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Clinicopathologic features between 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 of the last century. A general warning has been issued on the possibility that coinfections can make differential diagnosis and treatment difficult, especially in tropical countries. Some reports have pointed out that the presence of high Dengue antibodies can give a false-negative result for severe acute respiratory syndrome coronavirus 2. Mucocutaneous manifestations are very frequent, with an apparent overlap among different pathogens. A strong clinicopathologic correlation, however, may provide some clues to address the differential. 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 assessments, especially invasive exams such as biopsy, are less important in severely ill patients. A literature review was performed to collect information from other epidemics to counteract what has become the most frightening disease of our time.

Introduction: ever changing 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 the New World colonization and spread of smallpox virus and syphilis to the influenza virus pandemics after World War I.[1] What concerns the medical community is the explosive spread of novel diseases in the new millennium, which is thriving on the implementation of human travel and transport and is causing a collapse of public health systems worldwide. Since 2002, the emergence of severe acute respiratory syndrome (SARS) in China was followed by the 2012 Middle East respiratory syndrome (MERS) coronavirus spreading from Saudi Arabia to Asia, the 2014 Ebola virus (EBOV) expansion from West Africa, and Zika (ZIKV) and chikungunya (CHIKV) viruses circulating in South America.[2] Medicine is trying to evolve and find solutions just as quickly and protect populations lacking native immunity with effective vaccination campaigns.[3] An example is yellow fever containment in South America, preventing large-scale circulation in the United States.[4] The current 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), pandemic has completely upset any epidemiologic prevision,[4-9] because coronavirus disease 2019 (COVID-19) caused an unexpectedly high rate of mortality and morbidity reminiscent of the 1918 influenza pandemic.

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The skin is frequently affected in viral epidemics,[9-11] and recognitions of mucocutaneous manifestations might contribute to early diagnosis or provide prognostic significance, pointing out the disease phases. The main limitations are that skin manifestations are rather polymorphous and nonspecific, and strong epidemiologic, clinical, and pathologic correlation is necessary to address the differential diagnosis. Histopathologic characterization is often insufficient owing to the reluctance to perform invasive examinations in severely ill patients or because dermatopathology services are not available in emergency settings, especially in developing countries. Although expensive and time-consuming, refined immunohistochemical examination usually provides powerful insights on pathogenesis[10] and helps 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 purpose of this review is to provide an overview of mucocutaneous manifestations of the major epidemic viral infections (), with a special emphasis on clinicopathologic correlation and comparison with SARS-CoV-2.

Coronavirus

Over the past two decades, three zoonotic coronavirus outbreaks have occurred: (1) SARS starting in 2002 in China due to SARS-CoV, (2) MERS starting in 2012 in Saudi Arabia due to MERS-CoV, and (3) COVID-19 due to SARS-CoV-2 starting 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, however, has spread in the community more easily, exceeding 1 million cumulative deaths at the end of September 2020, following WHO data.[23] The mortality rate (2.3%) is lower than SARS (9.5%) and much lower than MERS (34.4%). SARS-CoV-2 in most patients causes mild or asymptomatic disease, which is probably favoring circulation of the virus.[12-16] The basic reproductive number, although variable among geographical areas, is currently attested around 2.0 to 2.5, slightly higher than that of SARS (1.7-1.9) and higher than that of MERS (<1). Social containment with quarantine of suspected cases and contacts, strict physical distancing, and hygiene measures are crucial to effectively reduce the reproductive number and associated mortality.[4]

From a dermatologic standpoint, the most relevant difference between COVID-19 and SARS or MERS is the absence of reported skin manifestations in the latter, whereas 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, means less attention has been given to skin signs.[15] Another consideration is the number of infected individuals, which has exceed 32 million (based on WHO data),[23] thus allowing the observation of relatively rare events. In COVID-19, the prevalence of skin involvement ranged 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 and/or necrotic lesions, and varicelliform-like and/or vesicular eruptions. 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 (Fig. 1) consist of erythematous–violaceous papules and macules with purpuric hue and possible vesicles, bullous, and pustules on an acral area, especially on the toes.[24,27,38-40] They affected young people in a high percentage never reported before the outbreak of COVID-19. Distribution is usually asymmetrical, and lesions may be asymptomatic, itching, or painful. Histopathology shows a superficial and deep perivascular lymphocytic infiltrate with signs of endothelial activation.[41–43] Angiotensin-converting enzyme 2 (ACE-2), the receptor for 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 highly suspect, several patients with chilblain-like lesions tested negative for SARS-CoV-2 polymerase chain reaction (PCR) and serology. The asymptomatic 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] The occurrence of chilblain-like lesions represents a potentially alerting sign of asymptomatic carriers in an at-risk population and can be used to address the strict adoption of preventive social containment measures. The second type of lesion, characterized by an ischemic or livedoid necrotic skin (Fig. 2) , is associated with severe illness, with microscopic findings including occlusive vasculopathy, extravasation of erythrocytes, and fibrin thrombi in the vessels similar to the pathological abnormalities of affected internal organs.[21,27,50-54] Blood examinations usually confirm a hypercoagulability state.[55-57] Advanced age together with comorbidities unleashes an exaggerated innate immune response named macrophage activation syndrome that is 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] By contrast, the varicella-like or vesicular eruption (Fig. 3) is usually associated with symptomatic disease occurring 3 days after fever and with respiratory symptoms in 9% to

Table 1 Clinicopathologic characterization of main viral epidemic infections

Disease - Pathogen	Skin findings	Histopathologic findings
COVID-19 SARS-CoV-2 (Coronaviridae family) Geographical diffusion: Pandemic Viral transmission to human: Airborne spread	1. Chilblain-like lesions 2. (Acro)Ischemic/livedoid/necrotic lesions; 3. Exanthematous eruptions including: - Varicelliform-like/Vesicular; - Confluent erythematous, maculopapular, morbilliform; - Urticarial. - Erythema multiforme-like - Purpuric/petechial 4. Multisystem inflammatory syndrome (atypical Kawasaki disease) 5. Miscellanea (Pityriasis rosea-like eruption; digitate papulosquamous; transient livedo reticularis; erythema nodosum/similar to Sweet syndrome)	1 Superficial and deep dermal perivascular lymphocytic infiltrate, perieccrine extension and intramural lymphocytes with thickening and enlargement of endothelium (lymphocytic vasculitis). Vacuolar interface dermatitis with scattered necrotic (apoptotic) keratinocytes. No evidence of thrombosis or leucocytoclastic vasculitis. 2 Epidermal and sweet gland necrosis; thrombotic vasculopathy of small and medium vessels (venules and small-medium arteries) in superficial and deep dermis, without leucocytoclastic vasculitis. 3 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 disease). Other skin eruption: less specific findings, superimposable to other viral eruptions. 4 Two different patterns from few biopsies: leucocytoclastic vasculitis or erythema multiforme-like 5 Variable findings.
H1N1 influenza virus (Orthomyxoviridae family) Geographical diffusion: Pandemic Viral transmission to human: Airborne spread	- Epistaxis - Dark blue cyanosis (heliotrope cyanosis)	- Massive necrosis of the respiratory epithelium
Dengue (Flaviviridae family) Geographical diffusion: Endemic in tropical and subtropical areas; epidemics in Hawaii, Florida, USA Mexico borders Viral transmission human: *Aedes aegyptus,* less frequently *Aedes albopictus*	- Transitory flashing 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.

(*continued on next page*)

Table 1 (*continued*)

Disease - Pathogen	Skin findings	Histopathologic findings
Chikungunya (Togaviridae family) Geographical 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, peri flexural, genitalia, and nails - Acral edema - Vesiculobullous 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 - Occasional focal lichenoid reaction - Increased basal pigmentation with pigmentary incontinence and melanophages.
Zika (Flaviviridae family) Geographical 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 - Face, palms, and soles involvement - 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) Geographical Diffusion: West and Central Africa Viral transmission to human: Contact with body fluids	- Absence of pruritus - Dermatitis 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 endothelial cells swelling - 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.

18% of patients but without a clear prognostic significance because patients either recovered or underwent an unfavorable course.[10,21,32,59] In Italy, 13.6% of these patients died of COVID-19.[32] Viral cytopathic effects have been documented in early skin biopsies, and interaction with ACE-2 seems able to induce acantholysis and dyskeratosis.[32,59-61] More skin biopsies and immunohistochemical staining with antibodies to SARS-CoV and 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 results are negative.

Influenza pandemic

High mortality rate and contagiousness of the coronavirus outbreak in the new millennium, related to interhuman airborne transmission and respiratory illness, reminds us of a similar occasion at the beginning of the last century. The 1918 influenza A virus, subtype H1N1, of the Orthomyxoviridae family is still not well understood.[65] The rapid

global spread of influenza was only partially explained by the massive movement of people and poor general conditions associated with World War I, because the virus was 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 is documented from March to June, whereas the second highly lethal wave started in August 1918, supporting two separate but interrelated influenza pandemics in a single year. Despite several hypotheses, there is no definitive explanation of how the virus suddenly increased its lethality worldwide.[62] The other troublesome novelty was the unexpectedly high mortality rate in younger people ranging in age from 20 to 40 years.[69] In most populations, the infection peak particularly decimated the 1890 birth cohort, who were vulnerable to a worse outcome. In that specific year, the H3N8 influenza pandemic had occurred, supporting the hypothesis that early-life influenza exposure in 1890 might have increased mortality after an H1N1 infection in adulthood.[70] One explanation of such enhanced disease, called the "original antigenic sin," is that subsequent serological reaction through nonneutralizing antibodies increases the virus's ability to infect the respiratory epithelial cells. The consequence of this appears to be that immunization is not always advantageous to the host. In line with such an alarming hypothesis, observational Canadian studies report that seasonal influenza immunization increased illness during the 2009 influenza pandemic.[68]

Two mucocutaneous signs that characterized this pandemic influenza, differing from every other influenza epidemic before and after, were nose bleeding and cyanosis.[69-74] The hemorrhagic phenomenon, although severe, was mainly confined to epistaxis. Frank hemoptysis was rare, as were other bleedings, except for an increased menometrorrhagia in women. The other distinctive sign was skin discoloration, described as a diffuse dark blue cyanosis and named heliotrope cyanosis.[75] Occurrence of such remarkable discoloration had prognostic significance because 95% of soldiers presenting such 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 of an initial acute tracheobronchitis, extending to the lung parenchyma and allowing the entry of bacteria, especially common pyogenic pathogens.[76] Fatal outcomes were related to entire lung failure; with oxygen saturation abruptly falling down, the alveoli filled with fluid.[77] Because this pandemic occurred in a preantibiotic era, the secondary bacterial pneumonia resulted in the death of approximately one-third of the influenza patients.

An important lesson from 1918 influenza pandemic is the crucial role of preventive measure strategies to contain spreading. Isolation of symptomatic patients was the best way to minimize their exposure to others and prevent acquired bacterial secondary infections.[66] Hospital admittance was not an efficacious measure because the wards were full of sick patients, increasing the exposure to many respiratory pathogens besides the influenza virus. The lack of effective treatment was a pivotal factor for fatal outcomes at that time, but people managing the illness at home showed better prognoses than those referred to hospitals.[66] In current times, the extensive use of antibiotics in intensive care units and in the general population exposes us to an equal or higher risk of bacterial superinfections, as currently experienced during the COVID-19 pandemic.

We can find analogies to current reluctance to admit mildly symptomatic patients into hospitals and implementation of home-based assistance to prevent COVID-19 circulation. The sudden passing of the 1918 pandemic is another difficult to explain fact about the most lethal influenza virus ever recorded, which hopefully could also happen with COVID-19 pandemic.

Arbovirus epidemics

The epidemics of recent decades have been characterized by the emergence of arboviruses, including dengue, ZIKV, and CHIKV. The skin is a major portal of entry for such pathogens, 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 the ships at the time of the slave trade. Another prevalent vector is the Asian tiger mosquito (*Aedes albopictus*), most recently also circulating in the southern United States and Europe, which came from Asia by way of egg-laden water amid shipments of disparate goods including used tires. Helped by human activities, transportation, and travel exchanges, cyclic epidemics spread from endemic areas between the Pacific and Atlantic oceans. Coinfections are an increasing problem, with all three arboviruses spreading in the intertropical countries, and the COVID-19 pandemic envisages the increasing danger of a very difficult differential already signaled with dengue fever.[78-80] Symptoms and signs are widely overlapping and include fever, myalgia, headache, arthralgia, and thrombocytopenia. Mucocutaneous manifestations with a hemorrhagic hue are common, but with respect to other viral exanthema, they occur characteristically late after constitutional symptoms and are not obligatory signals of progression to authentic hemorrhagic disease or shock. Individuals with predisposing conditions, especially microangiopathic diathesis, might favor bleeding and life-threatening complications, requiring inpatient management.[81-83] Another important increasing phenomenon is vertical transmission from pregnant woman, causing neurologic symptoms and malformations, including microcephalia, seizure, and/or encephalopathy.[84]

Because the symptomatology is similar in the three arboviruses, only serologica tests can differentiate one infection from another in most cases; however, some skin findings are useful for experienced physicians to steer the diagnosis.

Dengue

During the second 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(TTP).[83,84-88] A predisposing microangiopathic diathesis is believed to favor platelet hyper aggregation and formation of microthrombi in the endothelium[81]; however, viral infections including dengue fever 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 in suggesting the diagnosis in a very early phase of the infection in endemic regions. The first sign is the occurrence of a facial, neck, and trunk flushing, within 24 to 48 hours from general symptoms onset, followed by the widespread eruption on days 3 to 6. Itching is reported in a minority of patients, favoring a 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 pathognomonic sign. Mucosal involvement is described in 15% to 30% of cases,[85] especially in the conjunctiva and oral mucosa.[89,92,93] During the generalized eruption, the face is usually spared, and initial flashing has been explained with a temporary capillary dilatation. Pruritic palm and sole swelling have 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 TTP.[81]

Histopathology is seldom performed and 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, which used CD1a-positive Langerhans cells double-labeled with an antibody against dengue virus envelope glycoprotein from cadaveric skin explant, then confirmed by a skin biopsy from a vaccinated patient, suggested that skin Langerhans cells are a preferential target of dengue, 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 dermatitis, making differential diagnosis with dengue and treatment difficult.[78] From the first case reported in Thailand,[79] increasing reporting has pointed out that the presence of high dengue antibodies can give false-negative results for SARS-CoV-2. In this setting, only reverse transcription–PCR testing is definitive.[80]

Chikungunya

The human disease chikungunya was firstly described in Africa in 1952-1953,[97] then spread in several tropical countries across the globe, with recent large-scale outbreaks in the Western Hemisphere territories close to the United States.[98] Cases of chikungunya have occurred in Europe since 2007, with the presumed index case coming from India and causing an initial outbreak in northeastern Italy.[99] Since then, it has become autochthonous in France, Croatia, Spain, and Italy. The RNA virus belongs to the alphavirus genus of the Togaviridae family. Host cell entering occurs 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 woman.[82,101-103] Perinatal infection is also reported in endemic areas, such as India and Colombia.[101-104] Rarely, the occurrence of secondary TTP has been reported, leading hemolytic anemia, bleeding complications, and renal failure.[82,97]

Distinctive features of chikungunya 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 onset the onset of generalized symptoms and signs, but a more pathognomonic sign is the facial melanosis, especially nasalpigmentation, which might support a 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 striking findings. A vesiculobullous 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 were published about infants from India.[102] Atypical mucocutaneous manifestations, with ulcer occurrence in the scalp, abdomen, genital, and perianal region, were reported in newborns and infants in Colombia.[104]

Nail pigmentations (red lunula, melanonychia)[112] and eczematous changes over preexisting scars, resembling sarcoidosis scar phenomenon, have been reported.[101] Exacerbation of psoriasis or an eruption resembling guttate psoriasis

in patients without previous history of psoriasis has also been described.[108]

A skinkin biopsy is rarely performed, and histopathologic findings of the skin eruption are aspecific, showing features commonly seen in viral exanthems, including a mild superficial perivascular infiltrate of lymphocytes and occasional focal lichenoid reaction.[105] Vesiculobullous 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, but 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 CHIKV replication and amplification, as demonstrated *in vitro* in animal models, and in a skin biopsy specimen from a fatal neonate case.[113] Along with dermal fibroblasts, keratinocytes and melanocytes are also permissive for chikungunya, explaining the prevalence of hyperpigmented lesions. The infection induces a strong antiviral type I interferon response, and proinflammatory cytokines are released, 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 passes 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 due to a combination of direct cytopathic effect and immunologic factors.

Diagnosis is based on serology (anti-CHIKV immunoglobulin M) and reverse transcription–PCR confirmation

Chikungunya tends to resolve spontaneously or with mild symptomatic treatment. Administration of intravenous immunoglobulin therapy was reportedly effective in a severely ill Brazilian patient,[110] and severe TTP occurrence benefits from plasmapheresis.[81,114]

Zika

ZIKV 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 Western Pacific Region (2007) and French Polynesia (2013-2014) defined a combination of symptoms including fever, dermatitis, arthritis or arthralgia, conjunctivitis, and fatigue. The increased number of infants born with microcephaly in the Americas in 2015 and 2016 revealed the vertical transmission from pregnant infected women, extending surveillance for ZIKV to the European Union.[115] The possible person-to-person transmission through sexual intercourses was also noted, although it accounted for only 1% of cases.[116-119] A self-limiting factor of the epidemics relates to the type of mosquito species in the area, thus confining the disease to residents and occasional travelers. *Aedes albopictus,* which is the prevailing mosquito in Europe, does not seem to be an efficient vector, and no autochthonous cases have been detected in the surveillance European program from 2015 to 2017.[115] Incubation from mosquito bite inoculation ranges between 3 and 10 days.

Skin manifestations are considered a valuable hallmark of the disease. Although the dermatitis is by itself aspecific, it characteristically occurs 24 to 48 hours after the onset of the general flu-like symptoms.[120-123] This very short time lapse is the key to differentiate ZIKV disease from other exanthematous diseases that are common in the same geographic areas, including dengue and chikungunya, whose eruption manifests 4 to 5 days after symptom onset of clincial manifestations. The morphology is variable, mainly maculopapular, but it also arranged in a linear net-shaped pattern, or even wheals, which blanch on palpation. Intensity and distribution of the erythema is variable but is usually widespread and symmetric, also affecting the face, palms, and soles. A distinctive pattern with erythematous accentuation on the neckline, arms, and abdomen has been reported, as well as erythroderma.[123] Oral aphthous ulcerations are common. Another distinctive feature is intense itching, scratching emphasizing the papular components of the dermatitis, and representing the main reason for seeking medical advice,[121] accompanied by symmetric painful joint edema, most commonly on wrists and ankles. During the course of the disease, other lesions, such as petechiae, ecchymosis, subcutaneous hematomas, and jaundice, might occur as a consequence of viral immune-induced thrombocythemia. Peculiar psoriatic-like lesions may appear weeks after acute ZIKV symptoms, often in patients without previous history of psoriasis.

Cutanous histopathologic findings are non-specific 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, andit is suggestive of a direct viral cytopathic effect. A variable degree of spongiosis, acanthosis, and lymphocyte exocytosis into the epidermis is also reported. In psoriasis-like lesions, microscopic findings confirm a psoriasiform hyperplasia with regular acanthosis and perivascular lymphocytic infiltrate.

The diagnosis is confirmed through nucleic acid testing of whole blood, serum, or urine.

Ebola

EBOV, together with the 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. EBOV is subdivided into five species: Zaire, Cote d'Ivoire, Sudan, Reston, and Bundibugyo (recently discovered in Uganda), and classified as level four pathogens, among the most virulent and hazardous agents. EBOV 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 bodily fluids of infected large-animal carcasses or other humans, by accidental transmission during medical care or through burial practices. The disease occurs after a very variable incubation, from 1 to 21 days, and the 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 the absence of pruritus is a clue to differentiate the maculopapular eruption from other viral exanthema endemic in the same areas, such as ZIKV. Timing is characteristic, with the dermatitis occurring 4 to 6 days from symptoms onset and alerting to the second phase of disease transition. Patients have "ghost-like" features, and the dermatitis, more evident in light-skinned patients, often evolves in a centripetal fashion, from upper arms to flexor forearms and upper legs.[129] Mucosal involvement is also common, with a bilateral conjunctivitis in about 50% of patients, sore-like mouth lesions, gingivitis, glossitis, and pharynx inflammation. Enanthem on the soft palate can help to make a presumptive diagnosis with the presence of small whitish dots on the dry erythematous mucosa, resembling "tapioca granules." All mucosal lesions can bleed, alerting the onset of more hemorrhagic manifestations.[129] Around day 8, the entire body is usually diffusely erythematous with a dark livid huge, sometimes 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.

Skin biopsies are seldom,performedue tothe invasiveness of the examination in severely ill patients and because obtaining results is time-consuming; also, equipped pathology services are not usually available in the outbreak areas.[124] Formalin-embedded samples are not contagious, however, 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 vessels swelling. Alterations are mainly restricted to endothelial cells, dermal fibroblasts, and extracellular matrix around sweat glands.[130] Necrosis is also a common finding. Immunohistochemistry provides more information, showing EBOV antigen widespread distribution within dermal endothelial cells and fibroblasts, around and within sweat glands, although more scattered on the epidermis.[131] Electron microscopy confirms viral inclusions within the cytoplasm of endothelial cells, fibroblasts, and extracellular matrix.[129,131]

Discussion

As a consequence of the COVID-19 emergency, the medical community has been committed in a race against time to provide containment measures as well as management while waiting for effective treatments. Lessons from previous epidemics are valuable sources of information.[1,132] Skin involvement is common in any viral infection,[9-11,98] and considering the general alert on the possible occurrence of coinfection, especially in tropical countries,[78-80] indication of clinical and histopathologic clues to address the differential is paramount. A lesson learned from the only comparable pandemic, the 1918 influenza, is the importance of case identification and isolation, with patients managed at home showing 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 circulation of the virus, which is less lethal but more contagious than previous coronavirus epidemics.[13-16] Another alert from the influenza experience is the progressive involvement of younger patients with concern about the role of previous nonprotective immunization and the potential for an exaggerated immune response. Effective treatment experimentation and vaccination campaigns with different vaccines for COVID-19 are ongoing.

An increased reporting of mucocutaneous manifestations associated with SARS-CoV-2 has highlighted its analogies with arbovirus and EBOV findings. Strong clinicopathologic correlation might provide clues to address the differential. In the wait for laboratory and instrumental results, timing and distribution of skin lesions is often pathognomonic. Unfortunately, histopathologic sampling is seldom performed, but the few reports that are available 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 dengue and chikungunya eruptions occur on days 3 to 5, although a temporary facial flashing is reported for dengue between days 2 and 3. Pigmentation disorders are quite characteristic of chikungunya. Ebola disease skin manifestations are delayed (between days 4 to 5), extensive, not itching, and evolving to dark livedo or true cyanosis on day 8. COVID-19 skin manifestations are more heterogenous in clinical presentations and timing, somewhat encompassing

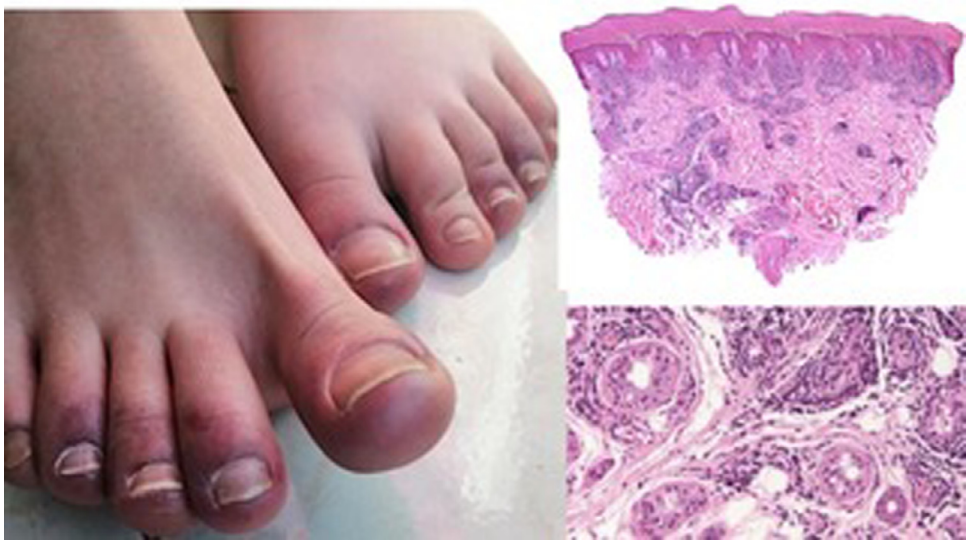

Fig. 1 **(A)** Chilblain-like lesions of the toes (coronavirus disease 2019 toe), with dusky erythematous edematous macule and purpuric plaques. **(B)** Edema of papillary dermis with a superficial and deep perivascular lymphocytic infiltrate (hematoxylin and eosin, 40x. **(C)** Close-up of the perieccrine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

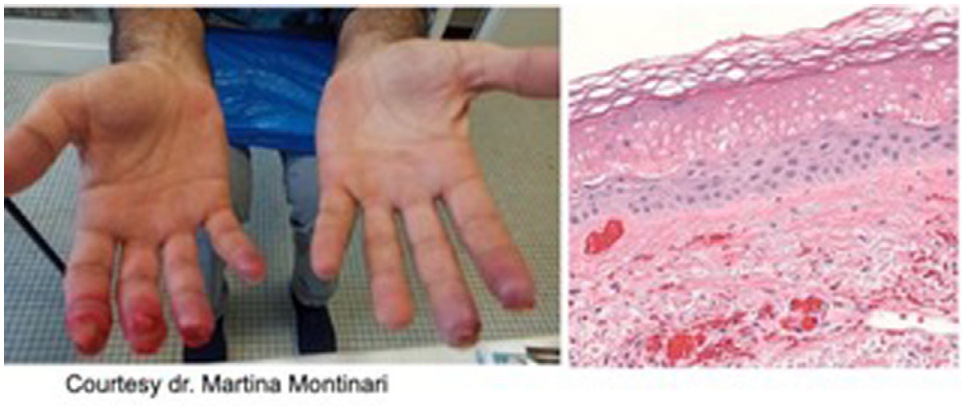

Fig. 2 **(A)** Acro-ischemiclivedoidnecrotic lesions of the hands. **(B)** Epidermal necrosis and thrombotic vasculopathy of the superficial vessels without sign of leucocytoclastic vasculitis (Hematoxylin & Eosin, 200x).

all others viral manifestations. The most specific presentation is the varicella-like or vesicular eruption that occurs few days after systemic symptoms, thus easily differentiable from the other maculopapular dermatitis of the arbovirus infection with early onset. During the course of the 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 not specific consequences of the viremia.

Purpuric, petechial manifestations are usually suggestive of overt disease in dengue, Ebola disease, and in several reports of COVID-19, although in the latter, the occurrences of true ischemic-livedoid or necrotic lesions are more characteristic. Such presentations are associated with a high mortality rate. Histopathologic findings document prevalent vessel damage and hyper aggregation 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 the 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, and appear late in the disease course in milder cases and last from 10 to 14 days. They sometimes persist 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

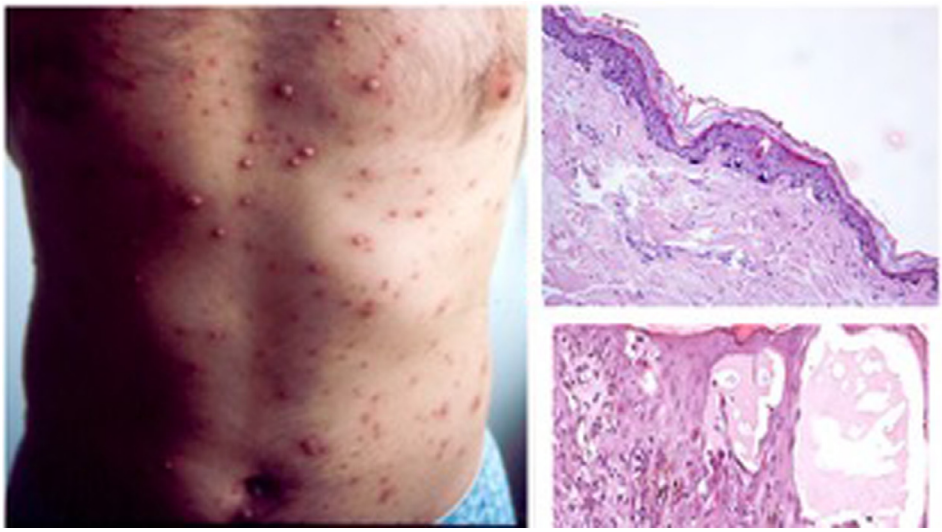

Fig. 3 **(A)** Varicelliform-like and vesicular eruption of the trunk. **(B)** Early findings showing vacuolar degeneration of the basal layer, dyskeratosis and multinucleate, and hyperchromatic keratinocytes with minimal inflammatory infiltrate (hematoxylin and eosin, 200x). Late findings characterized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

causative association; however, chilblains in young people have never been observed in such a high percentage before the outbreak of COVID-19.

There is still much more that needs to be known about skin manifestations associated with COVID-19, but an incontrovertible fact is that dermatologists are widely contributing to the understanding and definition of this new disease. Skin signs in a SARS-CoV-2 infection are part of the overt disease and can alert the physician to possible asymptomatic patients in an at-risk community. Clinicians should carefully look for skin lesions, especially in mild cases and young patients, to maximize SARS-CoV-2 testing and precautionary isolation measures.

Conclusions

Dermatologists are in the best position to identify minimal clinicopathologic signs helpful in the early recognition of viral exanthema and address presumptive differentials while waiting for laboratory and instrumental results. Postgraduate education and strict cooperation with multidisciplinary infectious disease teams is paramount to enrich both dermatologic and general medical community expertise to counteract the current COVID-19 pandemic, which has demonstrated an abrupt lethal potential and inexplicable surge similar to the influenza pandemic of 1918 but will hopefully implode just as quickly and definitely Figs. 1–3.

Declaration of Competing Interest

The authors declare no conflict of interest.

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