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COVID-19: Important updates and developments
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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.

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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.\textsuperscript{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.\textsuperscript{2} Medicine is trying to evolve and find solutions just as quickly, including protecting populations that lack native immunity with effective vaccination campaigns.\textsuperscript{3} An example is yellow fever containment in South America, which prevented large-scale circulation in the United States\textsuperscript{4} The current 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, however, has completely upset epidemiologic planning.\textsuperscript{4,5} 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,\textsuperscript{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 specific. 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,\textsuperscript{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\textsuperscript{12-16}

Phylogenetic analysis confirms strong homologies among coronaviruses,\textsuperscript{17-19} as well as respiratory symptoms and pathologic findings, supporting a similar cytokine cascade storm responsible for the patient’s rapid death.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{15} Another consideration is the number of infected individuals, which has exceed 32 million (WHO)\textsuperscript{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\textsuperscript{25} to 20.4% in an Italian study.\textsuperscript{26} A systematic review indicates a worldwide incidence of 1% to 2%.\textsuperscript{28} According to the Spanish prospective nationwide consensus study,\textsuperscript{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.\textsuperscript{28-34} Recently, a peculiar Kawasaki-like presentation during the COVID-19 pandemic has been described\textsuperscript{35,36} and named multisystem inflammatory syndrome with a 30-fold increased rate in Italian children.\textsuperscript{37}

Chilblain-like lesions consist of erythematous-violaceous papules and macules with purpuric hue and possible vesi-
cles, bullous, pustules on acral area, especially on the toes (Figure 1).\textsuperscript{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 asymmet-
rical, and lesions may be asymptomatic, itchy, or painful.
### Table 1  Clinicopathologic characterization of main viral epidemic infections

| Disease—pathogen | Skin findings | Histopathologic findings |
|------------------|---------------|--------------------------|
| COVID-19         | 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 andsweet gland necrosis, thrombotic vascuropathy 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. Massivenecrosisthetherapeutic epithelium. |
| SARS-CoV-2       | Epistaxis  
Dark blue cyanosis (heliotrope cyanosis) | |
| (Coronaviridae family) | 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. |
| Geographic diffusion: pandemic | Viral transmission to human: airborne spread | |
| H1N1 influenza virus | | |
| (Orthomyxoviridae family) | | |
| Geographic diffusion: pandemic | | |
| Viral transmission to human: airborne spread | | |
| 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 | | |

(continued on next page)
| Disease—pathogen | Skin findings | Histopathologic findings |
|------------------|---------------|--------------------------|
| **Chikungunya**  | Joint-related symptoms  
(Togaviridae family) | Superficial perivascular infiltrate of lymphocytes and  
Geographic diffusion:  
Africa, Asia, Caribbean, Latin America  
Viral transmission to human:  
*-* | Occasional focal lichenoid reaction.  
Increased basal pigmentation with pigmented incontinence, and melanophages. |
| **Zika**  
(Flaviviridae family) | Early symmetric generalized eruption (24-48 h after flu-like symptoms)  
Geographic diffusion:  
Central/South America,  
Caribbean, Micronesia,  
Polynesia, Cape Verde  
Viral transmission to human:  
*-* | 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) | Absence of pruritus  
Geographic diffusion:  
West and Central Africa  
Viral transmission to human:  
contact with body fluids | 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.
Histopathology demonstrates a superficial and deep perivascular lymphocytic infiltrate with signs of endothelial activation. 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. 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 adaptive immunity in young patients with asymptomatic or mild disease. 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). Blood tests usually confirm a hypercoagulability state. Advanced age, together with comorbidities, unleashes an exaggerated innate immune response (ie, macrophage activation syndrome) associated with a more severe prognosis. 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. 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. In the Italian experience, 13.6% of these patients died of COVID-19. 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. 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, especially in patients whose nasopharyngeal swab and serologic tests produced negative results.

**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. 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
circulating in most parts of the world many months before the spread of the lethal form in late 1918.  
\cite{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. \cite{52} The other troublesome novelty was the high mortality rate among young people, with those aged 20 to 40 years affected more than expected. \cite{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. \cite{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. \cite{68}

Two mucocutaneous signs characterized this influenza and differed from all other influenza epidemics before and after: nose bleeds and cyanosis. \cite{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 menorrhagia in women. The other distinctive sign was skin discoloration, described as a diffuse dark blue cyanosis (ie, heliotrope cyanosis). \cite{73} The occurrence of such a remarkable discoloration had prognostic significance, because 95\% of soldiers presenting with this cyanosis usually died within a single day. \cite{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. \cite{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. \cite{76} The fatal outcome was related to entire lung failure, with oxygen saturation abruptly falling and the alveoli filling with fluid. \cite{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. \cite{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. \cite{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. \cite{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. \cite{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. \cite{81-83} Another crucial increasing phenomenon is vertical transmission from pregnant women that causes neurologic symptoms and malformations, including microcephalia, seizure, and encephalopathy. \cite{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.
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. 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. A predisposing microangiopathic diathesis is supposed to favor platelet hyper aggregation and formation of microthrombi in the endothelium, however, viral infections including dengue are well-known inducers of inhibitor autoantibodies production, directed against the proteasome ADAMTS13, 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.

Regarding skin manifestations, a generalized skin eruption is described in 50% to 82% of patients 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. 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. 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. Skin necrosis and digital gangrene have been reported in patients with thrombotic thrombocytopenic purpura.

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. 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. The histopathologic findings are of no prognostic value in predicting the course of the disease.

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. From the first case reported in Thailand, 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.

Chikungunya

The human disease was first described in Africa between 1952 and 1953 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. 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. 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, 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. Perinatal infection is also reported in endemic areas, such as India and Colombia. Rarely, in regard to dengue, the occurrence of secondary thrombotic thrombocytopenic purpura has been reported, leading to hemolytic anemia, bleeding complications, and renal failure.

Chikungunya fever’s distinctive features, which go beyond aspecific fever, headaches, and general malaise, are prominent joint-related symptoms and peculiar dermatologic manifestations. A maculopapular eruption occurs in about one-third of patients 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. Acral edema, intertriginous hyperpigmentation, and aphthe-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. Bullous lesions and hyperpigmentation over the axilla, perioral, and genital areas have been reported in infants from India. Atypical mucocutaneous manifestations, with ulcers occurring on the scalp, abdomen, genital, and perianal region, have been reported in newborns and infants in Colombia.
Nail pigmentation (e.g., red lunula, melanonychia)\textsuperscript{112} and eczematous changes over pre-existing scars, resembling sarcoidosis scar phenomenon, have been reported.\textsuperscript{101} Exacerbation of psoriasis or an eruption resembling guttate psoriasis in patients with no history of psoriasis have also been described.\textsuperscript{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.\textsuperscript{105} Vesicle-bullous lesions have been described both as intraepidermal and subepidermal detachment.\textsuperscript{107} A characteristic finding is an increased basal pigmentation, with pigmentary incontinence and melanophages.\textsuperscript{101} Psoriasis-like lesions are superimposable to true psoriasis, although more dermal edema and melanophages are reported.\textsuperscript{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.\textsuperscript{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,\textsuperscript{110} whereas severe thrombotic thrombocytopenic purpura occurrence benefits plasmapheresis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{115} The possible person-to-person transmission through sexual intercourses was also noted, although accounting for only 1% of cases.\textsuperscript{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.\textsuperscript{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 24 to 48 hours after the onset of the general flu-like symptoms.\textsuperscript{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.\textsuperscript{122} 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,\textsuperscript{124} 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 thrombocytopenia, 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.\textsuperscript{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.
Ebola

Ebola virus, together with Marburg virus, belong to the Filoviridae family, order Mononegavirales, characterized by single-stranded RNA genomes of negative polarity, and an elongated filamentous morphology at electron microscopy. 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%. The main reservoir and infection sources are fruit bats, 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, 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. 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 erythematosus mucosa resembling “tapioca granules.” All mucosal lesions can bleed, indicating the onset of the more hemorrhagic manifestation. Around day 8, the entire body is usually diffusely erythematous, with a dark livid hue at times accompanied by true cyanosis. 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. Formalin-embedded samples, however, are not contagious and can be sent to specialized laboratories abroad. The few skin histopathologic reports suggest nonspecific findings, 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. 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. Electron microscopy confirms viral inclusions within the cytoplasm of endothelial cells, fibroblasts, and extracellular matrix.

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 and involvement is common in any viral infections and, considering the general alert on the possible coinfection’s occurrence, especially in tropical countries, 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. 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. 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
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 heterogeneous 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 palmo-plantar skin and mucosa. Histopathologic findings of direct viral cytopathic effects, with spongiosis 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.

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