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COVID-19: Important updates and developments
Edited by Franco Rongioletti, MD, and Leonard J. Hoenig, MD

Clinicopathologic features among different viral epidemic outbreaks involving the skin ☆,☆☆

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Abstract The current coronavirus disease 2019 pandemic has exceeded any epidemiologic prevision, but increasing information suggests some analogies with the major viral outbreaks in the last century, and a general warning has been issued on the possibility that coinfections can make the differential diagnosis and treatment difficult, especially in tropical countries. Some reports have noted that the presence of high dengue antibodies can give a false-negative result when testing for severe acute respiratory syndrome coronavirus 2. Mucocutaneous manifestations are very frequent, with an apparent overlap among different pathogens. However, strong clinicopathologic correlation might provide some clues to address differentials. Waiting for laboratory and instrumental results, the timing and distribution of skin lesions is often pathognomonic. Histopathologic findings characterize certain reaction patterns and provide insights on pathogenetic mechanisms. Unfortunately, skin assessment, especially invasive examinations such as biopsy, takes a back seat in severely ill patients. A literature retrieval was performed to collect information from other epidemics to counteract what has become the most frightening disease of our time.

Abbreviation: (COVID-19), coronavirus 2019 disease; (WHO), World Health Organization; (SARS), severe acute respiratory syndrome coronavirus; (Sars-Cov-2), novel coronavirus; (MERS), Middle East Respiratory Syndrome; (R0), basic reproductive number; (MIS), multisystem inflammatory syndrome; (IgA), immunoglobulin A; (ACE-2), Angiotensin-converting enzyme 2; (DENGV), Dengue virus; (TTP), thrombotic thrombocytopenic purpura; (vWF), von Willebrand factor; (CD1a), cluster of diffentiation 1-a; (RT-PCR), reverse transcription polymerase chain reaction; (CHIKV), Chikungunya virus; (E1, E2), envelope glycoprotein; (IFN-I), interferon-type-I; (ZIKV), Zika virus; (EBOV), Ebola virus.

☆ Founds: None

☆☆ Copyright: The authors certify that the manuscript is original, never submitted to other journal for publication before. All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text.

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Introduction: everchanging epidemiology

According to the World Health Organization (WHO), viral diseases continue to emerge as a serious issue to public health. Examples of the impact of globalization on infective disease epidemiology are abundant, from New World colonization and the spread of the smallpox virus and syphilis to the influenza virus pandemics after the Great War.[1] What is stirring the medical community's concern, however, is the explosive spread of novel diseases in the new millennium, which depends on the huge implementation of human travel and transport and is causing a collapse of public health systems worldwide. The emergence of severe acute respiratory syndrome (SARS) in 2002 in China was followed by the 2012 Middle East respiratory syndrome (MERS) coronavirus, which spread from Saudi Arabia to Asia. The Ebola virus expansion from West Africa occurred in 2014, and the Zika and chikungunya viruses then began circulating in South America.[2] Medicine is trying to evolve and find solutions just as quickly, including protecting populations that lack native immunity with effective vaccination campaigns.[3] An example is yellow fever containment in South America, which prevented large-scale circulation in the United States[4] The current 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, however, has completely upset epidemiologic planning,[4-9] because coronavirus disease 2019 (COVID-19) caused an unexpectedly high rate of mortality and morbidity reminiscent of the great influenza pandemic.

The skin is frequently affected in all viral epidemics,[9-11] and recognition of mucocutaneous manifestations might contribute to early diagnosis or even provide prognostic significance, pointing out the disease phases. A main limitation is that skin manifestations are polymorphous and aspecific. Strong epidemiologic, clinical, and pathologic correlation is necessary to address the differential diagnosis. Histopathologic characterization, moreover, is often insufficient owing to the reluctance to perform invasive examinations in severely ill patients or because dermatopathology services are not easily available in emergency settings, especially in developing countries. Although expensive and time-consuming, refined immunohistochemical examination usually provides powerful insights on pathogenesis,[10] helping to distinguish the direct cytopathic effects of the pathogen from the host's exaggerated immune response or other concomitant conditions exacerbating the final tissue damage.

The aim of this review is to provide an overview of mucocutaneous manifestations of the major epidemic viral infections (Table 1), with a special emphasis on the clinicopathologic correlation and comparison with SARS-CoV-2.

Coronavirus

During the past two decades, three zoonotic coronavirus (CoV) outbreaks have occurred:

1. SARS, beginning in 2002 in China due to SARS-CoV
2. MERS, beginning in 2012 in Saudi Arabia due to MERS-CoV
3. COVID-19 due to SARS-CoV-2, beginning in 2019 in Wuhan, China, resulting in an ongoing pandemic[12-16]

Phylogenetic analysis confirms strong homologies among coronaviruses,[17-19] as well as respiratory symptoms and pathologic findings, supporting a similar cytokine cascade storm responsible for the patient's rapid death.[20-22] SARS-CoV-2 has spread in the community more easily, however, exceeding 1 million cumulative worldwide deaths by the end of September 2020 according to WHO data.[23] Behind the dramatic numbers, the mortality rate (2.3%) is lower than SARS (9.5%) and much lower than that of MERS (34.4%). SARS-CoV-2 in most patients causes mild or asymptomatic disease, which is probably supporting the circulation of the virus.[12-16] The basic reproductive number (R0), although variable among geographic areas, is currently estimated as being around 2.0 to 2.5, slightly higher than SARS (1.7-1.9) and higher than MERS (<1). Social containment, with quarantine of suspected cases and contacts, and strict physical distancing and hygiene measures are crucial to effectively reduce R0 and the associated mortality.[4]

From a dermatology standpoint, the most relevant difference between COVID-19 and SARS/MERS is the absence of reported skin manifestations in the latter; however, COVID-19 is associated with an increasing list of skin eruptions.[24-33] One explanation for the apparent different skin tropism of the novel coronavirus is that the greater severity of lung and multiorgan involvement in SARS and MERS, with a relatively fast course, limited the attention paid to skin signs.[15] Another consideration is the number of infected individuals, which has exceed 32 million (WHO)[23] and allows for the observation of relatively rare events. In COVID-19, the prevalence of skin involvement ranges from 0.2% in a cohort of Chinese patients [25] to 20.4% in an Italian study.[26] A systematic review indicates a worldwide incidence of 1% to 2%.[24] According to the Spanish prospective nationwide consensus study,[27] the most characteristic presentations are chilblain-like lesions, ischemic-livedoid/necrotic lesions, and varicelliform-like/vesicular eruption. More frequent, albeit less specific, manifestations are the erythematous, urticarial, purpuric, and maculopapular eruptions, followed by an increasing list of anecdotal and unusual manifestations.[28-34] Recently, a peculiar Kawasaki-like presentation during the COVID-19 pandemic has been described[35,36] and named multisystem inflammatory syndrome with a 30-fold increased rate in Italian children.[37]

Chilblain-like lesions consist of erythematous-violaceous papules and macules with purpuric hue and possible vesicles, bullous, pustules on acral area, especially on the toes (Figure 1).[24,27,38-40] These lesions affect young people in a percentage higher than ever reported before the outbreak of COVID-19. Distribution is usually asymmetrical, and lesions may be asymptomatic, itchy, or painful.

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Table 1 Clinicopathologic characterization of main viral epidemic infections

Disease—pathogen	Skin findings	Histopathologic findings
COVID-19 SARS-CoV-2 (Coronaviridae family) Geographic diffusion: pandemic Viral transmission to human: airborne spread	Chilblain-like lesions (Acro)Ischemic/livedoid/necrotic lesions Exanthematous eruptions including: Varicelliform-like/vesicular Confluent erythematous, maculopapular, morbilliform Urticarial Erythema multiforme-like Purpuric/petechial Multisystem inflammatory syndrome (atypical Kawasaki disease) Miscellanea (pityriasis rosea-like eruption, digitate papulosquamous, transient livedo reticularis, erythema nodosum/sweet's like)	Superficial and deep dermal perivascular lymphocytic infiltrate, perieccrine extension and intramural lymphocytes with thickening and enlargement of endothelium (ie, lymphocytic vasculitis). Vacuolar interface dermatitis with scattered necrotic (apoptotic) keratinocytes. No evidence of thrombosis or leukocytoclastic vasculitis. Epidermal and sweet gland necrosis, thrombotic vasculopathy of small and medium vessels (venules and small-medium arteries) in superficial and deep dermis without leukocytoclastic vasculitis. Varicelliform-like eruption earlier lesions: vacuolar degeneration of basal layer, multinucleate, hyperchromatic keratinocytes with many dyskeratotic (apoptotic) cells. Pauci to absent inflammatory infiltrate varicelliform-like well-established lesions: intraepidermal vesicle containing multinucleated and ballooned keratinocytes with acantholytic and dyskeratotic cells (similar to herpetic lesions or pseudo-herpetic Grover's disease). Other skin eruption: fewer specific findings, superimposable to other viral eruptions. Two different patterns from few biopsies: leukocytoclastic vasculitis or erythema multiforme-like Variable findings.
H1N1 influenza virus (Orthomyxoviridae family) Geographic diffusion: pandemic Viral transmission to human: airborne spread	Epistaxis Dark blue cyanosis (heliotrope cyanosis)	Massive necrosis of the respiratory epithelium.
Dengue (Flaviviridae family) Geographic diffusion: endemic in tropical and subtropical areas; epidemics in Hawaii, Florida, borders of USA/Mexico Viral transmission to human: *Aedes aegyptus,* less frequently *Aedes albopictus*	Transitory flushing of face, neck, and trunk (24-48 h from systemic symptoms) Days 3-5, generalized morbilliform or maculopapular or petechial eruption White islands of sparing and blanchable erythema Frequent mucosal involvement, especially conjunctiva and mouth Pruritic palms and soles swelling Skin necrosis and digital gangrene in thrombotic thrombocytopenic purpura	Mild perivascular infiltrate of lymphocytes in the superficial dermis, exocytosis, and variable red cell extravasation. Prevalent vessel involvement in advanced disease, with endothelial swelling, perivascular edema, and mononuclear cell infiltration.

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Table 1 (*continued*)

Disease—pathogen	Skin findings	Histopathologic findings
Chikungunya (Togaviridae family) Geographic diffusion: Africa, Asia, Caribbean, Latin America Viral transmission to human: *Aedes aegyptus,* less frequently *Aedes albopictus*	Joint-related symptoms Maculopapular eruption 3-5 d after flu-like symptoms Hyperpigmentation of the face, especially of the nose, perioral, periflexural, genitalia, and nails Acral edema Vesicular-bullous eruption, becoming hemorrhagic Ulcers of the scalp, abdomen, genitalia Eczematous changes on pre-existing scars Psoriasis exacerbation or guttate psoriasis-like eruption. Skin necrosis and digital gangrene in thrombotic thrombocytopenic purpura	Superficial perivascular infiltrate of lymphocytes and Occasional focal lichenoid reaction. Increased basal pigmentation with pigmentary incontinence, and melanophages.
Zika (Flaviviridae family) Geographic diffusion: Central/South America, Caribbean, Micronesia, Polynesia, Cape Verde Viral transmission to human: *Aedes Aegyptus*, sexual contact spread, and vertical transmission	Early symmetric generalized eruption (24-48 h after flu-like symptoms) Intense itching Maculopapular, but also linear net-shaped arrangement with accentuation on neckline, radix of limbs, and abdomen Urticarial eruption Involvement of face, palms, and soles Evolution to erythroderma possible Late onset petechiae, ecchymosis, subcutaneous hematomas, jaundice Psoriasis-like lesions weeks after acute disease	Prevalent perivascular pattern with lymphocytic dermal infiltrate, variable erythrocyte extravasation, and slight papillary edema. Vacuolar degeneration of basal cell layer with focal necrotic keratinocytes. Variable degree of spongiosis, acanthosis, and lymphocytes exocytosis into the epidermis. Psoriasiform hyperplasia with regular acanthosis and perivascular lymphocytic infiltrate in psoriasis-like lesions.
Ebola (Filoviridae family) Geographic diffusion: West and Central Africa Viral transmission to human: contact with body fluids	Absence of pruritus Eruption 4-5 d after flu-like symptoms with centripetal spread: dark red pinpoint papules around hairs follicles on head, arms, legs, buttocks, then extending to the trunk Mucosal involvement common, white dots on the reddish soft palate (tapioca sign) Day 8: dark livid erythema of the whole body Survivors experience skin peeling on palms and soles, massive alopecia	Superficial and deep perivascular infiltrate with swelling of endothelial cells. Dermal fibroblasts and extracellular matrix around sweat glands changes. Necrosis is a common finding.

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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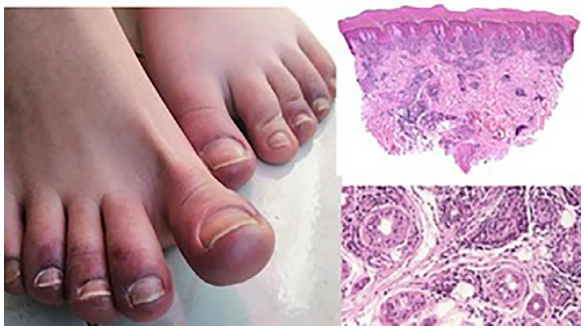

Fig. 1 **(A)** Chilblain-like lesions of the toes (COVID-19 toe) with dusky erythematous edematous macule and purpuric plaques. (B) Edema of papillary dermis with a superficial and deep perivascular lymphocytic infiltrate (HE, 40 ×). **(C)** Close-up of the perieccrine extension of the lymphocytic infiltrate (HE, 200 ×). COVID-19, coronavirus disease 2019; HE, hematoxylin and eosin stain.

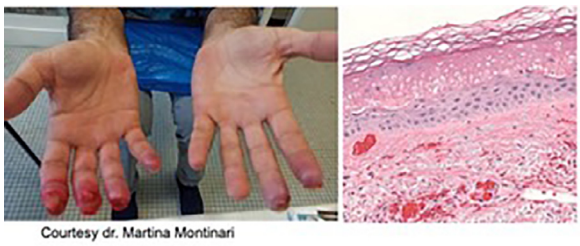

Fig. 2 **(A)** Acroischemic/livedoid/necrotic lesions of the hands. **(B)** Epidermal necrosis and thrombotic vasculopathy of the superficial vessels, with no sign of leukocytoclastic vasculitis (HE, 200 ×). HE, hematoxylin and eosin stain. Courtesy of Dr. Martina Montinari.

Histopathology demonstrates a superficial and deep perivascular lymphocytic infiltrate with signs of endothelial activation.[41-43] Angiotensin-converting enzyme 2, the receptor for the SARS-CoV-2 spike protein, is expressed in the dermal endothelial cells, as well as in the keratinocytes of epidermal basal layer and eccrine glands in chilblain-like lesions.[43,44,45] Although the results were highly suspect, several patients with chilblain-like lesions tested negative for SARS-CoV-2 in polymerase chain reaction (PCR) and serology tests, and the presence of the virus might be explained with a limited involvement of the adaptative immunity in young patients with asymptomatic or mild disease.[46-49] In any case, the occurrence of chilblain-like lesions represents a potentially alerting sign of asymptomatic carriers in a risky population and addresses the strict adoption of preventive social containment measures. The second type of lesions, characterized by ischemic/livedoid necrotic skin, is associated with severe illness, with microscopic findings including occlusive vasculopathy, extravasation of erythrocytes and fibrin thrombi in the vessels, similar to the pathologic abnormalities of affected internal organs (Figure 2).[21,27,50-54] Blood tests usually confirm a hypercoagulability state.[55-57] Advanced age, together with comorbidities, unleashes an exaggerated innate immune response (ie, macrophage activation syndrome) associated with a more severe prognosis.[10,21,24] Direct immunofluorescence on skin samples has outlined the presence of immunoglobulin A and complement in the vessel walls, which might be a key factor of the vasculopathic process.[58] Conversely, the varicella-like/vesicular eruption (Figure 3) is usually associated with symptomatic disease, occurring 3 days after fever, and respiratory symptoms occurring in 9% to 18% of patients, but without a clear prognostic significance, because patients might both recover or undergo a more unfavorable course.[10,21,32,59] In the Italian experience, 13.6% of these patients died of COVID-19.[32] Viral cytopathic effects have been documented in early skin biopsies, and interaction with the angiotensin-converting enzyme 2 seems able to induce acantholysis and dyskeratosis.[32,59-61] More skin biopsies and immunohistochemical staining with antibodies to SARS-CoV/SARS-CoV-2 spike protein on paraffin-embedded specimens and RNA detection of SARS-CoV-2 strain by real-time PCR-based assay will improve our capacity to distinguish coincidence from casual correlation to COVID-19,[62-64] especially in patients whose nasopharyngeal swab and serologic tests produced negative results.

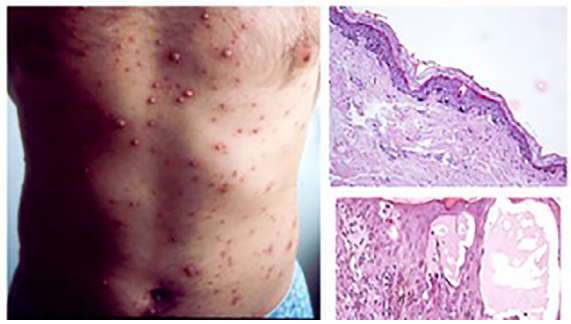

Fig. 3 **(A)** Varicelliform-like/vesicular eruption of the trunk. **(B)** Early findings showing vacuolar degeneration of the basal layer, dyskeratosis, and multinucleate, hyperchromatic keratinocytes with minimal inflammatory infiltrate (HE, 200 ×). Late findings characterized by unilocular vesicles, reticular degeneration of the epidermis, acantholytic cells, and scattered dyskeratotic keratinocyte, similar to herpetic lesions (HE, 200 ×). HE, hematoxylin and eosin stain.

Influenza pandemic

The high mortality rates and contagiousness of coronavirus outbreaks in the new millennium, related to interhuman airborne transmission and respiratory illness, remind us of what happened at the beginning of the 20th century. The 1918 influenza A virus, subtype H1N1, of the Orthomyxoviridae family, still represents an enigma.[65] The influenza's rapid global spread is only partially explicable with the massive movement of people and poor general conditions associated with the Great War, because the virus was

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circulating in most parts of the world many months before the spread of the lethal form in late 1918.[66-68] A first wave of infections was documented from March to June, whereas the second, highly lethal wave began in August 1918, supporting two separate but interrelated influenza pandemics in a single year. Despite several hypotheses, there is no final explanation for how the virus could suddenly increase its lethality worldwide.[62] The other troublesome novelty was the high mortality rate among young people, with those aged 20 to 40 years affected more than expected.[69] In most populations, an infection peak decimated the 1890 birth cohort, which was vulnerable to a worse outcome. The H3N8 influenza pandemic had occurred that year, supporting the hypothesis that early-life influenza exposure in 1890 might have increased mortality in adult H1N1 infections.[70] One explanation of such enhanced disease (ie, the original antigenic sin) is that subsequent serologic reactions through non-neutralizing antibodies increased the virus's ability to infect the respiratory epithelial cells. The consequence seems to be that immunization is not always advantageous to the host. In line with this alarming hypothesis, observational Canadian studies reported that seasonal influenza immunization increased illness during the 2009 influenza pandemic.[68]

Two mucocutaneous signs characterized this influenza and differed from all other influenza epidemics before and after: nose bleeds and cyanosis.[69-74] The hemorrhagic phenomenon, although severe, was mainly confined to epistaxis, because frank hemoptysis was rare, as well as other bleedings, except for an increased menometrorrhagia in women. The other distinctive sign was skin discoloration, described as a diffuse dark blue cyanosis (ie, heliotrope cyanosis).[75] The occurrence of such a remarkable discoloration had prognostic significance, because 95% of soldiers presenting with this cyanosis usually died within a single day.[76] Patients appeared conscious to nearly the point of death.

Histopathologic examination noted that both manifestations are related to the massive destruction of the respiratory epithelium with cellular necrosis.[77] The loss of respiratory epithelial cells was responsible for initial acute tracheobronchitis, which extended to the lung parenchyma and allowed the entry of bacteria, especially common pyogenic pathogens.[76] The fatal outcome was related to entire lung failure, with oxygen saturation abruptly falling and the alveoli filling with fluid.[77] During this pre-antibiotic era, the secondary bacterial pneumonia resulted in the death of approximately one-third of the patients with influenza.

An important lesson from the 1918 influenza pandemic is the crucial role of preventive measures to contain the spread. The isolation of symptomatic patients was the best weapon to minimize their exposure to other persons and to prevent the acquired-bacteria secondary infections.[66] Hospital admittance was not an effective measure because the wards were full of sick patients, increasing the exposure to many respiratory pathogens other than the influenza virus. The lack of an effective treatment was a pivotal factor for fatal outcomes at that time, and patients managed at home demonstrated a better prognosis than those referred to hospitals.[66] Today, the extensive use of antibiotics in intensive care units, as well as in the general population, expose us to an equally or even higher risk of bacterial superinfections, as experienced during the COVID-19 pandemic.

We can find analogies regarding the current reluctance to admit patients with COVID-19 with mild symptoms an signs to hospitals and the implementation of home-based assistance to combat COVID-19 circulation. The sudden passing of the 1918 pandemic is another difficult to explain fact about the most lethal influenza virus ever recorded, and hopefully a similar passing will happen with the COVID-19 pandemic.

Arbovirus epidemics

The most recent decade's epidemics have been characterized by the emergence of the arbovirus, especially the dengue, Zika, and chikungunya viruses. The skin is a major portal of entry for such pathogens, because these viruses are often transmitted through mosquito bites, mainly of the *Aedes* family.[75] The most competent mosquito is *Aedes aegypti*, commonly called the yellow fever mosquito, which is an African insect that reached the Americas hidden in ships at the time of the slave trade. The other prevalent vector is the Asian tiger mosquito (*Aedes albopictus*), more recently circulating also in southern United States and in Europe, coming from Asia by way of egg-laden water amid shipments of the most disparate goods, including used tires. Human activities are to blame, including transports and travel exchanges, as cyclic epidemics spread from endemic areas between the Pacific and Atlantic oceans. Coinfection is an increasing problem. All three arboviruses have spread among the intertropical countries, and the actual COVID-19 pandemic demonstrates the increasing danger of a difficult differential already signaled with dengue fever.[78-80] Symptoms are widely overlapping: fever, myalgia, headache, arthralgia, and thrombocytopenia. Mucocutaneous manifestations with a hemorrhagic hue are common, but in respect to other viral exanthema, they occur characteristically late after constitutional symptoms and are not an obligatory signal of progression to authentic hemorrhagic disease or shock. Individual predisposing conditions, especially microangiopathic diathesis, might favor bleeding and life-threatening complications requiring inpatient management.[81-83] Another crucial increasing phenomenon is vertical transmission from pregnant women that causes neurologic symptoms and malformations, including microcephalia, seizure, and encephalopathy.[84]

Because the symptomatology is common in all three arboviruses, in most cases only serologic tests can differentiate one infection from another. Some skin findings, however, are useful to steer the diagnosis in experienced physicians.

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Dengue

During the last half of the 20th century, dengue spread to most countries in the tropical zones, becoming the most common cause of human arbovirus infection, especially during the rainy season at the beginning of each year.[85] This RNA virus belongs to the genus Flavivirus. The infection is most often asymptomatic, with some patients developing arthralgia, thrombocytopenia, and episodes of vascular extravasation, which, if not adequately managed, can progress to severe forms. Dengue may be associated with neurologic and hematologic complications, including severe secondary thrombotic thrombocytopenic purpura.[83,84-88] A predisposing microangiopathic diathesis is supposed to favor platelet hyper aggregation and formation of microthrombi in the endothelium[81]; however, viral infections including dengue are well-known inducers of inhibitor autoantibodies production, directed against the proteinase ADAMTS13, deputy to the von Willebrand factor multimer cleavage. A severe deficiency of the ADAMTS 13 protein (defined as activity below 10%) substantially compromises the coagulation and platelet aggregation pathway.[81]

Regarding skin manifestations, a generalized skin eruption is described in 50% to 82% of patients[89] and can be helpful to suggest the diagnosis in the early phase of the infection in endemic regions. The first sign is the occurrence of facial, neck, and trunk flushing, within 24 to 48 hours from the onset of general symptoms followed by the widespread eruption on days 3 to 6. Itching is reported in a minority of patients, favoring the differential with Zika, which is highly pruritic.[90,91] Morphology is variable, predominantly morbilliform but also maculopapular or petechial. White islands of sparing "in a sea of red" are described as a very pathognomonic sign. Mucosal involvement, especially of the conjunctiva and oral mucosa, is described in 15% to 30% of cases[85,89,92,93] During the generalized eruption, the face is usually spared, and initial flushing has been explained with a temporary capillary's dilatation. Pruritic palm and soles swelling has been reported as a better prognostic sign, whereas hemorrhagic manifestations and genital involvement are associated with a higher rate of platelet infusions.[93] Skin necrosis and digital gangrene have been reported in patients with thrombotic thrombocytopenic purpura.[81]

Histopathology is seldom performed, because it is rather aspecific, showing a mild perivascular infiltrate of lymphocytes in the superficial dermis, exocytosis, and variable red cell extravasation, particularly in the hemorrhagic form of the disease.[94] An immunohistochemistry study using CD1a-positive Langerhans cells double-labeled with an antibody against dengue virus envelope glycoprotein, from cadaveric skin explants, than confirmed by a skin eruption biopsy from a vaccinated patient suggest that skin Langerhans cells are the preferential target of dengue virus, being 10-fold more permissive than blood monocytes and probably involved in the transmission via the lymphatics after the mosquito bite.[95] The histopathologic findings are of no prognostic value in predicting the course of the disease.[96]

A general alert has been diffused for the overlapping signs and symptoms with COVID-19, especially the petechial eruption, making a differential diagnosis of dengue and treatment difficult.[78] From the first case reported in Thailand,[79] an increasing amount of reporting has noted that the presence of high dengue antibodies can give false-negative test results for SARS-CoV-2. In this case, only reverse transcription PCR testing is resolutive.[80]

Chikungunya

The human disease was first described in Africa between 1952 and 1953[97] before spreading in several countries of the tropical areas across the globe, with recent large-scale outbreaks in the western hemisphere territories close to the United States.[98] Cases of chikungunya fever have occurred in Europe since 2007, the presumed index case coming back from India and causing an initial outbreak in northeastern Italy[99] then becoming autochthonous in France, Croatia, Spain, and Italy. The RNA virus belongs to the Alphavirus genus of the Togaviridae family. Host cells enter through the envelope glycoproteins interactions, especially E1 and E2. Most patients remain asymptomatic,[100] but an emerging occurrence of potentially severe immunologic phenomena have been described, including encephalitis, Guillain-Barré syndrome, immune-mediated thrombocytopenia, and congenital nervous system malformations from vertical transmission in pregnant women.[82,101-103] Perinatal infection is also reported in endemic areas, such as India and Colombia.[101-104] Rarely, in regard to dengue, the occurrence of secondary thrombotic thrombocytopenic purpura has been reported, leading to hemolytic anemia, bleeding complications, and renal failure.[82,97]

Chikungunya fever's distinctive features, which go beyond aspecific fever, headaches, and general malaise, are prominent joint-related symptoms and peculiar dermatologic manifestations.[105-112] A maculopapular eruption occurs in about one-third of patients[105] 3 to 5 days after the onset of general symptoms, but a more pathognomonic sign is the facial melanosis, especially the nose pigmentation, which might support retrospective diagnosis of chikungunya fever.[101,107-109] Acral edema, intertriginous hyperpigmentation, and aphthae-like lesions and purpuric lesions accentuated in photo-exposed areas are other quite striking findings. A vesicle-bullous eruption, becoming hemorrhagic, and ulcers in the most severe cases have also been reported.[110,111] Bullous lesions and hyperpigmentation over the axilla, perioral, and genital areas have been reported in infants from India.[102] Atypical mucocutaneous manifestations, with ulcers occurring on the scalp, abdomen, genital, and perianal region, have been reported in newborns and infants in Colombia.[104]

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Nail pigmentations (eg, red lunula, melanonychia)[112] and eczematous changes over pre-existing scars, resembling sarcoidosis scar phenomenon, have been reported.[101] Exacerbation of psoriasis or an eruption resembling guttate psoriasis in patients with no history of psoriasis have also been described.[108]

A skin biopsy is rarely performed and histopathologic findings of the skin eruption are aspecific, showing features commonly observed in viral exanthems: a mild superficial perivascular infiltrate of lymphocytes and occasional focal lichenoid reaction.[105] Vesicle-bullous lesions have been described both as intraepidermal and subepidermal detachment.[107] A characteristic finding is an increased basal pigmentation, with pigmentary incontinence and melanophages.[101] Psoriasis-like lesions are superimposable to true psoriasis, although more dermal edema and melanophages are reported.[101]

The skin is the first human organ to harbor the infection after the mosquito bite, and dermal fibroblasts constitute the main site of chikungunya virus replication and amplification, as demonstrated *in vitro* in animal models and in a skin biopsy from a fatal neonate case.[113] Along with dermal fibroblasts, keratinocytes and melanocytes are also permissive for chikungunya virus, explaining the prevalence of hyperpigmented lesions. The infection induces a strong antiviral interferon-type-I response and proinflammatory cytokines release, but components of the *Aedes* mosquito saliva seems to contrast it, favoring viral replication. The route from the skin to viremia and other organ involvement pass through draining lymph nodes and infected monocyte-derived macrophages. During the viremia, dissemination of the virus back into the skin results in epidermal, dermal, and capillary endothelial injury attributable to a combination of direct cytopathic effect and immunologic factors.

Diagnosis is based on serology (anti–chikungunya virus immunoglobulin M) and reverse transcription PCR confirmation. The chikungunya virus tends to resolve spontaneously, and almost symptomatic treatment is provided. Effective administration of intravenous immunoglobulin therapy, however, has been reported in a Brazilian patient with severe chikungunya fever,[110] whereas severe thrombotic thrombocytopenic purpura occurrence beneficiates plasmapheresis.[81,114]

Zika

The Zika virus belongs to the genus Flavivirus, evoking general attention because it has progressively moved from Africa and Asia to the Americas and Europe, causing limited epidemics, but with increasing pathogenicity.[98] Isolated for the first time in nonhuman primates in the Zika forest (Uganda), accidental infection in humans was considered mild or clinically inapparent until outbreaks in the western Pacific State (2007) and in French Polynesia (2013-2014) defined a combination of the following symptoms: fever, skin eruption, arthritis or arthralgia, conjunctivitis, and fatigue. The increased number of infants born with microcephaly in the Americas in 2015 and 2016 indicated a vertical transmission from pregnant infected women, extending surveillance for Zika to the European Union.[115] The possible person-to-person transmission through sexual intercourses was also noted, although accounting for only 1% of cases.[116-119] Self-limitation of the epidemics is related to the type of mosquito species in the area, thus confining the disease to residents and occasional travelers. In fact, *Aedes albopictus,* which is the prevailing mosquito in Europe, seems to not be an efficient vector, and no autochthonous cases have been detected in the European surveillance program from 2015 to 2017.[115] Incubation from the time of the mosquito bite inoculation ranges between 3 and 10 days.

Skin manifestations are considered a valuable hallmark of the disease, because, although the eruption is by itself aspecific, it characteristically occurs 24to 48 hours after the onset of the general flu-like symptoms.[120-123] This short period is the clue to differentiate Zika from other exanthematous diseases frequently found in the same geographic areas, including dengue and chikungunya, whose eruptions manifest 4 to 5 days after the onset of symptoms. Morphology is variable, mainly maculopapular, but also arranged in a linear net-shaped pattern or even wheals, bleaching on palpation. Intensity and distribution of the erythema are variable, but are usually widespread and symmetric, also affecting the face, palms, and soles. A distinctive pattern with erythema accentuation on the neckline, radix of limbs, and abdomen has been reported, as well as erythroderma.[123] Oral aphthous ulcerations are common. Another distinctive feature is intense itching and scratching, emphasizing the papular components of the eruption and representing the main reason for seeking medical advice,[122] accompanied by symmetric painful joints edema, most commonly on the wrists and ankles. During the course of the disease, other lesions might occur as a consequence of viral immune-induced thrombocythemia, such as petechiae, ecchymosis, subcutaneous hematomas, and jaundice. A peculiar psoriatic-like lesion appearance, weeks after acute Zika symptoms, often in patients with no history of psoriasis.

Skin histopathology findings are aspecific, showing a prevalent perivascular pattern, with lymphocytic dermal infiltrate, variable erythrocyte extravasation, and slight papillary edema.[123] Vacuolar degeneration of the basal cell layer, with focal necrotic keratinocytes, is also described and suggestive of a direct viral cytopathic effect; however, variable degrees of spongiosis, acanthosis, and lymphocytes exocytosis into the epidermis are also reported. In psoriasis-like lesions, microscopic findings confirm a psoriasiform hyperplasia with regular acanthosis and perivascular lymphocytic infiltrate. Diagnosis is confirmed through nucleic acid testing of whole blood, serum, or urine.

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Ebola

Ebola virus, together with Marburg virus, belong to the Filoviridae family, order Mononegaviruses, characterized by single-stranded RNA genomes of negative polarity, and an elongated filamentous morphology at electron microscopy.[124] They are closely related to measles (Paramyxoviridae) and rabies. Ebola virus is subdivided into five species, Zaire, Cote d'Ivoire, Sudan, Reston, and Bundibugyo (recently discovered in Uganda), classified as level 4 pathogens, among the most virulent and hazardous agents. Ebola virus causes outbreaks of fulminant hemorrhagic fever, mostly in equatorial Africa, with a mortality rate of up to 90%.[125-127] The main reservoir and infection sources are fruit bats,[128] but human infection might also occur through contact with body fluids of infected large-animal carcasses or other humans, by accidental transmission during medical care, or by burial practices. The disease occurs after a very variable incubation, from 1 to 21 days and onset is rather aspecific, with abrupt flu-like symptoms. Epidemiologic information is crucial to address presumptive diagnosis and detect circulating viral antigens, although genetic identification in material by PCR is not available in all laboratories. The second phase of the disease is characterized by multiorgan involvement, and evolution into the third terminal phase is widely conditioned by host factors. Death usually occurs after 2 to 3 days, whereas survivors experience a long, prostrating convalescence. There is no specific treatment or vaccine, and treatment is solely supportive. Isolation measures and aseptic burial are crucial.

Skin manifestations are not specific,[124] but absence of pruritus is a clue to differentiate the maculopapular eruption from other viral exanthema, endemic in the same areas, such as Zika. Timing is also characteristic, with the eruption occurring 4 to 6 days from the onset of symptoms and indicative of the phase 2 disease transition. Patients have "ghost-like" features, and the eruption, more evident in light-skinned patients, often evolves in a centripetal fashion, from the upper portion of the arms to the flexor aspects of the forearms and the thighs.[129] Mucosal involvement is also common, with bilateral conjunctivitis in about 50% of patients, sore-like mouth lesions, gingivitis, glossitis, and pharyngeal inflammation. Enanthem on the soft palate can help the presumptive diagnosis, indicated by the presence of small white dots on the dry erythematous mucosa resembling "tapioca granules." All mucosal lesions can bleed, indicating the onset of the more hemorrhagic manifestation.[129] Around day 8, the entire body is usually diffusely erythematous, with a dark livid hue at times accompanied by true cyanosis.[124] Survivors experience affected skin peeling, especially on palms and soles, lasting from a few days to weeks. Hair loss is also common after convalescence.

A skin biopsy is seldom performed due to its invasiveness in severely ill patients, the long wait time for the results, and the unavailability of pathology services in the outbreak areas.[124] Formalin-embedded samples, however, are not contagious and can be sent to specialized laboratories abroad. The few skin histopathologic reports suggest nonspecific findings,[129] showing a mainly perivascular superficial and deep perivascular infiltrate with vessel swelling. Alterations are mainly restricted to endothelial cells, dermal fibroblasts, and an extracellular matrix around the sweat glands.[130] Necrosis is also a common finding. Immunohistochemistry provides more information, showing the Ebola virus antigen's widespread distribution within dermal endothelial cells and fibroblasts, around and within sweat glands, and more scattered distribution on the epidermis[131,132] Electron microscopy confirms viral inclusions within the cytoplasm of endothelial cells, fibroblasts, and extracellular matrix.[129,132]

Discussion

As a consequence of the COVID-19 emergency, the medical community has been committed in a race against time to provide containment measures and management during the development of effective treatments. Lessons from previous epidemics are a valuable source of information.[1,133] Skin involvement is common in any viral infections,[9-11,98] and, considering the general alert on the possible coinfection's occurrence, especially in tropical countries,[78-80] an indication of the clinical and histopathologic clues to address differential is paramount. A first lesson, which comes from the only comparable pandemic—the 1918 influenza—is the importance of case identification and isolation, indicating that patients managed at home have a better prognosis than those referred to hospitals.[65] Of course, the severe pneumonia and acute respiratory distress syndrome require intensive care assistance, but preventive measures are paramount to stop the spread of the virus, which is less lethal but more contagious than previous coronavirus epidemics.[13-16] Another finding from the influenza experience is the progressive involvement of younger patients, with concern about the role of previous unprotective immunization and an exaggerated immune response; however, effective treatment experimentation as well as the hastened development of different vaccines for COVID-19 are ongoing.

Increased reporting of mucocutaneous manifestations associated with SARS-CoV-2 has highlighted the analogies with arbovirus and Ebola findings. Strong clinicopathologic correlation might provide clues to address differential diagnoses. Timing and distribution of skin lesions is often pathognomonic in the wait for laboratory and instrumental results. Unfortunately, histopathologic sampling is seldom performed, but retrieval of the few reports from the literature provide insights on repetitive pathogenetic mechanisms.

Zika pruritic maculopapular eruption occurs characteristically about 24 to 48 hours after aspecific flu-like symptoms, whereas in dengue and chikungunya fever it occurs on days 3 to 5, although a temporary facial flushing is reported for dengue fever on days 2 to 3. Pigmentation disorders are quite characteristic of chikungunya. Ebola skin

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manifestations are delayed (occurring on days 4-5), extensive, non-itching, and evolve to dark livedo or true cyanosis on day 8. COVID-19 skin manifestations are more heterogenous in clinical presentations and timing, somewhat encompassing all other viral manifestations. The most specific presentation is the varicella-like/vesicular eruption, occurring a few days after systemic symptoms, thus easily differentiable from the other maculopapular eruption of arbovirus infection with early onset. During the course of COVID-19 infection, maculopapular and morbilliform eruptions are also frequent, but usually appear at a late stage of the disease and spare the palmoplantar skin and mucosae. Histopathologic findings of direct viral cytopathic effects, with spongiotic features and vacuolar degeneration of the basal layer cells (rather than aspecific perivascular mixed inflammatory infiltrate, with or without vascular injury) might help to distinguish pathognomonic signs from the consequences of the viremia that are not specific.

Purpuric, petechial manifestations are usually suggestive of overt disease, both in dengue fever and Ebola and in several reports of COVID-19, although in the latter the occurrence of true ischemic-livedoid/necrotic lesions is more characteristic. Such presentations are associated with a high mortality rate. Histopathology findings document prevalent vessel damage, hyperaggregation, and formation of microthrombi in the endothelium, with or without clear signs of vasculitis.

A very peculiar SARS-CoV-2 manifestation, apparently never reported in other viral diseases, is the occurrence of chilblain-like lesions in children and young adults. These acral lesions closely resemble idiopathic chilblains, both clinically and histologically; appear late in the course of the disease in milder cases; and last from 10 to 14 days, although sometimes persisting for a few months, but the prognosis is good. Several patients with chilblain-like lesions tested negative for SARS-CoV-2 PCR and serology, questioning a causative association. Chilblains in young people, however, have never been observed in such a high percentage before the outbreak of COVID-19.

We have much more to learn about the skin manifestations associated with COVID-19, but an incontrovertible fact is that dermatologists are widely contributing to the understanding of this new disease. Skin signs are not an innocent bystander of SARS-CoV-2 infection, but rather are a part of the overt disease as well as a warning of possible asymptomatic patients in an at-risk community. Clinicians should carefully look for skin lesions, especially in patients with mild symptoms and in young patients, even children, to maximize SARS-CoV-2 testing and take precautionary isolation measures.

Conclusions

Dermatologists are in the best position to identify minimal clinicopathologic signs that are helpful in the early recognition of viral exanthema and to address presumptive differential diagnoses while waiting for laboratory and instrumental results. Postgraduate education and strict cooperation with a multidisciplinary infectious diseases team is paramount to enriching both the dermatologic and general medical community's expertise to counteract the current COVID-19 pandemic, whose abrupt lethal potential has inexplicably burst onto the scene as did the influenza pandemic in 1918. It is our hope that COVID-19 will implode just as quickly and completely as the influenza pandemic of 1918.

Conflict of interest

The authors have no conflict of interest to disclose.

References

1. Priyadarsini SL, Suresh M, Huisingh D. What can we learn from previous pandemics to reduce the frequency of emerging infectious diseases like COVID-19? *Glob Transit*. 2020;2:202–220.
2. Ellwanger JH, Chies JAB. Emergent diseases in emergent countries: we must study viral ecology to prevent new epidemics. *Braz J Infect Dis*. 2016;20:403–404.
3. Billington J, Deschamps I, Erck SC, et al. Developing vaccines for SARS-CoV-2 and future epidemics and pandemics: applying lessons from past outbreaks. *Health Secur*. 2020;18:241–249.
4. Petersen E, Koopmans M, Go U, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *Lancet Infect Dis*. 2020;20:e238–e244.
5. Adhanom T. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. World Health Organization. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020. Accessed May 2, 2021.
6. European Centre for Disease Prevention and Control. Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK—sixth update 2020, 20 March 2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/RRA-sixth-update-Outbreak-of-novel-coronavirus-disease-2019-COVID-19.pdf. Accessed May 2, 2021.
7. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) 2019. Available at: https://www.cdc.gov/coronavirus/2019-ncov/index.html. Accessed May 2, 2021.
8. Coronavirus Resource Center of the John Hopkins University. COVID-19 Dashboard by the Center for Systems Science for Engineering (CSSE) at Johns Hopkins University (JHU). Available at: https://coronavirus.jhu.edu/map.html. Accessed May 2, 2021.
9. Keighley CL, Saunderson RB, Kok J, Dwyer DE. Viral exanthems. *Curr Opin Infect Dis*. 2015;28:139–150.
10. Criado PR, Pagliari C, Carneiro FRO, Quaresma JAS. Lessons from dermatology about inflammatory responses in Covid-19. *Rev Med Virol*. 2020;30:e2130.
11. Drago F, Ciccarese G, Gasparini G, et al. Contemporary infectious exanthems: an update. *Future Microbiol*. 2017;12:171–193.
12. Peeri NC, Shrestha N, Rahman MS, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Int J Epidemiol*. 2020;49:717–726.
13. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? *Clin Microbiol Infect*. 2020;26:729–734.

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14. Contini C, Di Nuzzo M, Barp N, et al. The novel zoonotic COVID-19 pandemic: an expected global health concern. *J Infect Dev Ctries*. 2020;14:254–264.
15. Rongioletti F. SARS-CoV, Mers-CoV and COVID-19: what differences from a dermatological viewpoint? *J Eur Acad Dermatol Venereol*. 2020;34:e581–e582.
16. Xie M, Chen Q. Insight into 2019 novel coronavirus—an updated interim review and lessons from SARS-CoV and MERS-CoV. *Int J Infect Dis*. 2020;94:119–124.
17. Yu Chen, Qianyun Liu, Deyin Guo. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol*. 2020;92:418–423.
18. Coronaviridae Study Group of the International Committee on Taxonomy of VirusesThe species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. 2020;5:536–544.
19. Chan JF, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect*. 2020;9:221–236.
20. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8:420–422.
21. Kakodkar P, Kaka N, Baig M. A comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). *Cureus*. 2020;12:e7560.
22. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2020;71:762–768.
23. World Health Organization. Weekly epidemiological update. Available at. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200928-weekly-epi-update.pdf?sfvrsn=9e354665_6. Accessed May 2, 2021.
24. Matar S, Oulès B, Sohier P, et al. Cutaneous manifestations in SARS-CoV-2 infection (COVID-19): a French experience and a systematic review of the literature. *J Eur Acad Dermatol Venereol*. 2020;34:e686–e689.
25. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–1720.
26. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol*. 2020;34:e212–e213.
27. Galván Casas C, Català A, Carretero Hernández G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol*. 2020;183:71–77.
28. Zhao Q, Fang X, Pang Z, Zhang B, Liu H, Zhang F. COVID-19 and cutaneous manifestations: a systematic review. *J Eur Acad Dermatol Venereol*. 2020;34:2505–2510.
29. Freeman EE, McMahon DE, Lipoff JB, et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. *J Am Acad Dermatol*. 2020;83:1118–1129.
30. Wollina U, Karadağ AS, Rowland-Payne C, Chiriac A, Lotti T. Cutaneous signs in COVID-19 patients: a review. *Dermatol Ther*. 2020;33:e13549.
31. Criado PR, Abdalla BMZ, de Assis IC, van Blarcum de Graaff Mello C, Caputo GC, Vieira IC. Are the cutaneous manifestations during or due to SARS-CoV-2 infection/COVID-19 frequent or not? Revision of possible pathophysiologic mechanisms. *Inflamm Res*. 2020;69:745–756.
32. Marzano AV, Cassano N, Genovese G, Moltrasio C, Vena GA. Cutaneous manifestations in patients with COVID-19: a preliminary review of an emerging issue. *Br J Dermatol*. 2020;183:431–442.
33. Kaya G, Kaya A, Saurat JH. Clinical and histopathological features and potential pathological mechanisms of skin lesions in COVID-19: review of the literature. *Dermatopathology (Basel)*. 2020;7:3–16.
34. Seirafianpour F, Sodagar S, Mohammad AP, et al. Cutaneous manifestations and considerations in COVID-19 pandemic: a systematic review. *Dermatol Ther*. 2020;33:e13986.
35. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395:1607–1608.
36. Bapst T, Romano F, Müller M, Rohr M. Special dermatological presentation of paediatric multisystem inflammatory syndrome related to COVID-19: erythema multiforme. *BMJ Case Rep*. 2020;13.
37. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395:1771–1778.
38. Recalcati S, Barbagallo T, Frasin LA, et al. Acral cutaneous lesions in the time of COVID-19. *J Eur Acad Dermatol Venereol*. 2020;34:e346–e347.
39. Piccolo V, Neri I, Filippeschi C, et al. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. *Eur Acad Dermatol Venereol*. 2020;34:e291–e293.
40. de Masson A, Bouaziz JD, Sulimovic L, et al. Chilblains is a common cutaneous finding during the COVID-19 pandemic: a retrospective nationwide study from France. *J Am Acad Dermatol*. 2020;83:667–670.
41. El Hachem M, Diociaiuti A, Concato C, et al. A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection. *J Eur Acad Dermatol Venereol*. 2020;34:2620–2629.
42. Locatelli AG, Robustelli Test E, Vezzoli P, et al. Histologic features of long-lasting chilblain-like lesions in a pediatric COVID-19 patient. *J Eur Acad Dermatol Venereol*. 2020;34:e365–e368.
43. Kolivras A, Dehavay F, Delplace D, et al. Coronavirus (COVID-19) infection-induced chilblains: a case report with histopathologic findings. *JAAD Case Rep*. 2020;18:489–492.
44. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus.. *J Pathol*. 2004;203:631–637.
45. Colmenero I, Santonja C, Alonso-Riaño M, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. *Br J Dermatol*. 2020;183:729–737.
46. Roca-Ginés J, Torres-Navarro I, Sánchez-Arráez J, et al. Assessment of acute acral lesions in a case series of children and adolescents during the COVID-19 pandemic. *JAMA Dermatol*. 2020;156:992–997.
47. Caselli D, Chironna M, Loconsole D, et al. No evidence of SARS–CoV-2 infection by polymerase chain reaction or serology in children with pseudo-chilblain. *Br J Dermatol*. 2020;183:784–785.
48. Herman A, Peeters C, Verroken A, et al. Evaluation of chilblains as a manifestation of the COVID-19 pandemic. *JAMA Dermatol*. 2020;156:998–1003.
49. Docampo-Simón A, Sánchez-Pujol MJ, Juan-Carpena G, et al. Are chilblain-like acral skin lesions really indicative of COVID-19? A prospective study and literature review. *J Eur Acad Dermatol Venereol*. 2020;34:e445–e447.
50. Llamas-Velasco M, Muñoz-Hernández P, Lázaro-González J, et al. Thrombotic occlusive vasculopathy in skin biopsy from a livedoid lesion of a COVID-19 patient. *Br J Dermatol*. 2020;183:591–593.
51. Suarez-Valle A, Fernandez-Nieto D, Diaz-Guimaraens B, Dominguez-Santas M, Carretero I, Perez-Garcia B. Acro-ischaemia in hospitalized COVID-19 patients. *J Eur Acad Dermatol Venereol*. 2020;34:e455–e457.
52. Balestri R, Termine S, Rech G, Girardelli CR. Late onset of acral necrosis after SARS-CoV-2 infection resolution. *J Eur Acad Dermatol Venereol*. 2020;34:e448–e449.
53. Andersen MB, Lund ML, Jacobsn S, Kümle T, Simonsen S, Ravn P. [Acral ischaemia with multiple microthromboses and imminent gangrene in a 73-year-old woman with COVID-19]. *Ugeskr Laeger*. 2020;182 V05200379 [in Danish].

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54. Caputo V, Schroeder J, Rongioletti F. A generalized purpuric eruption with histopathologic features of leucocytoclastic vasculitis in a patient severely ill with COVID-19. *J Eur Acad Dermatol Venereol*. 2020;34:e579–e581.
55. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. 2020;220:1–13.
56. Zhang Y, Cao W, Jiang W, et al. Profile of natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients. *J Thromb Thrombolysis*. 2020;50:580–586.
57. Zhang Y, Cao W, Xiao M, et al. [Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia]. *Zhonghua Xue Ye Xue Za Zhi*. 2020;41:302–307 [in Chinese].
58. Schnapp A, Abulhija H, Maly A, et al. Introductory histopathological findings may shed light on COVID-19 paediatric hyperinflammatory shock syndrome. *J Eur Acad Dermatol Venereol*. 2020;34:e665–e667.
59. Fernandez-Nieto D, Ortega-Quijano D, Jimenez-Cauhe J, et al. Clinical and histological characterization of vesicular COVID-19 rashes: a prospective study in a tertiary care hospital. *Clin Exp Dermatol*. 2020;45:872–875.
60. Llamas-Velasco M, Chicharro P, Rodríguez-Jiménez P, et al. Comment on 'Clinical and histological characterization of vesicular COVID-19 rashes: a prospective study in a tertiary care hospital.' Pseudo herpetic Grover disease seems to appear in patients with COVID-19 infection. *Clin Exp Dermatol*. 2020;45:896–898.
61. Mahé A, Birckel E, Merklen C, et al. Histology of skin lesions establishes that the vesicular rash associated with COVID-19 is not 'varicella-like.'. *J Eur Acad Dermatol Venereol*. 2020;34:e559–e561.
62. Xue X, Mi Z, Wang Z, Pang Z, Liu H, Zhang F. High expression of ACE2 on keratinocytes reveals skin as a potential target for SARS–CoV-2. *J Invest Dermatol*. 2021;141:206–209.e1.
63. Jamiolkowski D, Mühleisen B, Müller S, Navarini AA, Tzankov A, Roider E. SARS-CoV-2 PCR testing of skin for COVID-19 diagnostics: a case report. *Lancet*. 2020;396:598–599.
64. Santonja C, Heras F, Núñez L, Requena L. COVID-19 chilblain–like lesion: immunohistochemical demonstration of SARS-CoV-2 spike protein in blood vessel endothelium and sweat gland epithelium in a polymerase chain reaction-negative patient. *Br J Dermatol*. 2020;183:778–780.
65. Shanks GD. Insights from unusual aspects of the 1918 influenza pandemic. *Travel Med Infect Dis*. 2015;13:217–222.
66. Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. *Lancet*. 2006;368:2211–2218.
67. Smith G, Bahl J, Vijaykrisna D, et al. Dating the emergence of pandemic influenza viruses. *Proc Natl Acad Sci U S A*. 2009;106:11709–11712.
68. Worobey M, Han GZ, Rambaut A. Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus. *Proc Natl Acad Sci U S A*. 2014;111:8107–8112.
69. Shanks GD, Brundage JF. Pathogenic responses among young adults during the 1918 influenza pandemic. *Emerg Infect Dis*. 2012;18:201–207.
70. Gagnon A, Acosta JE, Madrenas J, Miller MS. Is antigenic sin always "original?" Re-examining the evidence regarding circulation of a human H1 influenza virus immediately prior to the 1918 Spanish Flu. *PLoS Pathog*. 2015;11.
71. Skowronski DM, De Serres G, Crowcroft NS, et al. Association between the 2008-09 seasonal influenza vaccine and pandemic H1N1 illness during Spring-Summer 2009: four observational studies from Canada. *PLoS Med*. 2010;7.
72. Duque V, Vaz J, Mota V, Morais C, Da Cunha S, Meliço-Silvestre A. Clinical manifestations of pandemic (H1N1) 2009 in the ambulatory setting. *J Infect Dev Ctries*. 2011;5:658–663.
73. Muir R, Wilson GH. Observations on influenza and its complications. *BMJ*. 1919;1:3–5.
74. Abrahams A, Hallows N, French H. Influenzo-pneumococcal and influenzo-streptococcal septicaemia: epidemic influenzal "pneumonia" of highly fatal type and its relation to "purulent bronchitis.". *Lancet*. 1919;193:1–11.
75. Macpherson WG, Herringham W, Elliott T, Balfour AThis is a book London published by His Majesty's Stationery Office London. History of the Great War based on official documents. Medical services. *Diseases of the war*. 1923;2:1–621.
76. Taubenberger JK, Morens DM. The pathology of influenza virus infections. *Annu Rev Pathol*. 2008;3:499–522.
77. Brem WV, Bolling GE, Casper EJ. Pandemic influenza and secondary pneumonia at camp Fremont, Calif. *JAMA*. 1918;71:2138–2144.
78. Miah MA, Husna A. Coinfection, coepidemics of COVID-19, and dengue in dengue-endemic countries: a serious health concern. *J Med Virol*. 2021;93:161–162.
79. Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. *J Am Acad Dermatol*. 2020;82:e177.
80. Lokida D, Lukman N, Salim G, et al. Diagnosis of COVID-19 in a dengue-endemic area. *Am J Trop Med Hyg*. 2020;103:1220–1222.
81. Bastos MLA, Araújo RMO, Oliveira DS, Cavalcante ANM. Silva Junior GBD. Thrombotic thrombocytopenic purpura associated with dengue and chikungunya virus coinfection: case report during an epidemic period. *Rev Inst Med Trop Sao Paulo*. 2018;60:e48.
82. Epelboin L, Bidaud B, Mosnier E, Le Turnier P, Vesin G, Walter G, et al. Fatal case of chikungunya and concomitant thrombotic thrombocytopenic purpura in French Guiana during air flight medical evacuation. *J Travel Med*. 2017;24 10.1093/jtm/tax028.
83. Deepahjali S, Naik RR, Mailankody S, Kalaimani S, Kadhiravan T. Dengue virus infection triggering thrombotic thrombocytopenic purpura in pregnancy. *Am J Trop Med Hyg*. 2015;93:1028–1030.
84. Ferreira ML, Cavalcanti CG, Coelho CA, Mesquita SD. Manifestações neurológicas de dengue: estudo de 41 casos [Neurological manifestations of dengue: study of 41 cases]. *Arq Neuropsiquiatr*. 2005;63:488–493 [in Portuguese].
85. Teixeira MG, Barreto ML. Diagnosis and management of dengue. *BMJ*. 2009;339:b4338.
86. Albuquerque PLMM, Júnior GBS, Diógenes SS, Silva HF. Dengue and aplastic anemia: a rare association. *Travel Med Infect Dis*. 2009;7:118–120.
87. Ehelepolar ND, Gunawadhan MB, Sudusinghe TN, Sooriyaarachchi SK, Manchanayake SP, Kalupahana KL. A dengue infection without bleeding manifestation in an adult with immune thrombocytopenic purpura. *Trop Med Health*. 2016;44:36.
88. Itoda I, Masuda G, Suganuma A, Imamura A, Ajisawa A, Yamada KI, et al. Clinical features of 62 imported cases of dengue fever in Japan. *Am J Trop Med Hyg*. 2006;75:470–474.
89. Azfar NA, Malik LM, Jamil A, et al. Cutaneous manifestations in patients of dengue fever. *J Pak Assoc Dermatol*. 2012;22:320–324.
90. Thomas EA, John M, Kanish B. Mucocutaneous manifestations of dengue fever. *Indian J Dermatol*. 2010;55:79–85.
91. Chadwick D, Arch B, Wilder-Smith A, Paton N. Distinguishing dengue fever from other infections on the basis of simple clinical and laboratory features: application of logistic regression analysis. *J Clin Virol*. 2006;35:147–153.
92. Mahboob A, Iqbal Z, Javed R, et al. Dermatological manifestations of dengue fever. *J Ayub Med Coll Abbottabad*. 2012;24:52–54.
93. Huang HW, Tseng HC, Lee CH, et al. Clinical significance of skin rash in dengue fever: a focus on discomfort, complications, and disease outcome. *Asian Pac J Trop Med*. 2016;9:713–718.
94. Martyn-Simmons CL, Powell SE, Sudhanva M, et al. A florid skin rash in a returning traveller. *Clin Exp Dermatol*. 2007;32:779–781.
95. Wu SJ, Grouard-Vogel G, Sun W, et al. Human skin Langerhans cells are targets of dengue virus infection. *Nat Med*. 2000;6:816–820.

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96. Saadiah S, Sharifah BI, Robson A, Greaves MW. Skin histopathology and immunopathology are not of prognostic value in dengue haemorrhagic fever. *Br J Dermatol*. 2008;158:836–837.
97. Booth KK, Terrell DR, Vesely SK, George JN. Systemic infections mimicking thrombotic thrombocytopenic purpura. *Am J Hematol*. 2011;86:743–751.
98. Patterson J, Sammon M, Garg M. Dengue, zika and chikungunya: emerging arboviruses in the new world. *West J Emerg Med*. 2016;17:671–679.
99. Rezza G, Nicoletti L, Angelini R, et al. Infection with chikungunya virus in Italy: an outbreak in a temperate region. *Lancet*. 2007;370:1840–1846.
100. Haby MM, Pinart M, Elias V, Reveiz L. Prevalence of asymptomatic zika virus infection: a systematic review. *Bull World Health Organ*. 2018;96:402–413D.
101. Kumar R, Sharma MK, Jain SK, Yadav SK, Singhal AK. Cutaneous manifestations of chikungunya fever: observations from an outbreak at a tertiary care hospital in southeast Rajasthan, India. *Indian Dermatol Online J*. 2017;8:336–342.
102. Kumar S, Agrawal G, Wazir S, et al. Experience of perinatal and neonatal chikungunya virus (CHIKV) infection in a tertiary care neonatal centre during outbreak in north India in 2016: a case series. *J Trop Pediatr*. 2019;65:169–175.
103. Barr KL, Vaidhyanathan V. Chikungunya in infants and children: is pathogenesis increasing? *Viruses*. 2019;11:294.
104. Muñoz CM, Castillo JO, Salas D, et al. Atypical mucocutaneous manifestations in neonates and infants with chikungunya fever in the municipalities of Cúcuta, Los Patios and Villa del Rosario, Norte de Santander, Colombia, 2014.. *Biomedica*. 2016;36:368–377 [in Spanish].
105. Inamadar AC, Palit A, Sampagavi VV, Raghunath S, Deshmukh NS. Cutaneous manifestations of chikungunya fever: observations made during a recent outbreak in south India. *Int J Dermatol*. 2008;47:154–159.
106. Townson H, Nathan MB. Resurgence of chikungunya. *Trans R Soc Trop Med Hyg*. 2008;102:308–309.
107. Riyaz N, Riyaz A, Abdul Latheef EN, et al. Cutaneous manifestations of chikungunya during a recent epidemic in Clicut, north Kerala, south India. *Indian J Dermatol Venereol Leprol*. 2010;76:671–676.
108. Seetharam KA, Sridevi K, Vidyasagar P. Cutaneous manifestations of chikungunya fever. *Indian Pediatr*. 2012;49:51–53.
109. Shivakumar V, Rajendra O, Rajkumar V, Rajasekhar TV. Unusual facial melanosis in viral fever. *Indian J Dermatol*. 2007;52:116–117.
110. Fernandes AIV, Souza JR, Silva AR, Cruz SBSC, Castellano LRC. Immunoglobulin therapy in a patient with severe chikungunya fever and vesiculobullous lesions. *Front Immunol*. 2019;10:1498.
111. El Sayed F, Dhaybi R. Chikungunya associated with cutaneous ulcerations. *Clin Exp Dermatol*. 2008;33:463–464.
112. Singal A, Pandhi D. Isolated nail pigmentation associated with chikungunya: a hitherto unreported manifestation. *Skin Appendage Disord*. 2018;4:312–314.
113. Matusali G, Colavita F, Bordi L, et al. Tropism of the chikungunya virus.. *Viruses*. 2019;11:175.
114. Kumar V, Jain R, Kumar A, et al. Chikungunya fever presenting as life threatening thrombotic thrombocytopenic purpura. *J Assoc Physicians India*. 2017;11765:96–100.
115. Spiteri G, Sudre B, Septfons A, Beauté J. The European Zika Surveillance Network. Surveillance of Zika virus infection in the EU/EEA, June 2015 to January 2017. *Euro Surveill*. 2017;22:17–00254.
116. Counotte MJ, Kim CR, Wang J, et al. Sexual transmission of Zika virus and other flaviviruses: a living systematic review. *PLoS Med*. 2018;15.
117. Hastings AK, Fikrig E. Zika virus and sexual transmission: a new route of transmission for mosquito-borne flaviviruses. *Yale J Biol Med*. 2017;90:325–330.
118. Tang B, Zhou WK, Xiao YN, Wu JH. Implication of sexual transmission of Zika on dengue and Zika outbreaks. *Math Biosci Eng*. 2019;16:5092–5113.
119. Kim CR, Counotte M, Bernstein K, et al. Investigating the sexual transmission of Zika virus. *Lancet Glob Health*. 2018;6:e24–e25.
120. Farahnik B, Beroukhim K, Blattner CM, Young 3rd J. Cutaneous manifestations of the Zika virus. *J Am Acad Dermatol*. 2016;74:1286–1287.
121. Joob B, Wiwanitkit V. Cutaneous manifestations of Zika. *J Cutan Med Surg*. 2020;24:220.
122. Ramos W, Luna M, Alarcón T, et al. Cutaneous manifestations of Zika in Peru. *J Cutan Med Surg*. 2020;24:33–40.
123. Paniz-Mondolfi AE, Blohm GM, Hernandez-Perez M, et al. Cutaneous features of Zika virus infection: a clinicopathological overview. *Clin Exp Dermatol*. 2019;44:13–19.
124. Nkoghe D, Leroy EM, Toung-Mve M, Gonzalez JP. Cutaneous manifestations of filovirus infections. *Int J Dermatol*. 2012;51:1037–1043.
125. Gates B. The next epidemic—lessons from Ebola. *N Engl J Med*. 2015;372:1381–1384.
126. Coltart CE, Lindsey B, Ghinai I, Johnson AM, Heymann DL. The Ebola outbreak, 2013-2016: old lessons for new epidemics. *Philos Trans R Soc Lond B Biol Sci*. 2017;372.
127. Kucharski AJ, Edmunds WJ. Case fatality rate for Ebola virus disease in west Africa. *Lancet*. 2014;384:1260.
128. Leroy EM, Kumulungui B, Pourrut X, et al. Fruit bats as reservoirs of Ebola virus. *Nature*. 2005;438:575–576.
129. Blattner CM, Mortazie MB, Murase JE. Cutaneous manifestations of the Ebola virus. *Dermatol Online J*. 2015;21 13030/qt7429f9vf.
130. Bwaka MA, Bonnet M-J, Calain P, et al. Ebola hemorrhagic fever in Kikwit, Democratic Republic of Congo: clinical observations in 103 patients. *J Infect Dis*. 1999;1:S1–S7.
131. Martines RB, Ng DL, Greer PW, Rollin PE, Zaki SR. Tissue and cellular tropism, pathology and pathogenesis of Ebola and Marburg viruses. *J Pathol*. 2015;235:153–174.
132. Zaki SR, Shieh W-J, Greer PW, et al. A novel immunohistochemical assay for detection of Ebola virus in skin: implications for diagnosis, spread, and surveillance of Ebola hemorrhagic fever. *J Infect Dis*. 1999;179(Suppl 1):S36–S47.
133. Ling L, Joynt GM, Lipman J, Constantin JM, Joannes-Boyau O. COVID-19: a critical care perspective informed by lessons learnt from other viral epidemics. *Anaesth Crit Care Pain Med*. 2020;39:163–166.

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