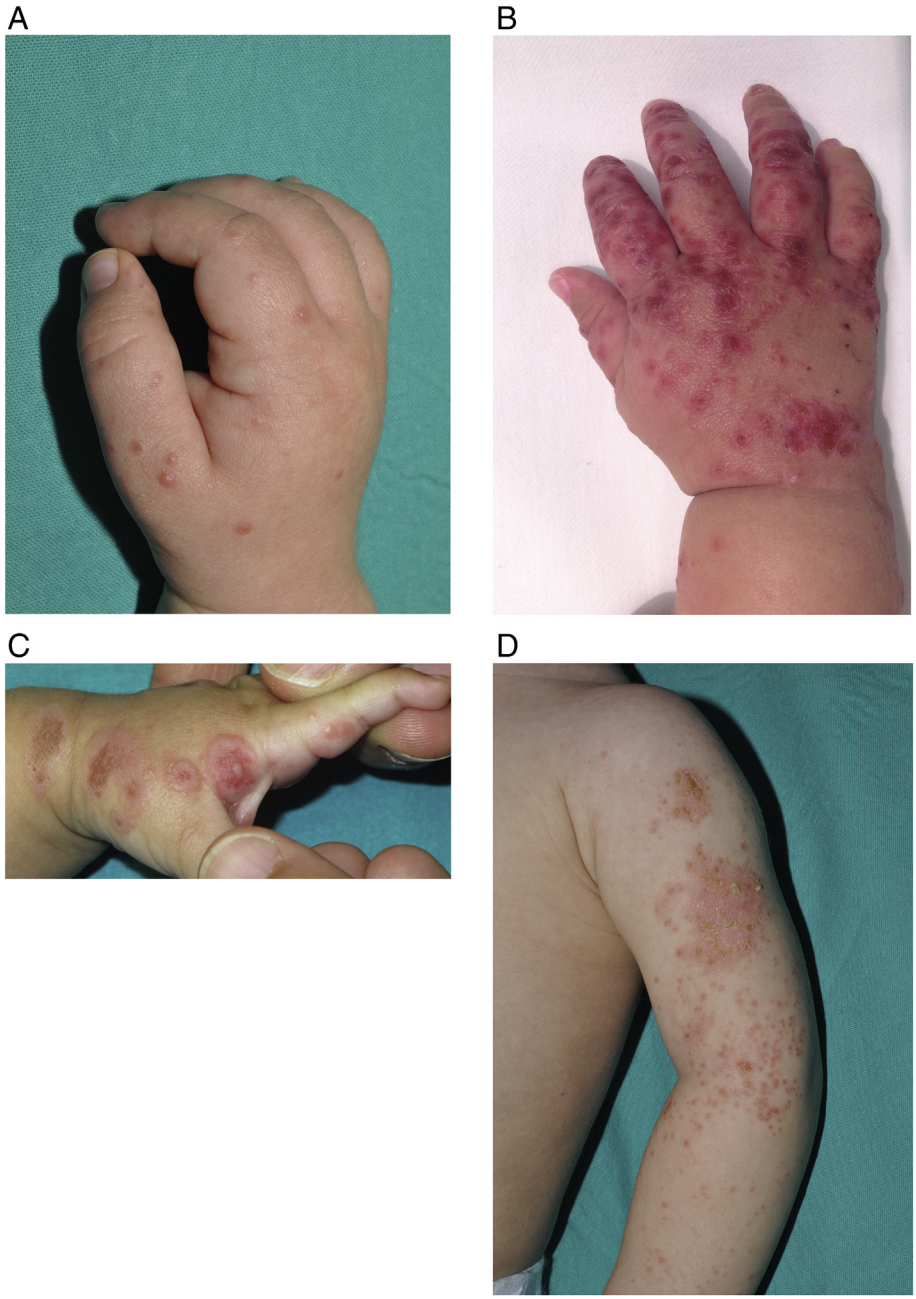

Fig. 1 A-D, Vesiculobullous eruption of coxsackie virus. C, Bullae and target lesions mimicking erythema multiforme may occur. B, Reproduced with permission from Dr. Lisa Weibel. C, Reproduced with permission from Ana Martín, MD.

AHE and GCS. The typical cockade purpura of AHE is not seen in purpuric lesions of GCS. Erythema multiforme (EM) has a similar distribution of lesions to GCS, and a distinction between mainly papular EM and papulovesicular GCS can be difficult. Other conditions that may be confused with GCS include insect bites, eosinophilic pustulosis of infancy, urticaria, lichen planus, pityriasis lichenoides, and cutaneous drug reactions; dermatitis herpetiformis may show edematous papules and papulovesicles in a similar distribution to GCS. All these are usually accompanied by pruritus, and a skin biopsy can be helpful to establish the correct diagnosis.

GCS follows a self-limited course, and resolution comes after 3 to 4 weeks, though some cases may last several months. In these cases, papular, disseminated granuloma annulare can be mimicked. Treatment is supportive with emollients and topical steroids, if the lesions appear inflammatory.

Papular purpuric gloves and socks syndrome

Papular purpuric gloves and socks syndrome (PPGSS) is an acute acral exanthem that most commonly affects young adults but has been reported in children. Parvovirus B19 was first

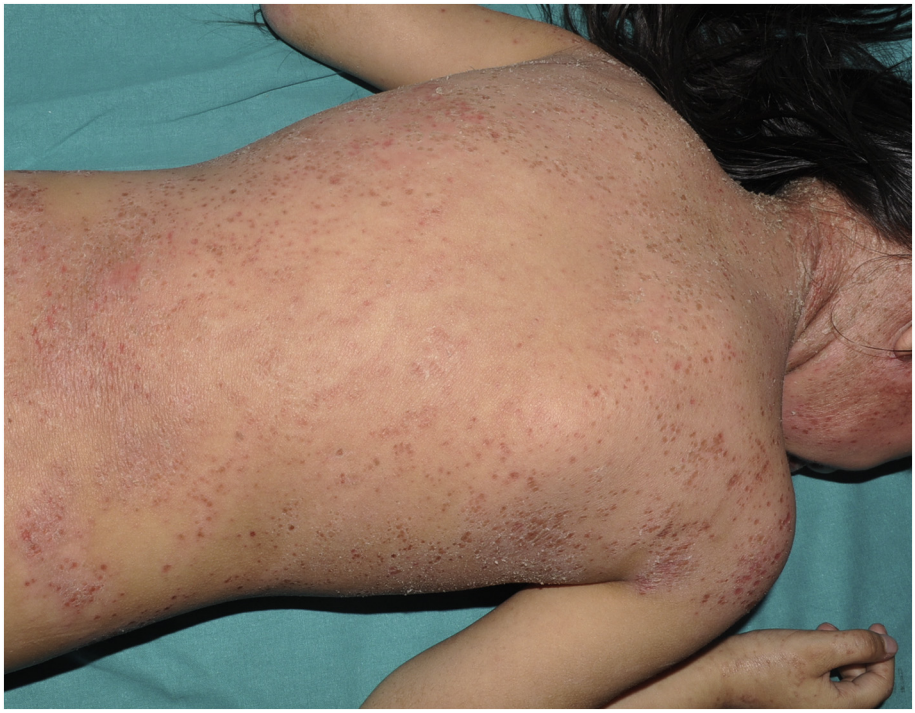

Fig. 2 Eczema coxsackium: viral vesicles spread on areas affected with atopic dermatitis.

identified as causing this syndrome and remains the most frequently associated virus.[29] Other cases attributed to coxsackie virus, cytomegalovirus, measles, Epstein-Barr virus, or hepatitis B have been documented[30]; however, only the parvovirus has been demonstrated to be present in a biopsy specimen and peripheral blood along with serologic conversion.[31]

The clinical presentation consists of a symmetrical, painful or burning, bright red exanthem, and edema of the hands and feet that gradually progresses to purpuric confluent papules and petechiae (Figure 4). These lesions are sharply demarcated on the wrists and ankles; hence, the designation of gloves and socks. Some patients may also present with lesions on the cheeks, elbows, knees, buttocks, and genitals. The acral exanthema is preceded by mild viral clinical manifestations, and patients usually show oral mucosal involvement in the form of petechiae on the hard palate, oral erosions, and vesicles.

The recognition of the distinctive, sharply bordered acral purpuric exanthema in a child with no signs of illness

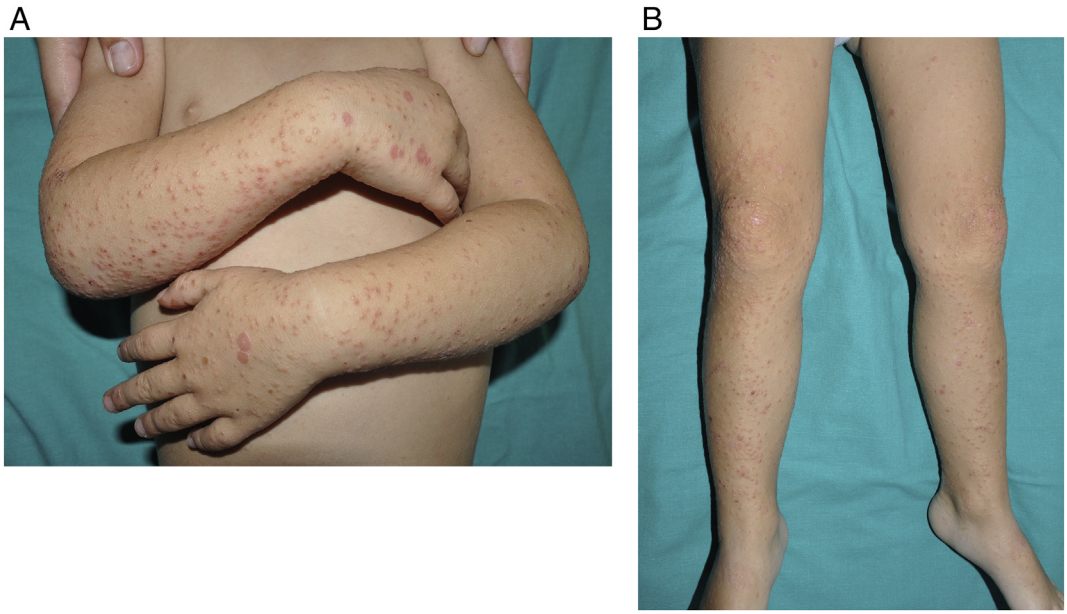

Fig. 3 Gianotti-Crosti syndrome. Papules and papulovesicles on extensor areas of the arms and legs, sparing the trunk.

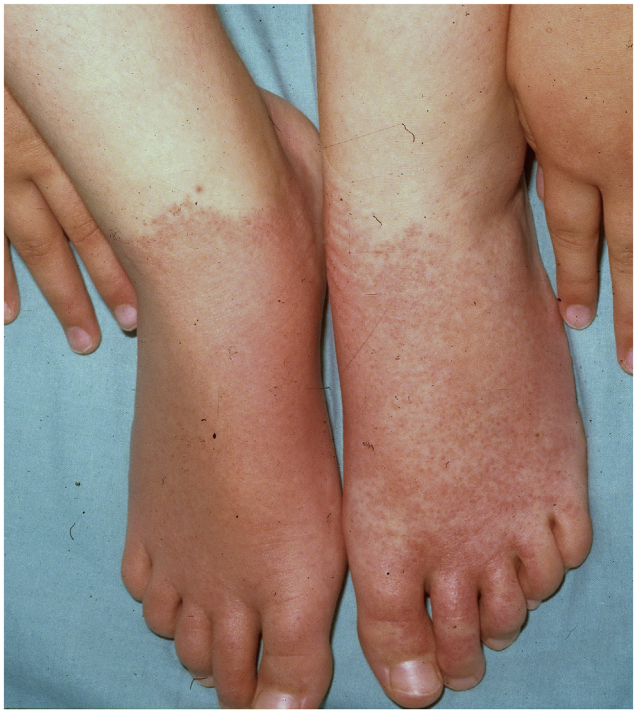

Fig. 4 Papular purpuric gloves and socks syndrome.

generally allows a straightforward diagnosis. A similar abrupt border is seen in children with localized pityriasis rubra pilaris, but these have diffuse involvement and not the discrete, purpuric papules of the PPGSS. Other nonviral diseases in the differential mainly include early stage EM, Kawasaki disease (with fever, acral edema, and mucosal involvement), and meningococcemia (with fever and widespread acute purpura).

PPGSS resolves spontaneously in 1 to 2 weeks, and complications are associated with underlying parvovirus B19 infection; patients with hemoglobinopathies are at risk for aplastic anemia, and pregnant women are at risk for nonimmune hydrops fetalis or fetal death.[2,3]

Besides PPGSS and erythema infectiosum (Table 1), parvovirus B19 is known to induce a wider spectrum of skin lesions. A retrospective review of parvovirus B19 primary infection in 29 adults classified the skin manifestations in four patterns: (1) exanthem, (2) vasculitis, (3) periflexural, and (4) acral involvement.[32] These forms have also been reported in children.[33] Parvovirus B19-related vasculitis closely resembles HSP and may have systemic clinical manifestations. The generalized exanthem of parvovirus B19 can present as acute, widespread purpura, and thus a differential with common causes of purpura is necessary (eg, idiopathic thrombocytopenic purpura, meningococcemia, and many others) (Figure 5). Most recently, parvovirus B19 has been linked to juvenile spring eruption, reinforcing the role of ultraviolet light and reactivation of viral infections in photodermatosis.[34] The causal role of parvovirus B19 alone in these eruptions is unlikely.

Varicella-zoster infection

Varicella (chickenpox) is the primary manifestation of varicella-zoster virus (VZV) infection and is a very common childhood exanthem, though its incidence has markedly declined since the introduction of a vaccine.[6] The VZV is highly contagious and transmitted by airborne droplets and by direct contact with the infectious lesions. After an incubation period of 10 to 21 days, children present with a prodromal state of fever, mild fatigue, and headache, which is followed by a typical exanthem that begins at the hairline and spreads cranial to caudal with a centripetal distribution.[5] Skin lesions are pruritic and rapidly evolve from macules to papules to vesicular and crusted lesions. The characteristic vesicular lesion of varicella shows an erythematous base (dewdrops on a rose petal), and the synchronous manifestation of older and new lesions defines the polymorphous phenotype of varicella exanthem.[3] Lesions may heal with scarring, and the most common complication is bacterial superinfection, followed by neurologic complications (meningitis, encephalitis, Guillain-Barré). Less commonly, glomerulonephritis, keratitis, hepatitis, and hematologic complications, manifesting as thrombocytopenic purpura and purpura fulminans, have been associated. Immunosuppressed children are at higher risk of developing such complications, including a high mortality rate.[2,3]

Varicella is usually diagnosed on clinical grounds alone in normal healthy children, and laboratory tests are not necessary for diagnosis. In case of uncertainty or in immunosuppressed patients, direct detection of VZV should be sought under rapid molecular techniques such as PCR, direct immunofluorescence, and DNA-hybridization.[5] Differential diagnoses in these cases include disseminated HSV, generalized HFMD, and pityriasis lichenoides et varioliformis acuta.

A peculiar variant of varicella infection may appear in patients immunized against VZV, when they are exposed to the wild-type virus; a milder maculopapular exanthema with few vesicles develops. This clinical presentation is usually not accompanied by fever and may be misinterpreted as eosinophilic pustulosis or a nonspecific viral exanthem.[5]

Treatment is symptomatic and relies on local therapy and pruritus relief. Acyclovir may be prescribed to reduce duration and severity of varicella infection. Treatment should be initiated within 24 hours of development of skin lesions and is recommended in high-risk individuals (older patients, those with chronic skin or lung disease, and those under chronic treatment with salicylates). Intravenous acyclovir is recommended in immunosuppressed patients and in significant complications.[3,35]

Herpes zoster (HZ) represents the reactivation of VZV, which had remained in a latent state in the sensory nerve root ganglia. It typically manifests with pain, burning, or hyperesthesia, and 2 to 3 days later, erythema and clustered vesicles develop following a dermatome. HZ has been reported in immunocompetent children accounting for less than 1% of all cases.[36] It has been suggested that a younger age of varicella infection is associated with a greater susceptibility of developing HZ in childhood or early adulthood. In children, there is a

Table 1 Classic viral exanthems during childhood

Classic exanthems	Virus	Incubation period (days)	Exanthem	Enanthem	Extracutaneous findings	Comments/Special remarks differential diagnosis
Measles (1st disease)	Paramyxoviridae family, genus *Morbillivirus*	10-12	Maculopapular confluent exanthem Craniocaudal dissemination	Koplik spots	Fever, rhinoconjunctivitis, dry cough	Morbiliform exanthem in 1. Drug-induced exanthem: recent intake of antibiotics, NSAIDs, exanthem mainly on extensor surface of extremities, pruritus 2. DRESS: history of antiepileptics, allopurinol, antibiotics, facial edema, lymphadenopathy, hepatomegaly in addition to fever, rapid desquamation of exanthem reminiscent of eczema
Scarlet fever (2nd disease)	Group A β-hemolytic streptococci	1-7	Sandpaper-like dermatitis that blanches on digital pressure, flexures accentuation, perioral pallor	Strawberry tongue	Fever, tonsillitis	Other classic viral exanthems. Epstein-Barr viral infection
Rubella (3rd disease)	Togaviridae family, genus *Rubivirus*	14-21	Discrete maculopapular confluent exanthem Craniocaudal dissemination	Forchheimer spots	Mild fever, symmetric lymphadenopathies, mainly occipital and postauricular	Rubella-like exanthem in other classic viral exanthems, adenovirus, parainfluenza virus, drug-induced exanthem
Erythema infectiosum (5th disease)	Parvovirus B19	4-14	First slapped cheeks, then reticulate macular exanthem mainly affecting the extensor surface of the extremities	Usually not involved	Fever, arthralgia/ arthritis	Initial stage of slapped cheeks: photodermatoses, erythema migrans (though mainly unilateral) Macular reticulate or lacelike exanthem: other viral infections including enterovirus, exanthem secondary to mycoplasma and drug-induced exanthem
Exanthema subitum (6th disease)	Herpes virus type 6 and type 7	5-15	Discrete macular or maculopapular exanthem after fever subsides Trunk predominance	Usually not involved	Fever, lymphadenopathies	Other viral exanthems, drug-induced exanthem

DRESS, Drug dermatitis with eosinophilia and systemic clinical manifestations; NSAID, nonsteroidal antiinflammatory drug.

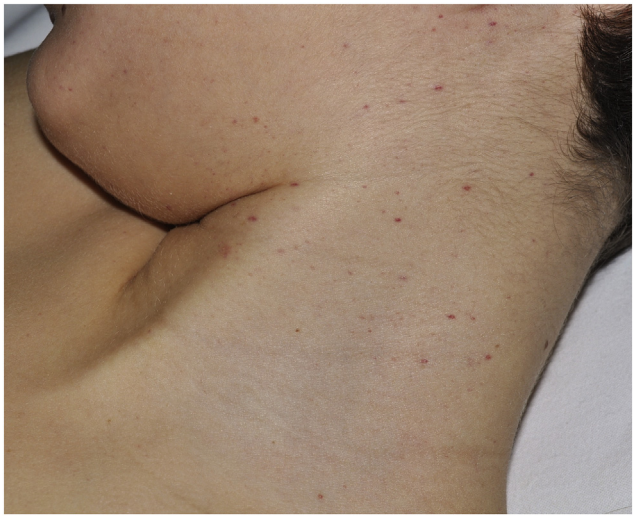

Fig. 5 Acute flexural purpura in a child with parvovirus B19 infection.

predilection for the cervical and sacral dermatomes and, contrary to adults, postherpetic neuralgia is uncommon.[3] Immunosuppressed patients are at higher risk.[37] Vaccine-strain HZ in pediatric patients without illness has been reported, and the clinical presentation does not differ significantly.[36] The main differential diagnosis of clustered vesicles with underlying erythema remains with *Herpes simplex* infection, but this virus tends to recur at the same site. Confirmation of VZV is based on the same techniques used for varicella infection.

HZ may be confused with other nonviral diseases, such as bullous impetigo, acute eczema, lichen striatus (due to the linear involvement), and linear atopic dermatitis (Figure 6).

Acyclovir is the only antiviral agent approved for the treatment of HZ in children. Therapy is usually given orally, and intravenous administration is recommended in immunosuppressed children.

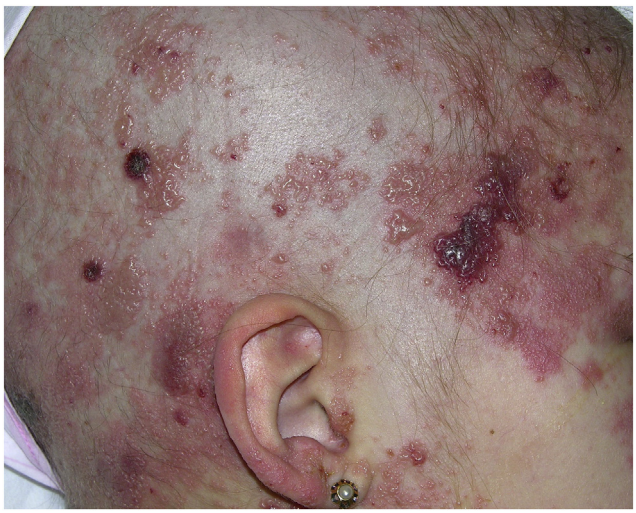

Fig. 6 Disseminated varicella-zoster infection in an immunocompromised child.

Unilateral laterothoracic exanthem of childhood

Unilateral laterothoracic exanthem, also known as asymmetric periflexural exanthem of childhood, most often affects children between 1 and 5 years of age and begins near an axilla or, less often, on the inguinal crease, only to then spread centrifugally, remaining unilateral or at least overtly asymmetric, with much less involvement contralaterally.[38] A predominance in girls has been observed, and there is a typical peak during the spring.[2] The exanthem consists of discrete erythematous papules and is followed by development of ill-defined eczematous patches separated by normal skin that invariably involve the thorax but extend to the inner surface of the arm, the flank, and, less often, the thigh (Figure 7). A conspicuously single, enlarged lymph node is usually easily palpated in the axilla or the groin. Bilateral involvement may occur as the eruption progresses.

The etiology of this exanthem remains unknown; since its first description, it has inconsistently been linked to a viral infection, as most cases are preceded by a mild upper respiratory

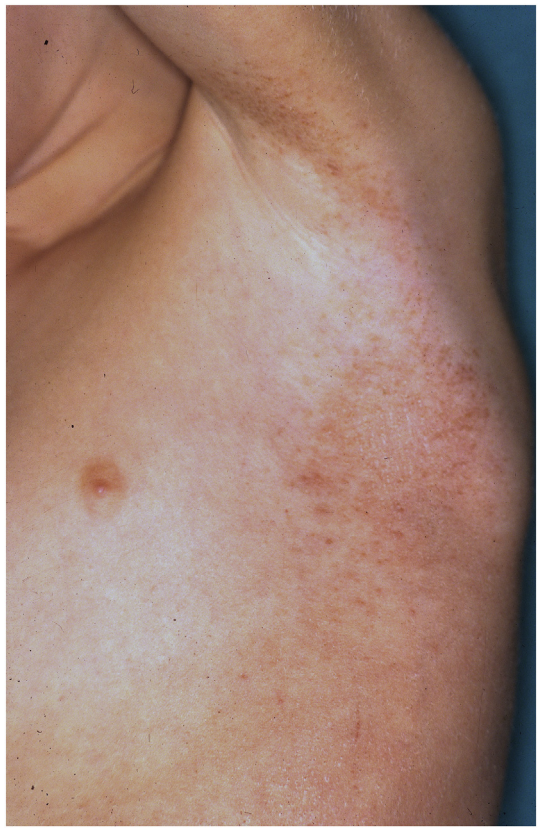

Fig. 7 Unilateral laterothoracic exanthema. Mild scaly erythema on the side of thorax and inner side of the arm; the axilla is typically spared.

illness. Concomitant cases within family members and community outbreaks have been observed.[39] Asymmetric periflexural exanthem of childhood can mimic other nonviral conditions, such as contact dermatitis, systemic drug-related intertriginous and flexural eruption, flexural dermatitis, tinea, pityriasis rosea (inverse variant), acute exanthamatous pustulosis, and scarlet fever. The exanthem usually resolves after a few weeks, and only symptomatic treatment is needed.

Eruptive pseudoangiomatosis

Eruptive pseudoangiomatosis represents an uncommon, self-limiting exanthem that occurs primarily in children. It is characterized by the sudden appearance of a few to numerous bright-red blanchable, 2- to 4-mm size, angiomalike papules, surrounded by a pale halo on the face, trunk, and extremities (Figure 8).[40] The perilesional halo may not be seen in lesions located on the face, and an annular configuration of lesions has also been described.[41] The etiology of this eruption is still unknown. The presence of an echovirus in the four original cases has been confirmed,[40] but further isolated reports have associated other viral infections (coxsackie B, adenovirus, cytomegalovirus, and Epstein-Barr virus).[42] Most children present with viral prodromes of mild fever, diarrhea, or upper airway respiratory clinical manifestations. Cases in adult patients attributed to mosquito bites have been documented. Histopathologic examination shows a mild to moderate perivascular lymphocytic infiltrate and ectatic dilated capillaries in the superficial dermis with plump endothelial cells protruding into the lumen[43]; hence, eruptive pseudoangiomatosis is best regarded as a vascular reaction pattern of a parainfectious exanthem. The differential diagnoses of acute onset of angioma-like lesions in children include multiple hemangiomas (if occurring in the neonatal period), spider angiomas (telangiectasias), Bier spots, multiple pyogenic granulomas, and bacillary angiomatosis.

The eruption usually resolves spontaneously within 1 to 2 weeks, although it may last up to 3 to 4 months. Seasonal recurrences have also been reported.[44]

Epstein-Barr virus

Epstein-Barr virus (EBV) is a ubiquitous, double-stranded DNA herpes virus with a high prevalence in the general population, around 60% to 80% in children and up to 95% in adults. Primary infection occurs in the oropharyngeal mucosa and then extends to the B cells in the lymphoid tissues. Other cells can also host the infection, such as T lymphocytes, other epithelial cells, and monocytes.[45]

In young children, the primary infection may be asymptomatic, but during adolescence, the classic clinical picture mimics infectious mononucleosis, characterized by fever, pharyngitis, lymphadenopathy, fatigue, and a maculopapular eruption,

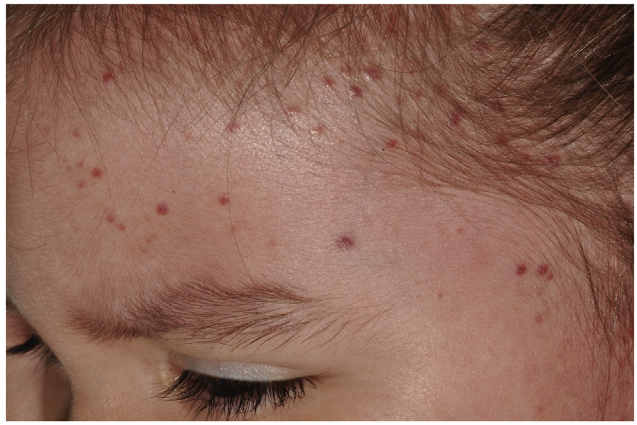

Fig. 8 Eruptive pseudoangiomatosis.

initially located on the trunk and then extended to the face and extremities. This eruption can be a mimicker for many reasons, especially because it can occur with the concomitant administration of an antibiotic, frequently ampicillin or amoxicillin, and can be interpreted as a drug allergy. It has been demonstrated that the responsible antibiotic can be readministered after resolution of infectious mononucleosis without any adverse effect.[46,47] In some patients, EBV primary infection may present as an urticarial eruption, a scarlet feverlike eruption, and a vesicular or purpuric eruption.[45,48]

EBV can also manifest under other dermatologic conditions, as a result of either primary infection or viral reactivation. GCS or EM can occur in the context of EBV infection.[48] Less frequently, EBV infection manifests as:

- **Oral hairy leukoplakia**, which occurs in the context of viral reactivation in immunocompromised children. It presents as irregular, corrugated, white or gray plaques along the lateral borders or any part of the oral mucosa. Lesions are often asymptomatic or produce a mild discomfort or alteration of taste. It can be distinguished from oral candidosis, because the plaques are firmly attached to the mucosa and cannot be scrapped off. Histopathologic features consist of epithelial hyperplasia with papillomatosis, acanthosis, and ballooning degeneration of the stratum spinosum. The demonstration of EBV in the lesional tissue can confirm the diagnosis.[48]
- **Hydroa vacciniforme** (HV). Classic HV is a childhood scarring photosensitivity disorder of unknown pathogenesis, characterized by a mild burning or stinging sensation within a few hours of sun exposure, with the appearance of vesicles and pustules on sun-exposed areas that evolve with central necrosis and eventually heal with a small scar in 1 to 2 weeks. This condition is not consistently associated with a lymphoproliferative disorder, although in some cases high numbers of EBV copies and activated lymphocytes may raise a suspicion. There are severe forms of HV-like eruption with ulcerative cutaneous lesions and systemic complications, which represent true skin lymphomas (HV-like lymphoma).[49,50]

Fig. 9 Acute genital ulcer due to the Epstein-Barr virus.

Several other mucocutaneous manifestations of EBV infection are mimickers of nonviral diseases. Acute genital ulcers of Lipschütz due to EBV can be misdiagnosed as syphilis or child abuse (Figure 9). Hypersensitivity to mosquito bites, erythema nodosum, erythema annulare centrifugum, granuloma annulare–like eruptions, pityriasis lichenoides, linear immunoglobulin A dermatosis, leukocytoclastic vasculitis, and even a drug dermatitis with eosinophilia and systemic signs (DRESS) has been related to EBV, but its pathogenic role of EBV in most of these conditions is still uncertain.[48]

Emerging viral infectious diseases with prominent cutaneous manifestations

In recent years, large-scale outbreaks of viral infections, once considered typical of certain areas, have gained medical attention. A history of travel to endemic areas should prompt the differential diagnosis of tropic diseases. Dengue, Zika, and chikungunya are viral infections produced by arboviruses, transmitted through mosquito bites from an infected animal or human to another animal or human host. *Aedes*-genus mosquitoes are responsible for the transmission worldwide. It can also be transmitted vertically or through blood transfusions. The diagnosis is made on clinical grounds, but serologic testing or PCR is necessary in nonendemic areas for epidemiologic characterization. Treatment is mostly symptomatic and directed to complications; acetaminophen is preferred over nonsteroidal anti-inflammatory drugs.[51]

Dengue fever

Dengue fever is the most prevalent and severe tropic disease in this group. Dengue virus is a member of the family Flaviviridae which includes other medically important vector-borne viruses (eg, Zika virus, yellow fever virus, West Nile virus, etc). The incubation period is 3 to 14 days. The infection may be asymptomatic in up to 50% of patients. The spectrum of illness is variable, ranging from a mild, nonspecific febrile syndrome to classic dengue fever, to the severe forms of the disease, dengue hemorrhagic fever and dengue shock syndrome. The course of infection is divided into three phases: (1) febrile phase (2-7 days); (2) critical or leakage phase (24-48 hours); and (3) convalescence phase (2-7 days).

The febrile phase presents with acute onset of high fever, headaches, nausea and vomiting, and abdominal pain, and it can be associated with severe myalgias and joint pain (dengue is also known as the break-bone fever or bonecrusher disease). Cutaneous manifestations vary along the course of the infection. Initially, a transient facial flushing due to capillary dilation can be seen, followed by an erythematous macular or maculopapular eruption of the trunk and extremities with isles of spare skin, occasionally with petechiae (Figure 10). Mucosae are rarely affected and can present erythema, crusting, vesicles and bullae; gingival bleeding or epistaxis are also described. After the febrile phase, up to 95% of patients enter into a convalescence phase and 5% of patients develop a critical phase with increased capillary permeability (pulmonary edema, pleural effusion, ascites and shock). Laboratory findings can show leukopenia in mild dengue, with thrombocytopenia and hemorrhagic diathesis in critical dengue. Severely affected patients may present with increased capillary permeability with elevated hematocrit, elevation of liver enzymes, and other signs of multisystem organ failure.[51,52]

Dengue is rarely suspected out of endemic areas. A few cases of dengue in patients who have not traveled to endemic areas have been reported.[53] Dengue can be confused with not only other viral exanthems but also with such nonviral diseases as dermatomyositis, systemic lupus erythematosus, Stevens-Johnson syndrome, and mycoplasma infection.[51,52]

Zika virus

Zika virus is closely related to dengue. The incubation period is not well defined, but it is estimated to be around 14 days. The infection may be asymptomatic in 80% of patients. The clinical presentation can be similar to the febrile phase of dengue. Mucocutaneous manifestations include conjunctival injection, cervical lymphadenitis, and a maculopapular or scarlatiniform exanthem indistinguishable from other viral eruptions or nonviral exanthems (eg, drug reactions or scarlet fever). Hyperemia of the hard palate, gingival bleeding, and petechiae can also be present. A strong link between maternal Zika infection and spontaneous abortions or birth defects (microcephaly, ophthalmologic, and neurologic defects) has been established, although the full range of illness in neonates is not yet completely understood.[51,52,54,55]

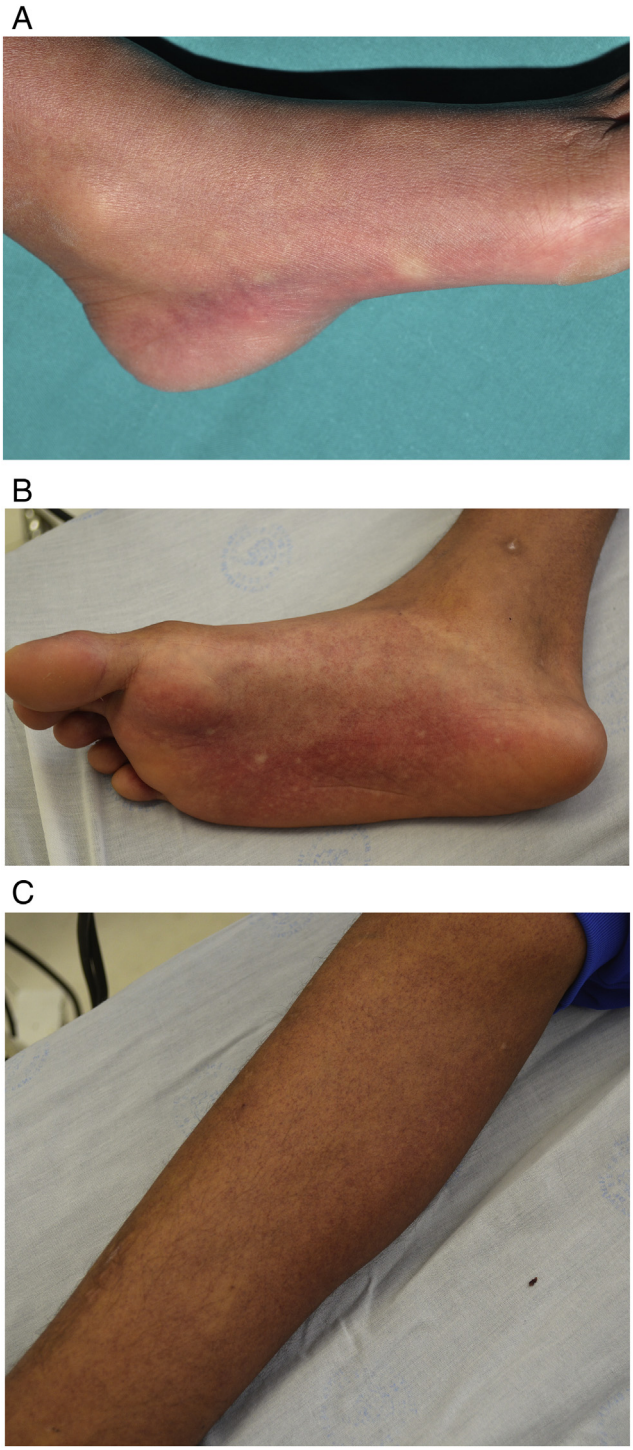

Fig. 10 A-C, Dengue. Deep erythematous or purpuric exanthema. B, C, Reproduced with permission from Angella López-Cedeño, MD.

Chikungunya fever

Chikungunya is a member of the Togaviridae family which also produces a febrile illness with severe arthralgias and cutaneous manifestations, although most patients are asymptomatic. Cutaneous manifestations has been thoroughly described in recent outbreaks (Figure 11). Incubation period is 1 to 12 days. Patients present with acute onset of fever and can show the typical morbilliform eruption or the macular generalized erythema with islands of normal skin similar to that seen in dengue fever. Up to 50% of children present with hyperpigmentation, either as a diffuse or generalized brown to black pigmentation of the skin predominantly on the face and extremities, or a more discrete form with scattered pigmented macules in the absence of erythema. It appears to be a form of postinflammatory hypermelanosis, although the exact mechanism is unknown; it can appear soon after the erythematous eruption clears or a few weeks later, but it has also been described without any prior eruption. Vesicular-bullous lesions may be seen and are more frequent in infants. The presence of petechiae, mucosal involvement with erosions and crusting, acrocyanosis, or the exacerbation of a pre-existent dermatologic condition has also been described. Hemorrhagic complications are rare in chikungunya. Patients usually recover in 1 to 3 weeks, and arthralgias

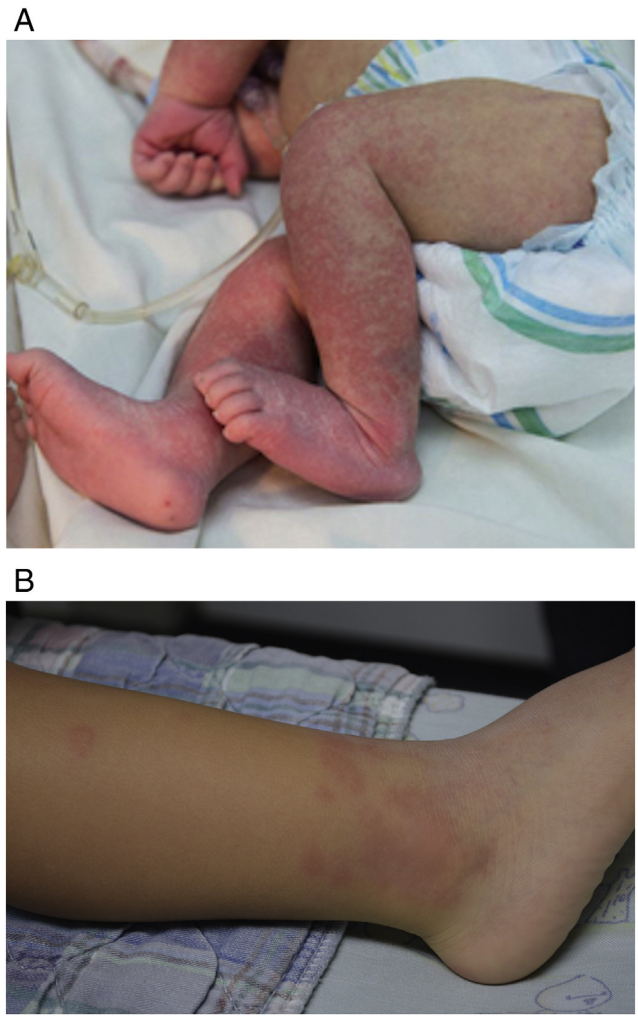

Fig. 11 A-B, Maculopapular eruption in chikungunya infection. Reproduced with permission from Angella López-Cedeño, MD.

Table 2 Nonviral skin diseases that can be mimicked by viruses

Nonviral skin condition	Mimicking viral disease	Diagnostic remarks
Infections & infestations		
Scarlet fever	Measles, fifth disease, viral dermatitis *	Search for pharyngeal streptococcus; Pastia lines of scarlet fever
Staphylococcal scalded skin syndrome	Viral dermatitis, enterovirus	Cultures for staphylococcus; perioral and flexural dermatitis typical of SSSS
Rickettsial diseases	Viral dermatitis	Epidemiologic context; serology; inoculation site
Toxic shock syndrome	Viral dermatitis	Cultures for staphylococcus/streptococcus; signs of organ failure
Superantigen-related exanthem	Viral dermatitis	Recurrent; flexural and groin involvement
Primary syphilis	EBV ulcers	Syphilis is painless, with minimal fevers; search for lymph nodes
Secondary syphilis	Rubella, viral dermatitis, HIV dermatitis	Typical palmoplantar dermatitis in syphilis
Meningococcemia	Measles, parvovirus B19, EBV, purpuric viral dermatitis	Organ failure in meningococcemia; progression of purpura, purpura fulminans
Scabies	Enterovirus	Pruritus, other affected family members
Mycoplasma-induced mucositis	Enterovirus, *herpes simplex infection*	Severe oral, eye and genital involvement; cultures for mycoplasma; some purpuric targets
Impetigo	*Herpes simplex infection*	Melliceric crusts, typical scaling
Pityriasis versicolor	Flat warts	PVlike lesions present in epidermodysplasia verruciformis
Acute paronychia	*Herpes simplex*, infection, orf,	Multilocular hemorrhagic bullae in herpetic whitlow and orf
Furuncle, carbuncle	Milker nodule, orf	Epidemiologic context
Inflammatory conditions		
Acute pityriasis lichenoides	Varicella, bullous viral eruption	Typical crusts and scales in PL; skin biopsy recommended
Pityriasis rubra pilaris	PPGSS, viral dermatitis	Palmoplantar hyperkeratosis and papulosquamous lesions in PRP
Eosinophilic pustulosis	Enterovirus, herpes zoster	Recurrent papulovesicles; prominent scalp involvement
Sweet syndrome	Viral dermatitis, herpes zoster	Fever, neutrophilia; biopsy with neutrophils
Eczema	Enterovirus, eczema herpeticum, molluscum eczema, APEC	Viruses can spread throughout eczema lesions and make it worsen; rule out bacterial overinfection
Kawasaki disease	Viral dermatitis, enterovirus	Tongue and lip dermatitistypical of KD
Systemic juvenile arthritis	Viral dermatitis, rubella, fifth disease	Joint involvement in sJIA; biopsy helpful if neutrophils in the infiltrate
Kikuchi disease (necrotizing lymphadenitis)	Viral dermatitis	Prominent lymph node enlargement
Systemic lupus erythematosus (SLE)	Fifth disease	Malar dermatitis in SLE different from slapped face in fifth disease
Dermatomyositis (DM)	Fifth disease	Cheek involvement possible in DM; search for eyelid involvement
Psoriasis	Viral dermatitis, enterovirus	Guttate psoriasis and acute pustular psoriasis may be mimicked
Palpable purpura, Henoch-Schönlein purpura	Parvovirus B19	Biopsy helpful; parvovirus B19 can induce arthritis and skin vasculitis
Mucosal lesions		
Genital aphthae	EBV ulcers	Febrile in EBV; no sexual activity recorded
Oral aphthae	*Herpes simplex*, enterovirus	Herpangina and other enteroviruses can mimic; aphthae are recurrent
Periodic fevers with aphthous stomatitis, pharyngitis, and adenitis	*Herpes simplex*, enterovirus	Recurrent course, pharyngeal involvement in PFAPA
Skin diseases in the immunocompromised host		
Graft-versus-host disease	Herpes virus 6 infection, viral dermatitis	Skin biopsy needed; other organs involved by GVHD
Lymphocyte recovery eruption	HHV6 infection, viral dermatitis	Associated with lymphocyte recovery
Chemotherapy reactions	HHV6	HHV6 reactivation can play a role in drug reactions

(continued on next page)

Table 2 (*continued*)

Nonviral skin condition	Mimicking viral disease	Diagnostic remarks
Benign and malignant tumor conditions		
Lymphoma	Viral dermatitis	Skin biopsy necessary
Leukemia cutis	Viral dermatitis, purpuric viral dermatitis	Nonspecific leukemia cutis with variable presentations
NonLangerhans cell histiocytosis	Molluscum, flat warts	Skin biopsy required for papules; dermatoscopy helpful; yellow color in nonLCH
Neonatal disorders		
Bednar aphthae	*Herpes simplex*, enterovirus	Solitary palate lesions from vigorous sucking
Transient neonatal pustular melanosis	*Herpes simplex*	No systemic involvement; excellent recovery in TNPM
Congenital leukemia	*Herpes simplex*, TORCH	Blueberry muffin baby presentation
Epidermolysis bullosa	Enterovirus, congenital varicella	Bullae on pressure sites
Congenital candidosis	Enterovirus, congenital varicella	Erythroderma with pustules; newborn may be severely affected in candidosis
Acrocyanosis, acral erythema	Parechovirus	Striking erythema of hands and feet
Neonatal lupus erythematosus	Roseola infantum, viral dermatitis	Raccoon eyes and annular lesions in NLE
Congenital syphilis	Enterovirus	Perioral and perianal lesions and palmoplantar erythema in syphilis; serologies useful
Langerhans cell histiocytosis	TORCH	Blueberry muffin baby presentation
Aicardi-Goutières syndrome	TORCH	Blueberry muffin baby presentation
Miscellaneous conditions		
Drug eruptions	Viral dermatitis	Very difficult differentiation in many cases
Erythema multiforme	*Herpes simplex*, enterovirus, orf, viral dermatitis	Typical targets only in EM
Stevens-Johnson syndrome, toxic epidermal necrolysis	Enterovirus, viral dermatitis, varicella	Severe mucosal involvement, purpuric targets and severe illness
Hyperpigmentation	Chikungunya	Can be the only manifestation of chikungunya
Polymorphous light eruption	Varicella	Varicella can be photoaggravated
Urticaria	Viral dermatitis	Viral infections are a common cause of urticarial in children
Urticaria multiforme	Viral dermatitis	Viral infection can trigger urticaria multiforme
Child abuse	Purpuric viral dermatitis	Purpura with unusual shapes in child abuse
Pityriasis rosea	APEC, viral dermatitis	Extensive PR with erythema and diffuse scaling can look like a viral dermatitis
Bullous pemphigoid	Enterovirus, varicella	Acute vesicles and blisters on acral regions in infants with BP. Biopsy and DIF required
Dermatitis herpetiformis	Gianotti-Crosti syndrome	Wheals and vesicles with annular shape in DH; intense pruritus in DH; search for celiac disease
Acrodynia, acral erythema	PPGSS	Acral erythema can be induced by drugs

APEC, asymmetric periflexural exanthem of childhood; BP, bullous pemphigoid; DH, dermatitis herpetiformis; DIF;DM, dermatomyositis; EBV, Epstein-Barr virus; EM, erythema multiforme; GVHD, graft-versus-host disease; HHV, human herpes virus; KD, Kawasaki disease; NLE, neonatal lupus erythematosus; nonLCH, nonLangerhans cell histiocytosis; PFAPA, periodic fevers with aphthous stomatitis, pharyngitis, and adenitis; PL, pityriasis lichenoides; PPGSS, papular purpuric glove and sock syndrome; PR, pityriasis rosea; PRP, pityriasis rubra pilaris; PV, pityriasis versicolor; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; SSSS, staphylococcal scaled skin syndrome; TNPM, transient neonatal pustular melanosis; TORCH, toxoplasma, rubella, cytomegalovirus and herpes virus.

* Viral dermatitis is a viral exanthema without specific diagnostic features.

may persist for months to years, especially in immunocompromised patients.[51,55–58]

Dermatoses mimicked by viruses

Many skin diseases can show features that resemble certain specific or nonspecific viral infections of the skin. Examples of these are listed in Table 2.

Conclusions

Viral exanthems during childhood are a polymorphous spectrum of skin lesions, ranging from classic viral exanthems to most unusual or atypical presentations, that can mimic nonviral diseases. Modified expression in immunocompromised patients may be even more challenging for the diagnosing clinician. Laboratory viral investigation or serologic tests may contribute to confirm the viral etiology, but a high index of

clinical suspicion is the most valuable tool. A detailed history, associated signs and clinical manifestations, and a careful physical examination of the pattern and type of cutaneous lesions may be enough to identify the viral cause in children with exanthems.

Conflict of interest

There are not conflicts of interest to declare.

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