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

David Andina, MD [a]
Anna Belloni-Fortina, MD [b]
Christine Bodemer, MD [c]
Ernesto Bonifazi, MD [d]
Anca Chiriac, MD [e]
Isabel Colmenero, MD [f]
Andrea Diociaiuti, MD [g]
May El-Hachem, MD [g]
Laura Fertita MD [h]
Dirk van Gysel, MD [i]
Angela Hernández-Martín, MD [a]
Thomas Hubiche, MD [j]
Catalina Luca, MD [e]
Luisa Martos-Cabrera, MD [a]
Annabel Maruani, MD [k]
Francesco Mazzotta, MD [d]
A. Deniz Akkaya, MD [l]
Miquel Casals, MD [m]
Juan Ferrando, MD [n]
Ramón Grimalt, MD [o]
Ivan Grozdev, MD [p]
Veronica Kinsler, MD [q]
Marianne Morren, MD [r]
Malathy Munisami, MD [s]
Arti Nanda, MD [t]
Mónica P. Novoa, MD [u]
Hagen Ott, MD [v]
Suzane Pasmans, MD [x]
Carmen Salavastru, MD [y]
Vijay Zawar, MD [z]
Antonio Torrelo, MD [a]
The ESPD group for the skin manifestations of COVID-19

[a]Department of Dermatology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain
[b]Pediatric Dermatology Unit, Department of Medicine DIMED, University of Padua,Italy
[c]Department of Dermatology, Hospital Necker Enfants Malades, Paris centre University Paris France
[d]Dermatologia Pediatrica Association, Bari, Italy
[e]Nicolina Medical Center, Iasi, Romania
[f]Department of Pathology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain
[g]Dermatology Unit, Bambino Gesù Children's Hospital- IRCCS, Rome, Italy
[h]St Parascheva Infectios Diseases Hospital, Iasi, Romania
[i] Department of Pediatrics, O.L.Vrouw Hospital, Aalst, Belgium
[j]Department of Dermatology, Université Côte d'Azur, Nice 06200, France.
[k]University of Tours, SPHERE-INSERM1246, Department of Dermatology, Unit of Pediatric Dermatology, CHRU Tours, 37000 Tours, France
[l]Department of Dermatology, Ulus Liv Hospital, Istanbul, Turkey
[m]Department of Dermatology, Hospital Universitari de Sabadell, Barcelona, Spain
[n]Department of Dermatology, Hospital Clìnic, Barcelona, Spain

[o]Facultat de Medicina i Ciències de la Salut, Universitat Internacional de Catalunya, Barecelona, Spain
[p]Department of Dermatology, Children's University Hospital Queen Fabiola, Brussels, Belgium
[q]Paediatric Dermatology, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK
[r]University hospital Lausanne and University of Lausanne, Pediatric dermatology unit, Department of Pediatrics and Dermato-Venereology, Lausanne Switzerland
[s]Department of Dermatology and STD. Jawaharlal Institute Of Postgraduate Medical Education & Research (JIPMER), Puducherry, India
[t]As'ad Al-Hamad Dermatology Center, Kuwait.
[u]Hospital San Jose, Bogota, Colombia
[v]Division of Pediatric Dermatology, Children's Hospital Auf der Bult, Hannover, Germany
[x]Erasmus MC University Medical Center Rotterdam. Sophia Children's Hospital. Rotterdam, Netherlands
[y]Department of Paediatric Dermatology, "Colentina" Clinical Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[z]Department of Dermatology, Dr Vasantrao Pawar Medical College, Nashik, India.

Introduction

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses with a nucleocapsid of helical symmetry, infecting humans, animals, birds and mammals. Coronavirus infection in humans can cause a spectrum of conditions ranging from the seasonal common cold to deadly infections. Two highly pathogenic and transmissible coronavirus infections were previously recognized: the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV).

The new SARS-CoV-2-induced disease started in Wuhan City, China in December 2019, and soon spread around the world, being declared a pandemic on 11th March 2020. Initially, presenting with respiratory symptoms, the disease was called Wuhan pneumonia in China. Later, involvement of other symptoms was gaining recognition. The initial reports of cutaneous manifestations in SARS-CoV-2 were from Italian dermatologists (1,2) probably because Italy was the first European country to be heavily affected by the pandemic.

The overall clinical presentation, course and outcome of SARS-CoV-2 infection in children differ from those in adults. Similarly, the cutaneous manifestations of childhood COVID-19 also differ from those of adults. While manifestations such as urticaria, maculo-papular rash or vesicular rash can occur at all ages, certain manifestations such as chilblains, erythema multiforme, and cutaneous manifestations of Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-COV-2 (PIMS-TS) are more frequently seen in children and young patients.

In this review, we summarize the current knowledge on cutaneous manifestations of COVID-19 in children after thorough and critical review of articles published in the literature and from the personal experience of a large panel of paediatric dermatologists in Europe.

Skin manifestations of COVID-19 infection in children

Chilblain-like lesions

Classic chilblains (also called pernio) have been defined as inflammatory skin lesions of the acral regions that persist for more than one day (3). They are characterized by erythematous and oedematous macules, nodules and sometimes ulcerated plaques on the dorsal surface of fingers and toes. Skin lesions are triggered by cold, but may be rarely associated with connective tissue disease or hematologic malignant disorders. Patients usually report pain and itching. Treatment is conservative as spontaneous resolution usually occurs. Lesions typically recur yearly during winter. Increased mean capillary diameter and increased apical capillary diameter have been described in nailfold capillaroscopy (4).

Since March 2020 a great number of acral lesions resembling chilblain circulated on social media. Simultaneously, the relative search volumes provided by Google Trends demonstrated a worldwide increase in queries for “chilblains”, “fingers”, “toes” and lesions associated with “coronavirus” in France (5,6). The first paediatric case of possible SARS-CoV-2-associated chilblain-like lesions was published from Italy, followed by many report of similar cases from Italy, Spain and Middle East (2,7,8). Interestingly, chilblain-like manifestations observed during the COVID-19 pandemic differ from classic pernio by showing an equal sex distribution, absence of triggering factors, and involvement of the feet and sometimes the distal third of the legs. Patients with chilblains associated with COVID-19 were mostly young, confined at home due to the spring lockdown, and without previous history of pernio. However, clinical and laboratory data confirming the link are incomplete and contradictory (9).

In a Spanish consensus, “pseudo-chilblains” were reported in 19 % of cases (10). Only 1 of the 71 cases had a previous history of pernio and SARS-CoV-2 infection was confirmed in 41 % of them, and suspected in the remaining 59 %. Interestingly, SARS-CoV-2 infection manifested with less severe disease in pernio patients, and these acral skin manifestations were considered different from acral ischemic lesions described in adult patients with severe pulmonary disease associated with hypercoagulability (11,12).

In a French retrospective study (13) on 277 patients chilblain-like lesions were the most frequent cutaneous manifestation in a mix of confirmed or suspected cases. A handful of series have been published in children and adolescents, with a male/female ratio roughly 1 except for one with a 2.8:1 ratio (14-18).

Clinical manifestations

The lesions usually occur in children and adolescents in good health; they are rarely seen below 10 years of age (15). They appear on the feet in 74-100% of the cases, but are described on hands and fingers (15-17). Lesions are usually multiple, round, and vary from a few millimetres to centimetres in size, affecting the entire toe with a clear demarcation at the metatarsophalangeal level (Figure 1). Erythematous violaceous or

purpuric, patches and swellings have been observed, which may appear infiltrative. Periungual and subungual skin is usually affected. In the subsequent evolution, the lesions may become vesiculobullous or present dark purple or black crusts. The plantar region, the lateral aspect of the feet and the heels may also be involved with coarse, ecchymotic and infiltrated lesions.

Unlike adult cases, where 45% of the patients experienced COVID-19 symptoms (19), children/adolescents are usually asymptomatic; local pain and itch may occur (9,4-57,8%) (8,15-17).

In four Spanish children with chilblains on the feet, of which two also had involvement of the hands, complete clinical examination additionally revealed skin lesions consistent with erythema multiforme, involving hands, feet, forearms, elbows, arms, ankles, thighs, legs, and ears (20). Skin target lesions of erythema multiforme developing after chilblains have been reported in an Italian patient (21).

Chilblain-like manifestations in a series of 14 French patients presented similarities with lesions observed in type 1 interferonopathies such as Aicardi-Goutières syndrome and STING-associated vasculopathy of infancy (SAVI) (22).

Dermoscopic features of COVID-19 chilblains have been described in children and teenagers (23). Three main features were observed: a background area, globules and reticule. The background area is present in al cases and ranges from red, purple and brown to grey. Globules are seen in most cases, and are of red to purple colour. Finally, the grey-brown reticular network is seen in almost 30 % of lesions, and is usually located peripherally within the background area. Nail splinter haemorrhages, dilated nail folds capillaries with loss of polarity, and subcorneal haemorrhagic dots were anecdotally seen.

Nineteen Italian adolescents were studied with videocapillaroscopy (16). The capillary anomalies of both the fingers and the toes were described, even in cases where the skin lesions were limited to the feet only. Dilated capillaries were found with the same frequency on the fingers and toes, whereas pericapillary oedema and microhaemorrages were more frequent on the toes. These findings could potentially suggest that COVID-19 chilblains may be part of systemic involvement rather than induced by local factors. Moreover, these features appear more severe than those described in idiopathic chilblains, where microhemorrhages are not detected (4).

Testing

SARS-CoV-2 testing by PCR of nasopharyngeal swabs has been negative in almost all children and adolescents with COVID-related chilblains (24,25). PCR for SARS-CoV-2 in children, admitted to hospital with the suspicion of COVID-19, has been reported positive in only 11% of the cases (26) perhaps because of a lower viral load in children or that chilblains are a late manifestation when viral RNA is no longer detectable (27, 28).

IgG and IgM antibodies against SARS-CoV-2 have been tested in a very limited number of cases, and have been positive in only 2 out of 6 serologically tested patients, both of them with positive RT-PCR (9,16,17). Interestingly, in an Italian series of 19 adolescents, 6 were positive for IgA specific for the S1 domain of the spike protein and 3 were borderline for this antibody (16). Moreover a family history of close contact with a symptomatic adult was reported in 47 % of children in this series.

Treatment and outcome

All children and adolescents published thus far had a favourable outcome with spontaneous regression of the lesions and no complications. Rarely oral analgesics and antihistamines were administered (16,17,18). Oral gabapentin was used in one case for pain control (8). Steroids have been prescribed when associated erythema multiforme-like eruption (20).

Resolution of the lesions may take 12 days (10) to more than 8 weeks (15). Some patients experience new lesions during this time, but this did not affect the outcome.

SARS-CoV-2 infection pathogenesis and chilblain lesions

COVID-19 severity ranges from asymptomatic to severe clinical manifestations, including lung, heart and kidney injuries, and hypoxic encephalopathy (29-31). If chilblains are related then suggested pathogenic mechanisms are summarised below.

Viral induced type I interferonopathy hypothesis

It has been shown that severe COVID-19 patients have impaired interferon (IFN) type I response and increase tumour necrosis factor (TNF) and interleukin (IL)-6 production (32). Patients with chilblains have a higher IFN-α response compared to patients with mild and mostly moderate-to-severe COVID-19 disease (33). One hypothesis is that the younger patients exhibit an early IFN-I response, thereby attenuating early viral replication (34). The IFN-I response, however, induces microangiopathic changes, producing a chilblain LE-like eruption. Interestingly, chilblains are the most consistent feature of type I interferonopathies, and histological findings observed in COVID-19 chilblains are similar to virus-induced type I interferonopathy (14-16,33). Furthermore, the production of IFN-α is higher in children and young adults(35).

The innate response, particularly production of type I IFNs (IFN-α and IFN-β), constitutes the first line of defence against multiple viral infections (36). Chilblains are rarely seen in severe COVID-19 and patients presenting with chilblains do not develop severe COVID-19; indicating in part a good immune response (3) as in influenza virus infection (37).

Thrombosis/coagulopathy hypothesis

SARS-CoV-2 infected patients have an increased risk of thromboembolism with increased D-dimer levels (38), fibrin thrombi within distended small vessels and capillaries in lung and heart on autopsy (39,40), and acral ischemia (41). Thrombotic manifestations only complicate disease in a minority of COVID-19 patients (42,43). Microthrombi have been observed in chilblains (44), plus slightly increased D-dimers (15) and no prothrombotic factor, such as cryoglobulinemia nor circulating lupus anticoagulant, has yet been found (16).

Vasculitis hypothesis

Patients with neurological signs revealed perfusion abnormalities in 100% of cases (31) and patients with COVID-19 pneumonia have perfusion defects even without pulmonary emboli (45). The hypothesis of a specific microvascular pathology directly induced by SARS-CoV-2 has been proposed. Particular microvascular anomalies have been reported in lung biopsies suggesting a direct viral effect on vessels (41,45). Viral

proteins were found in endothelial cells and eccrine glands on skin biopsies from two patients with erythema multiforme and chilblains (20) and chilblains alone (44). Endothelialitis or lymphocytic vasculitis are seen in COVID-19 chilblains (44).

Angiotensin converting enzyme-2 (ACE2) has been proposed as the membrane receptor of SARS-CoV-2 (48). Endothelial cells have a very weak expression of ACE2 but pericytes are among the cells that have the highest expression of ACE2, thus making the pericyte a good candidate to explain microvascular inflammation and hypercoagulopathy in SARS-CoV-2 infection (45,49,50). Moreover, positive immunostaining for SARS-CoV-2 in epithelial cells of eccrine glands may be explained by the presence of ACE2 in these cells (51).

Other factors

A change in habits during the pandemic and lock down could be responsible of COVID-19 chilblains (e.g., lack of physical activity, walking barefoot at home, and physical and mental stress) (24,25). While these factors may play a role, they have been inadequately studied. An increase in the frequency of chilblains has not been reported in other immobility or lock down conditions such as immobilized elders, youngsters under periods of examinations or children or adolescents immobilized by fractures or surgical operations.

Figures

Figure 1. A-D: the spectrum of acroischaemic lesions in children in the setting of COVID-19

Learning points

- Acral ischaemic lesions, similar to chilblains, have been reported worldwide during the COVID-19 outbreak
- They are more common in adolescents and young adults,
- These lesions most commonly involve the toes and feet, and less frequently fingers and hands
- They may appear as erythematous or violaceous swellings, dark purpuric macules or vesiculobullous lesions
- Most patients have an excellent general status, with mild general symptoms or none
- A prominent vascular damage is the hallmark of COVID-19-related chilblains
- In most cases, nasopharyngeal PCR and blood serologies have been negative
- Outcome is excellent, with recovery in all cases after 4 to 8 weeks
- The link between COVID-19 and chilblains still remains to be proven, but seems likely

Questions and answers

Questions and answers

1. **One of the following facts is true about chilblains in the setting of COVID-19**
   A. Lesions predominate on the fingers
   B. Severe itch and pain are associated in most cases
   C. Chilblains often precede the other systemic symptoms and signs
   D. More than 90 % of the patients had systemic symptoms of COVID-19
   E. Chliblains are much more common in adolescents and young adults than in young children

Answers to question 1
   A. Incorrect. Lesions predominate on the toes and feet
   B. Incorrect. Most cases are asympomatc or mildly symptomatic
   C. Incorrect. Chilblains are most commonly occurring after systemic symptoms
   D. Incorrect. Only 40 % of cases have mild respiratory or GI symptoms
   E. Correct.

2. **One of the following is true about COVID-19 related chilblains**
   A. Most cases occurred in patients with household contacts with proven COVID-19
   B. Most patients have been positive when tested for nasopharyngeal PCR
   C. Most patients have been positive for serologic SARS-CoV-2 tests
   D. Chilblains have only been reported in patients with negative PCR
   E. The incidence of COVID-19 related chilblains paralleled the incidence of cases during the COVID-19 outbreak

Answers to question 2
   A. Incorrect. Contact with suspected cases occurs roughly in 50 % of cases
   B. Incorrect. Most cases are PCR negative
   C. Incorrect. Most cases are negative by serology
   D. Incorrect. PCR-proven cases also have presented chilblains
   E. Correct.

3. **What is the expected evolution of COVID-19 related chilblains?**
   A. Evolution to thromboembolism in 20 % of cases
   B. Digital necrosis and amputations in 25 % of cases
   C. Rapid spontaneous resolution in less than 5 days
   D. Spontaneous resolution in less than 10 weeks, without sequelae
   E. Chronic course for months

Answers to question 3
   A. Incorrect.
   B. Incorrect.
   C. Incorrect.
   D. Correct.
   E. Incorrect.

4. **What is the most consistent anomaly in lab testing in patients with COVID-19 related chilblains?**
   A. Positive lupus anticoagulant

B. Elevated D-dimer
C. Elevated cryoglobulins
D. Decreased fibrinogen levels
E. No abnormal lab analysis is usually detected

Answers to question 4

A. Incorrect.
B. Incorrect.
C. Incorrect.
D. Incorrect.
E. Correct.

5. The recommended treatment for COVID-19 related chilblains is

A. Oral corticosteroids
B. Subcutaneous heparin
C. Oral antihistamines
D. Oral gabapentin
E. No treatment is necessary in most cases

Answers to question 5

A. Incorrect.
B. Incorrect.
C. Incorrect.
D. Incorrect.
E. Correct.

References

(See complete list of references at the end of Part III)