THE SKIN MANIFESTATIONS OF COVID-19 IN CHILDREN (PART III)

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Dermatopathology of cutaneous COVID-19 infection in children

A systematic review demonstrated that skin lesions are present in only 0.25% of 2445 pediatric patients in 119 published studies (130). Besides, biopsies from skin lesions in children with confirmed or suspected COVID-19 have rarely been described in the literature. Most of the histopathological descriptions come from isolated cases or small series and some lesions have only been biopsied in adults. Since cutaneous lesions may be related to the direct effect of the virus and/or to the immune responses secondary to the infection, histological findings may reflect the direct cytopathic effect of the virus or secondary inflammatory responses.

Histology often follows usual patterns (table 1)

Table 1 – Table of histological appearances of COVID-19 associated rashes in children

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Histological appearance</th>
<th>Immunohistochemistry</th>
<th>Has the virus been present in the biopsied tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chillblains (Figure 1) (15,16,39,44)</td>
<td>Moderate to dense superficial and deep perivascular lymphocytic infiltrate, exocytosis to the epidermis and acrosyringia, perieccrine accentuation, necrotic keratinocytes, mild vacuolar degeneration of the basal layer, papillary dermal oedema and spongiosis. Lymphocytic</td>
<td>T cell infiltrate with a predominance of CD4 over CD8 T lymphocytes. Scattered CD30+ cells are occasionally observed. Mature B cells represent a minor proportion of the infiltrate</td>
<td>Presence of cytoplasmic granular positivity for SARS-CoV-2 spike protein in endothelial cells in upper dermis and epithelial cells of the secretory portion of eccrine glands. Round membrane-bound structures within the cytoplasm</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Positivity for SARS-CoV/SARS-CoV-2 spike protein was demonstrated in endothelial cells and epithelial cells of eccrine glands</td>
<td></td>
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<td>------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Vasculitis, fibrinoid necrosis, endothelialitis and thrombosis, red cell extravasation and dermal oedema</td>
<td>of endothelial cells showing an electrolucent centre, and surrounded by tiny spikes in keeping with viral particles</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Urticarial rashes

As far as we are aware, no reports on histological features of urticarial rashes have been published in children. Histology in adults reveal perivascular infiltrates of lymphocytes, eosinophils and upper dermal edema (63) and vacuolar-type interface dermatitis with occasional necrotic keratinocytes without the presence of eosinophils, resembling erythema multiforme (131).

Vesicular exanthem

Biopsies from vesicular lesions in adults with COVID-19 have shown suprabasal interepidermal unilocular vesicles with prominent non-ballooning acantholysis and eosinophilic dyskeratosis, with a striking “pomegranate-like” aspect. No nuclear atypia or large multinucleated cells were noted. No vasculitis was seen. Direct immunofluorescence and SARS-CoV-2 PCR tests performed on vesicles were reported to be negative (85). The findings described can mimic other acantholytic disorder like autoimmune or familial pemphigus or Grover's transient acantholytic dermatosis (132) and it is important to rule out herpetic infection (133,134).

Purpuric and livedoid lesions

In a case series of adult patients with COVID-19 and purpuric skin lesions, a pauci-inflammatory thrombogenic vasculopathy, with deposition of C5b-9 and C4d and a colocalization of COVID-19 spike glycoproteins and C5b-9 and C4d in the cutaneous microvasculature was demonstrated (46).

Pityriasis rosea-like lesions

The histology of a digitate papulosquamous eruption reminiscent of pityriasis rosea in an adult patient revealed mild diffuse epidermal spongiosis, and spongiotic vesicles containing lymphocytes and Langerhans cells. Papillary dermis was slightly oedematous, and a mild lymphohistiocytic infiltrate was seen in the upper dermis (136).

Testing and management of children with COVID-19 skin disease

There is no test of high sensitivity and specificity for diagnosing COVID-19 featuring skin lesions in the paediatric population. Therefore, the epidemiologic context, the context of exposure to COVID-19, the personal history of flu signs, and the characteristics of cutaneous signs (acute signs, not very specific however) are key points that allow for a tentative diagnosis of COVID-19-related skin lesions in children.

Data published by the Chinese Novel Coronavirus Pneumonia Emergency Response Epidemiology Team showed that about 2% of the patients infected with COVID-19, or SARS-CoV-2 (out of 72,314 subjects) were children aged 0 to 9 years (137). The incubation period in children is usually about 2 days, with a range of 2-10 days. Children usually undergo more asymptomatic forms, less severe symptoms and better prognosis than adults (90,137,138). Because more than 90% of the children have asymptomatic, mild or moderate disease, the diagnosis of COVID-19 may be
overlooked. On the other hand, it may be necessary to characterize the cases of COVID-19 in children perfectly, for a better pandemic control.

Some indications for the proper testing and diagnosis of children with suspected COVID-19 is provided. Figure 2 shows an algorithm that can help clinicians to work-up children with skin rashes suspected of COVID-19 infection.

SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR)

The gold standard for confirmation of COVID-19 in subjects with clinical symptoms consists of testing samples taken from the respiratory tract to assess for the presence of nucleic acid targets specific to SARS–CoV-2. Nasopharyngeal swabs are the preferred choice for testing, although oropharyngeal swabs also are acceptable (Centers for Disease Control and Prevention. Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19). Accessed at www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html. on 05 June 2020). RT-PCR was shown to be very specific, but sensitivity is heterogeneous, thus negative results do not allow for excluding the infection. RT-PCR results varies over time, and testing is all the more positive as it is performed during the first days of symptoms (139).

RT-PCR testing is reported in the paediatric population who presented with COVID-19 related cutaneous signs (14-16,20,33,119,140). Among them, 68 had pseudo-chilblains, 4 had erythema multiforme, and one was a neonate with diffuse livedo associated with acute respiratory signs. Sixty-one among 69 underwent nasopharyngeal or oropharyngeal swabs for RT-PCR testing, and 59 (97 %) were negative. The 2 positive cases included a neonate with livedo (119), and a child with chilblains and associated erythema multiforme who had GI signs 2 days before occurrence of the chilblains (20).

The published data suggest that when skin manifestations are concomitant with general signs of viral infection, PCR might be positive and is thus recommended (however, with a low sensitivity), whereas when signs appear several days later, as is the case with pseudo-chilblains, testing is usually negative.

Search for other infectious agents

Among most of the adult patients diagnosed with COVID-19 with acute respiratory symptoms, the occurrence of concomitant respiratory viral infections (influenza viruses-A and -B, Mycoplasma pneumoniae, Streptococcus pneumoniae, Legionella pneumophila, among others) has been reported in more than 50% cases (141). In children with isolated cutaneous signs, especially pseudo-chilblains, immunoassays for Parvovirus B19 were performed in 31 cases and they were either negative or in favour of an old infection (16,33). However, the associations with other infections were not looked for.

The published data suggest that there is no need to search for Parvovirus B19 antibodies by serologic immunoassays in children having COVID-19 related cutaneous signs.

Serologic immunoassays (COVID-19 IgM, IgG, IgA antibodies)
Various serological assays to determine antibodies against COVID-19, such as enzyme-linked immunosorbent assays, are currently available which provide information about the development of immunity against reinfection. With the available data, the utility of serologic assays for diagnosing acute COVID-19 infection seems limited. It has been shown that seroconversion occurs with a median time of 5-12 days for IgM antibodies and after 14 days for IgG and IgA (139,142). Cross-reactivity is also a potential problem(143). Cross-reactive antibody response has been shown between SARS-CoV-2 and SARS-CoV infection (144). Interestingly, SARS-CoV-2 CD4+ cells are detected in 40 to 60% of unexposed individuals. This result suggests that cross-reactive T cell recognition might exist between previous common cold coronavirus and SARS-CoV-2 (145).

We have very limited data on serologic assays in children with skin COVID manifestations, but when performed they were negative for IgG and IgM in all cases (16,33,140). Only one patient showed positive IgA against COVID-19 (33). In an Italian series, specific serology against S1 domain of SARS-Cov-2 spike protein performed was positive in 6/19 cases for IgA, and in 1/19 for IgG (16).

The relevance of serologic assay in dermatologic conditions needs to be confirmed (146). The published data suggest that the presence of IgM and IgG by immunoassays has very low diagnostic relevance to cutaneous signs of COVID-19 in children. The observations related to presence of IgA antibody responses need to be further investigated.

**Routine laboratory tests, inflammation markers and coagulation panels**

Lab tests are necessary in presence of severe general symptoms of COVID-19 and in case of cytokine storm syndrome and may require hospitalization. This is usually not the case for isolated skin lesions except when they are associated with general symptoms or persist beyond expected. Unwell patients may demonstrate decreased albumin (~75%), elevated C-reactive protein (~60%), elevated lactate dehydrogenase levels (~60%), and lymphopenia (~40%). No biomarker or combination of biomarkers currently exists that is sensitive/specific enough to establish a diagnosis of COVID-19, or to pragmatically predict its clinical course (138).

In most reported children with common COVID-19 related skin lesions who underwent routine lab tests, no significant abnormalities in serum chemistry were observed. The various coagulation markers were observed to be within the normal range in children except for D-dimer levels that were slightly raised in 3 cases, whereas most others had a value < 1000 ng/ml (14,15,33). Adult patients with acral cyanosis often have a hypercoagulable and disseminated intravascular coagulation (147).

In children with the severe disease PIMS, abnormalities in lab values have been extensively reported.

Markers of autoimmunity including ANA and cryoglobulins tested in 14 of the 69 published cases in children, showed no significant anomalies, except one child with COVID-19-related chilblains who had raised anti-cardiolipin IgG antibodies (33).

**Interference of COVID-19 with chronic skin diseases in children**

During the COVID-19 pandemic, follow-up for children affected by chronic diseases has been interrupted or moved to remote methods, especially in countries heavily
affected. Outdoor play, activities and even schooling in most cases has been interrupted.

A study to evaluate the influence of COVID-19 on the hospitalizations in a tertiary dermatology department in South West Poland, compared the number of hospitalized patients during COVID-19 pandemic with the same period in 2019 (148). Hospitalized children (2-18 years old) decreased from 81 (12.9%) in 2019 to 12 (6.8%) during the period of study, especially for patients with chronic inflammatory diseases (atopic dermatitis, lichen, eczema, psoriasis, urticaria, and pityriasis rubra pilaris) (148). Similar data have been reported in Italy (149,150). A study described the management of 6,890 patients with psoriasis, including 120 children, during pandemic in the major three reference centres for psoriasis in Sardinia, Italy; about 23% of patients were affected by severe psoriasis. The Italian drug agency (AIFA) declared an automatic renewal of the therapeutic plan of patients with rare diseases or under biologics treatment. However, the dermatologists found difficulties including limitations to face-to-face consultations for severe cases, high infection rate among dermatologists (40%, compared to the national average 7-8%), and cancellation of outpatient clinics (150).

Dermatological consultations in Konya (Turkey) during the pandemic were mainly carried out by teledermatology (72.8 % of consultations), which allegedly allowed for reducing the risk of disease transmission (151).

A task force of 37 expert paediatric dermatologists filled out a survey concerning the management of systemic immunosuppressive therapies for children during SARS-CoV-2 infection spread and developed educational contents for patients, caregivers and providers accessible online (152). Three main areas where analysed: (i) treatment initiation, (ii) treatment continuation and (iii) laboratory monitoring of systemic therapies. COVID-19 significantly affected the management of immunosuppressive medications (97 % of the respondents), depending on: the drug (87 %), the condition being treated (78 %), family/patient preferences (62 %) and risks of COVID-19 versus not treating skin disease (84 %). The management of specific immunosuppressive medications was analyzed based on different clinical circumstances: (i) asymptomatic patients (ii) upper respiratory tract infection (URI) with unknown COVID-19 status, (iii) confirmed exposure to COVID-19, and (iv) confirmed SARS-CoV-2 infection. Selected drugs were classified into systemic therapy (methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, systemic steroids, apremilast, JAK inhibitors) and biologic therapies (anti-TNFa, anti-IL17, anti-IL-12/23, anti-IL-23, dupilumab).

The majority of dermatologists agreed that in SARS-CoV-2-negative patients all treatment should be continued or adapted to the context (152). In patients with URI most drugs were temporary discontinued, except for systemic steroids that were also decreased in dosage (30 % of respondents); apremilast and dupilumab were mostly continued (46% and 68 %, respectively). In patients exposed to confirmed households and with confirmed COVID-19 infection, all the selected drugs were mostly discontinued or decreased in dose, including systemic steroids (24% and 19% of respondents, respectively), apremilast (30% and 24 %, respectively) and dupilumab (49% and 16%, respectively). In addition, the frequency of laboratory monitoring was also reduced. Notably, discontinuance of a biologic therapy could lead to failure after reintroduction and tapering of corticosteroids may need to be assessed for adrenal suppression, especially in case of infection when stress-dose steroids may be required. In conclusion, a final statement for the management of immunosuppressive medications was not achieved, and it was advised that the decisions regarding treatment were regularly discussed with the patients and their caregivers (152).
The European Task Force on Atopic Dermatitis (ETFAD) published a statement on SARS-CoV-2 and atopic dermatitis (153). They suggested continuing all ongoing medications to prevent disease worsening, to observe hygienic procedures and to moisturize their skin regularly. In addition, if systemic treatment should be stopped, it should be replaced by a topical therapy. Dupilumab is preferred over other medications, because it does not increase the risk of viral infection.

Another evaluation of the use of systemic drugs during COVID outbreak suggested that dupilumab, aprelimast, and acitretin are not associated with increased risk of infection and seem to be safe during COVID-19 pandemic (154). Other suggestions to optimize the care of patients with atopic dermatitis during the outbreak included encouraging the skin care (hygiene, moisturizing...), the access to telehealth, and follow published indications on systemic drugs in this setting (155).

Similar indications to the above mentioned have been advocated for the use of immune-suppressive medications in psoriasis, autoimmune bullous diseases, and atopic dermatitis (156-159). The treatment of autoimmune bullous diseases should be maintained due to the high rate of morbidity and mortality of this disease group (160). In patients infected with SARS-CoV-2, azathioprine, mycophenolate mofetil/sodium, cyclophosphamide, methotrexate and cyclosporine may be stopped, while topical corticosteroids, dapsone/sulphapyridine, low dose prednisone/prednisolone, doxycycline/tetracycline, colchicine and IVIG can be continued. Systemic corticosteroids should be tapered, and not suddenly interrupted. Regular update through WHO/CDC homepage and the European Academy of Dermatology and Venereology, which published specific recommendations on the website, are recommended (160).

COVID-19 pandemic means a psychosocial impact on health-care providers and patients with chronic skin disorders (161). Also, the quarantine may have negative effects on chronic inflammatory conditions. Immobilization, decrease of physical activity and lockdown induce higher caloric intake, obesity, and a negative impact on mood. All these factors worsen psoriasis and hidradenitis suppurativa and decrease adherence to treatment (162).

Teledermatology and telemedicine appear as an opportunity for continuing health care delivery (163-165).

Some suggestions on dermoscopy during pandemic COVID-19 have been proposed: (i) avoid dermoscopy in specific body sites: mucosa, hands, nails, face and eyes, (ii) patient and doctors should respect distancing in waiting room, wear mask, and wash or sanitize hands before and after the exam, (iii) the dermoscope should also be sanitized before and after each patient, (iv) the examined skin should also be sanitized before and after the exam, and (v) digital report should be encouraged instead of printed paper (166).

**Recommendations for paediatric dermatologists attending children with suspected COVID-19 skin disease.**

The following advice may continue to change over the following months. Only 1-5% of confirmed COVID-19 positive cases are children. Overall, children have milder disease and deaths in children are exceptional (167).
The initial evaluation, like in adults, should be carried out at the department where the patient is attended first (emergency room, inpatient room), to avoid unnecessary patient movements in the hospital and avoid contacts with patients in waiting areas. Dermatologists attending children with skin lesions suspected of COVID-19 should wear proper personal protective equipment, which may include mask, goggles, protective suits, head caps and gloves (168).

A thorough evaluation by an experienced paediatrician is highly recommended. Whereas most children with SARS-CoV-2 infection are expected to preserve a good general status and normal vital signs, a poor general status and tachycardia are early signs of shock in COVID-19 (94,95).

Severe gastrointestinal symptoms appear to me more frequent than respiratory symptoms in severely ill children and can indicate the possibility of PIMS (95). However, most patients with cutaneous lesions do not present with systemic symptoms or, if present, these are mild, and usually occur days to weeks before the appearance of the skin lesions (15).

If history and clinical examination suggest SARS-CoV-2 infection, it is recommended to test by PCR and follow-up household contacts according to the local health authority protocols. In children with mild symptoms, the likelihood of transmission of the infection beyond the first week after the onset of symptoms is very low, (169,170) so home lockdown for 10 days is recommended. If you need to see an infectious child then one should try to see them in a COVID-19 area, as late as possible during the day to allow cleaning and caregivers with symptoms must not attend. Informative announcements in the dermatology clinics must clearly explain medical requirements, such as fever screening at the clinic entrance, questionnaires about presence of symptoms in the last two weeks or close contact with suspected or confirmed COVID-19 cases, using alcohol-based hand sanitizer, wearing surgical mask for children and caregivers and maintaining appropriate distancing. Proper cleaning and disinfecting of the office should be carried out after every suspected or confirmed child is attended. Surfaces should be cleaned and disinfected regularly, such as doorknobs, light switches, computer keyboards, phones and tools using during examination such as dermoscopes (171). Surfaces should be disinfected with 1% sodium hypochlorite solutions, and the electronic gadgets with the alcohol based disinfectant.

After an initial in-person evaluation, teledermatology is a good choice for follow-up of COVID-19 children until the skin lesions are completely solved (172).

All health professionals involved in the care of children should try to stay updated, in spite of the increasing number of articles appearing in the literature. Up until the 11th of June 2020, only 3 months after the WHO declared the pandemic, 38,903 articles about COVID-19 had been published in PubMed, with 1,502 references regarding the paediatric population.

**Figures**

Figure 1. Histopathology of chilblains in COVID-19. A, Low power view showing intense previscular and perieccrine infiltrates; B, Edema in the papillary dermis with both dermo-epidermal and perivascular infiltrates. C, D, Prominent lymphocytic vasculitis with vessel wall damage in dermal vessels.

Figure 2. Algorithm for diagnosis of COVID-19 in children with a skin eruption
Learning points

- The histopathology of COVID-19 related chilblains is similar to classic primary chilblains.
- Sensitivity and specificity of PCR and serology tests are not high in children, and epidemiologic data are important in the diagnosis of COVID-19 in children.
- More than 90% of children have asymptomatic, mild or moderate COVID-19, and the diagnosis may thus be overlooked.
- COVID-19 may interfere with the course of chronic skin diseases and with the access of patients to specialized care. Teledermatology may partly overcome this latter problem.
- COVID-19 may interfere with the use of immunosuppressive drugs for skin diseases. The continuation of these drugs should be balanced with the risk of withdrawal and worsening of the skin condition.
- Dupilumab appears to be safe and not associated with increased risk of infection.

Questions and answers

1. Which of the following is not a histologic feature of COVID-19 related chilblains?
   A. Lymphcytic vasculitis
   B. Leukocytoclasis
   C. Endothelialitis
   D. Thrombosis
   E. Red cell extravasation

Answers to question 1
   A. Incorrect.
   B. Correct.
   C. Incorrect.
   D. Incorrect.
   E. Incorrect.

2. What percentage of proven COVID-19 patients are children?
   A. < 5 %
   B. 10-20 %
   C. 20-40 %
   D. 40-60 %
   E. 60-80 %

Answers to question 2
   A. Correct. Children are a minimal part of the COVID-19 proven patients. This figure is probably an underestimate, because many children remain asymptomatic and the detection of SARS-CoV-2 by PCR has a low sensitivity in this age.
   B. Incorrect.
   C. Incorrect.
   D. Incorrect.
   E. Incorrect.
3. What is the most agreed option for children with atopic dermatitis treated with immunosuppressive drugs and no symptoms of COVID-19?  
A. Continue therapy  
B. Reduce dose to half  
C. Taper for 2 weeks and then discontinue therapy  
D. Discontinue therapy  
E. Increase dose  

Answers to question 3  
A. Correct. The majority of dermatologists agree that in SARS-CoV-2-negative patients all treatments should be continued or adapted to the context.  
B. Incorrect.  
C. Incorrect.  
D. Incorrect.  
E. Incorrect.  

4. Which of the following is the preferred systemic treatment for severe atopic dermatitis during COVID-19 pandemic?  
A. Cyclosporin  
B. Methotrexate  
C. Azathioprine  
D. Mycophenolate  
E. Dupilumab  

Answers to question 4  
A. Incorrect.  
B. Incorrect.  
C. Incorrect.  
D. Incorrect.  
E. Correct. Though all the drugs in the list are acceptable, dupilumab is preferred over other medications, because it is the only one that does not increase the risk of viral infection.  

5. In a child with chilblains suspected to be related to COVID-19, what of the following measures is correct?  
A. PCR is not necessary  
B. The patient should be quarantined for 2 weeks regardless of the PCR result  
C. The patient should be admitted to hospital  
D. If PCR is negative, the likelihood of transmission of the infection is very low  
E. A complete blood cell count, serum chemistry and coagulation studies should be obtained.  

Answers to question 5  
A. Incorrect. PCR is recommended for any patient suspected to have COVID-19  
B. Incorrect. If PCR is negative, the patient should not be locked down  
C. Incorrect. The condition is mild, regardless of the PCR result, and the patient should not be admitted.  
D. Correct.
E. Incorrect. No further testing is recommended.

References


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