Review paper

Dermatological manifestations of the Coronavirus disease 2019 in children: a systemic review

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Abstract

Introduction: An increasing number of publications describing dermatoses associated with Coronavirus disease 2019 (COVID-19) have shown differences in the morphology and incidence of dermatoses in children compared to the general population.

Material and methods: Among 22 selected full-text articles, dermatoses associated with COVID-19 have been described in 196 children (average age: 12.57 years). Dermatoses were the only symptom in most patients (n = 134; 68.4%). RT-PCR tests of nasopharyngeal swabs confirmed SARS-CoV-2 infection in only 18 cases (n = 18/69; 26.1%).

Results: Dermatoses described include chilblain-like lesions (n = 173; 88.3%), maculopapular rash (n = 16; 8.2%), erythema multiforme-like lesions (n = 12; 6.1%), varicella-like exanthema (n = 1; 0.5%), and urticaria (n = 1; 0.5%).

Conclusions: This publication aims to summarise existing data on dermatoses and to draw attention to how identification of dermatological symptoms in paediatric patients can provide a quick and reliable indicator of COVID-19.

Key words: COVID-19, coronavirus, SARS-CoV-2, paediatric, skin lesion, chilblain-like.

Introduction

The first cases of COVID-19 caused by SARS-CoV-2 appeared in Wuhan, China in December 2019 and the World Health Organisation (WHO) officially declared a pandemic on 11 March 2020 [1].

The most common symptoms include fatigue, fever, dry cough, muscle pain, and dyspnoea. Clinical symptoms also include gastrointestinal symptoms: nausea, vomiting, diarrhoea, as well as other symptoms such as rhinitis, sore throat, and loss of smell and taste. In severe cases the patients may develop acute respiratory distress syndrome (ARDS), arrhythmia and septic shock [2, 3]. COVID-19 clotting disorders may lead to pulmonary embolism [4, 5] and ischaemic stroke [6].

However, studies worldwide have shown an increasing number of cases of skin lesions in patients with SARS-CoV-2 infections [7]. Galván Casas *et al.* [8] proposed a classification for skin lesions seen in the course of COVID-19 (based on 375 cases in paediatric and adult patients). The study identified maculopapular lesions (47%), pseudo-chilblain-like lesions (19%), urticaria lesions (19%), follicular lesions (9%) and reticular bruising/necrotic lesions (e.g. livedo reticularis, necrosis, and acral ischaemia) (6%) [8].

Although the basic symptoms of COVID-19 in children and adults are similar [9], the course of the disease in the paediatric population is more often mild or asymptomatic [10]. Thus, skin lesions may come to the forefront of the clinical picture of the disease.

However, there are some differences in the nature and incidence of individual dermatoses in adults and children.

Aim

This study aims to summarize data from publications on COVID-19-related skin lesions in the paediatric population.

Material and methods

Searching strategy

The systematic review was performed according to the Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA) guidelines. The articles for this

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review were published or pre-print between 31 December 2019 and 1 June 2020 and can be found in PubMed and medRxiv. The following search phrases were used: "((COVID-19) OR (coronavirus) OR (Coronavirus disease) OR (SARS-CoV-2)) AND ((children) OR (paediatric)) AND ((skin) OR (Dermatology) OR (rash) OR (cutaneous))" as key words or MeSH terms. A number of 130 records were found through database searches. Duplicates and non-English language articles were excluded.

Studies selected were required to be cross-sectional studies, cohort studies, case reports, and case series of paediatric patients meeting clinical criteria for diagnosis of COVID-19 and/or children with RT-PCR-confirmed SARS-CoV-2 infection. From 43 potentially appropriate articles that underwent evaluation, 22 full-text articles were found to be suitable for analysis (review articles, hypothesis articles, and publications with duplicated patients were excluded).

Results

General overview (Table 1)

Clinical cases of 196 patients with skin lesions in the course of COVID-19 were analysed. The average age of patients was 12.57 years; most of them were male.

Extracutaneous symptoms of COVID-19 occurred only in 62 described patients. The most common were: fever, gastrointestinal symptoms, and cough.

Analysing all available data on clinical cases with general symptoms, these were preceded by skin lesions by 8.9 days on average. Only in 3 patients, dermatoses appeared before other COVID-19 symptoms and in another 3 at the same time.

RT-PCR tests from nasopharyngeal swabs were performed in 69 patients, 18 of whom were positive.

In the analysed articles the most frequently observed symptom was chilblain-like lesions (n = 173, 88.3%). Moreover, there were maculopapular rash (n = 16, 8.2%) and erythema multiforme-like lesions (n = 12, 6.1%). One case each of a child with varicella-like exanthema (0.5%) and urticaria (0.5%) were described.

Characteristics of skin lesions (Table 2)

Chilblain-like lesions

Vascular dermatoses in the form of acute ischaemic lesions were initially described in adult patients with severe SARS-CoV-2 infection [11]. The above changes are likely to result from clotting disorders and are associated with microthrombi formation, leading to pulmonary embolism, strokes, and disseminated intravascular coagulation [12, 13].

However, recently, an increasing number of paediatricians, particularly those from regions most affected by COVID-19, have reported the occurrence of chilblain-like dermatoses among patients who have never previously experienced perniosis or Raynaud symptoms [14–16].

These changes initially manifest as erythematous-bluish spots usually limited to the distal parts of the limbs, often with blisters, erosions and dry scab-covered ulcers. Upon healing, these lesions become spotted lesions [14, 17, 18].

Pseudo-chilblain skin lesions occurred in 173 patients. The average age in this group of patients was 13.2 years and most of them were female. Dermatoses were most often located only on feet (143 patients). In 13 patients, lesions concerned only hands, in 13 cases both hands and feet. The average duration of skin lesions was 18.5 days; in 54.9% they were accompanied by the following symptoms: pruritus, pain, burning and coldness (Table 2).

Authors of many publications show that patients with pseudo-chilblain-like lesions present mild or no symptoms of viral disease, and RT-PCR tests from the nasopharyngeal swabs are often negative. This is probably due to the delayed occurrence of skin lesions in the course of COVID-19 in children and young adults [15, 19–21].

In our analysis, extradermal symptoms appeared only in 44 out of 173 described patients and were preceded by chilblain-like lesions by 10.4 days on average. The most common symptoms were cough, gastrointestinal symptoms and fever.

Of the 49 RT-PCR tests performed from nasopharyngeal swabs, only 10 were positive for SARS-CoV-2 (Table 2). Kolivras *et al.* [22] presented a histopathological picture of chilblain skin lesions, in which they described the papillary oedema of the skin with perivascular lymphocytic infiltration together with diffuse necrotic keratinocytes in superficial layers of the epidermis. Microangiopathic changes may be caused by an increased reaction associated with increased type 1 interferon production, which occurs during SARS-COV-2 infection, especially in children and young adults. However, it may be a protective factor against the occurrence of a 'cytokine storm' and full COVID-19 [19, 22, 23].

Erythema multiforme-like lesions

Erythema multiforme-like dermatosis (n = 12/196) is another type of a skin lesion described in the publications we analysed. The mean age was 12.1 years, the lesions were more common in boys.

Erythema multiforme-like dermatoses were most often located on feet. Less commonly, they were found on hands face, conjunctiva, lips, and in the oral cavity. The average duration of skin lesions was 16.7 days; 58.3% of them were accompanied by pruritus and pain. General symptoms associated with COVID-19 appeared in 5 out of 12 described patients and were preceded by erythema multiforme-like lesions by 21 days on average. The

Table I. General overview

Study	Year, country	Type of the study	Number of cases (paediatric/ total in the study)	Age [years]	Sex (F/M)	History of dermatological conditions	Other chronic disorders	Morphological features of the lesions	Anatomical location of skin lesions	Symptoms associated with skin changes	Duration of skin changes	Nasopharyngeal swab RT-PCR test result	Serological test results for COVID-19	Systemic symptoms of COVID-19	Time from the onset of non-cutaneous COVID-19 symptoms to the onset of skin lesions – days	Histopathological examination
Mazzotta *et al.*	2020, Italy	Retrospective, case report	1/1	13	M	No	No	Chilblain-like	Feet	Pruritus and burning	NR	Positive	No	Fever, muscle pain, headache	–2 days	No
Recalcati *et al.*	2020, Italy	Retrospective, cross-sectional study	11/11	14	F	No	No	Chilblain-like and erythema multiforme-like	Feet and hands	No	NR	Negative	No	No	–	Diffuse perivascular involvement of the dermis and hypodermis by a dense lymphoid infiltrate, with saving of the epidermis; Thickening of the vessel wall and activation of the endothelium with nuclear enlargement
				15	F	No	No	Chilblain-like	Hands	No	NR	No	No	No	–	No
				15	F	No	No	Chilblain-like	Feet	No	NR	Negative	No	No	–	No
				18	F	No	No	Chilblain-like	Feet and hands	No	NR	Negative	No	No		No
				13	F	No	No	Chilblain-like	Feet	No	NR	No	No	No		No
				16	M	No	No	Chilblain-like	Feet	No	NR	No	No	Cough	+14	No
				13	M	No	No	Chilblain-like	Feet	No	NR	No	No	No	–	No
				15	M	No	No	Chilblain-like	Hands	No	NR	No	No	No	–	No
				14	M	No	No	Chilblain-like	Feet	No	NR	Negative	No	Diarrhoea	+7	No
				11	M	No	No	Chilblain-like and erythema multiforme-like	Hands	No	NR	Negative	No	Fever	+21	No
				14	M	No	No	Chilblain-like	Feet	No	NR	No	No	Fever, rhinitis, headache, fatigue	+21	No

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Garcia-Lara *et al.*	2020, Spain	Retrospective, Cross-sectional study	27/27	Median age: 14.4	M (*n* = 18)	No	No	Chilblain-like (*n* = 25) Erythema multiforme-like (*n* = 2)	Feet (*n* = 20) Hands (*n* = 6) Both (*n* = 1)	No (*n* = 18) Pruritus (*n* = 3) Pain (*n* = 6)	NR	Negative (*n* = 2)	Ig M negative (*n* = 9) Ig A negative (*n* = 9) Ig G negative (*n* = 9)	Diarrhoea (*n* = 1)	NR	No
Colonna *et al.*	2020, Italy	Retrospective, case series	4/4	11	F	No	No	Chilblain-like	Feet	Coldness and mild pain	19	Negative		Headache, rhinitis	+ > 14	No
				6	F	No	No	Chilblain-like	Feet	Pruritus and pain	5	Negative		Fever	+10	No
				5	M	No	No	Chilblain-like	Feet and hands	Pain	25	Negative		Pneumonia (fever, cough, dyspnoea, fatigue, muscle pain) Fever	+43 +4	No
				11	F	No	No	Chilblain-like	Feet	Pain	> 20	Negative		Fever	+10	Dense lymphocytic perivascular cuffing and periadnexal infiltration. Signs of vasculitis were evident in small to medium sized vessels with endothelial cell swelling and red blood cell extravasation. Fibrin thrombus was evident in superficial capillary
Piccolo *et al.*	2020, Italy	Retrospective, cross-sectional study	63/63	Median age: 14	F (*n* = 36) M (*n* = 27)	No	History of autoimmune disorders *n* = 6 patients (ANA positivity *n* = 1), with familial or personal history of coagulation defects *n* = 4 cases.	Chilblain-like	Feet (*n* = 54) Hands (*n* = 4) Both (*n* = 5)	Pain (*n* = 17) Pruritus (*n* = 17) Pain and pruritus (*n* = 13) No (*n* = 16)	NR	(*n* = 11) Positive (*n* = 2) Negative (*n* = 9)	IgM positive (*n* = 2), Negative (*n* = 4)	Gastrointestinal symptoms (*n* = 7) Cough, dyspnoea (*n* = 5) Fever *n* = 3	Systemic symptoms preceded by cutaneous findings	

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							Wolff-Parkinson-White $n = 1$, peripheral neuropathy $n = 1$, drug allergy $n = 1$									
Landa *et al.*	2020, Spain	Retrospective, case series	2–6	15	M	No	No	Chilblain-like	Feet	No	NR	Negative	IgM negative, IgG negative	No	–	No –
				15	F	No	No	Chilblain-like	Feet	No	NR	Positive	No	Rhinitis, diarrhoea	+7	No
Tosti *et al.*	2020, Italy	Retrospective, case series	2–4	16	F	AA Universalis	No	Chilblain-like	Feet	Pain	NR	No	No	Pharyngodynia	+14	No
				18	F	No	No	Chilblain-like	Feet	Pain and Pruritus	NR	No	No	No	–	No
Locatelli AG	2020, Italy	Retrospective, case report	1–1	16	M	No	No	Chilblain-like	Feet and hands	No	> 20	RT-PCR positive	No	Dysgeusia, diarrhoea.	+3	Oedema of the papillary dermis, superficial and deep lymphocytic infiltrate in a perivascular and strong perieccrine pattern; no signs of endothelial damage
Ramondetta *et al.*	2020, Italy	Retrospective, case series	3–7	4	M	No	No	Chilblain-like	Feet	No	NR	NR	No	No	–	No
				9	F	No	No	Chilblain-like	Feet	No	NR	NR	No	No	–	No
				11	M	No	No	Chilblain-like	Feet	No	NR	NR	No	No	–	No

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Ruggiero *et al.*	2020, Italy	Retrospective, case series	33/33	15	F	No	NR	Chilblain-like	Feet	Burning and pain	4	No	No	No	–	No
				12	F	No	NR	Chilblain-like	Feet	No	NR	No	No	Cough	NR	No
				10	F	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				11	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				14	F	No	NR	Chilblain-like	Feet	Pruritus, pain	NR	No	No	No	–	No
				12	F	No	NR	Chilblain-like	Feet	Pruritus, pain	NR	No	No	No	–	No
				10	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				8	M	No	NR	Chilblain-like and Erythema Multiforme-like	Feet, face	Pruritus	NR	No	No	No	–	No
				15	F	No	NR	Chilblain-like	Feet	Pruritus	NR	No	No	No	–	No
				15	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				13	F	No	NR	Chilblain-like	Feet	Pruritus	NR	No	No	No	–	No
				13	F	No	NR	Chilblain-like	Feet	Pruritus	NR	No	No	No	–	No
				15	M	No	NR	Chilblain-like	Feet	Pain	NR	No	No	No	–	No
				10	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				17	F	No	NR	Chilblain-like	Feet	Burning and pain	NR	No	No	No	–	No
				14	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				17	M	No	NR	Chilblain-like	Hands	No	NR	No	No	No	–	No

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				13	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				< 1	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				10	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				14	M	No	NR	Chilblain-like	Hands	No	NR	No	No	No	–	No
				9	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				13	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				12	M	No	NR	Chilblain-like	Feet	Pain	NR	No	No	Pharyngodynia	NR	No
				10	M	No	NR	Chilblain-like	Feet	Pruritus	NR	No	No	No	–	No
				13	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				5	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				4	M	No	NR	Chilblain-like	Hands	No	NR	No	No	No	–	No
				9	F	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				15	M	No	NR	Chilblain-like	Feet and hands	Burning and pain	NR	No	No	Fever	NR	No
				9	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	–	No
				17	F	No	NR	Chilblain-like	Feet and hands	No	NR	No	No	No	–	No
				11	F	No	NR	Chilblain-like	Feet	Pruritus	NR	No	No	No	–	No

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Guarneri *et al.*	2020, Italy	Retrospective, case series	3/3	14	M	No	No	Chilblain-like	Feet	Pruritus and burning	14	RT-PCR positive	No	No	–	No
				14	M	No	No	Chilblain-like	Feet	Pruritus and burning	20	RT-PCR positive	No	No	–	No
				18	M	No	No	Chilblain-like	Feet	Pruritus and burning	10–15	RT-PCR positive	No	fever	+2	No
Papa *et al.*	2020, Italy	Retrospective, case report	1/1	11	F	No	No	Chilblain-like	Feet	Pain and pruritus	15–20	RT-PCR negative Serology: IgG positive IgM negative	No	No	–	No
Andina *et al.*	2020, Spain	Retrospective, cross – sectional study	22/22	Median age: 12 (6–17)	F (*n* = 9) M (*n* = 13)	No	ADHD (*n* = 5)	Only Chilblain-like (*n* = 18) Chilblain-like and erythema multiforme-like (*n* = 4)	Feet (*n* = 19) Feet and hands (*n* = 3)	Pruritus (*n* = 9) Pain (*n* = 7)	7–21	RT-PCR *n* = 19: positive *n* = 1 negative *n* = 18	No	(*n* = 10) Cough or rhinitis (*n* = 8) Abdominal pain, diarrhoea (*n* = 1) Both (*n* = 1)	+ 0–7 (*n* = 4) + 8–14 (*n* = 2) + 15–28 (*n* = 4)	*n* = 6 (similar results) Dense, superficial, and deep angiocentric and eccrinotropic lymphocytic infiltrate Papillary dermal oedema, vacuolar degeneration of the basal layer and lymphocytic exocytosis Endothelia of small vessels appear swollen Intense lymphocytic vascular reaction in dermal vessels Red cell extravasation and focal thrombosis (arrow) in papillary dermis capillaries

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Diotallevi *et al.*	2020, Italy	Retrospective, case series	2/4	12	F	No	No	Chilblain-like	Feet	No	NR	RT-PCR positive	No	No	-	No
				8	M	No	NR	Chilblain-like	Feet	No	NR	No	No	No	-	No
García-Gil *et al.*	2020, Spain	Retrospective, case report	1/1	12	M	No	NR	Erythema multiforme-like	Feet	Pruritus	> 15	RT-PCR negative	IgM negative, IgG negative	No	-	Partial epidermal necrosis and perivascular lymphoid infiltrate in superficial and deep dermis; Microthrombi in capillaries in papillary dermis, with extravasation of red blood cells; Vasculitic changes only in relation to the lymphoid component (not in the thrombotic)
Janah *et al.*	2020, Morocco	Retrospective, case series	1/2	17	M	No	No	Erythema multi-forme-like	Hands	Pruritus	> 15	No	No	Fever, rhinitis, headache	+15	No
Labé *et al.*	2020, France	Retrospective, case report	2/2	6	M	No	No	Erythema multi-forme-like	Oral cavity, conjunctiva, feet and hands, face, lips	No	> 15	RT-PCR one negative the other positive	No	Loss of appetite	NR	No

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				3	M	No	No	Maculopapular rash with desquamation; erythema of the lips, oral cavity; cracking of the lips	Generalized rash, lips, oral cavity, conjunctiva	NR	NR	RT-PCR negative	No	Fever	0	No
Yozgat *et al.*	2020, Turkey	Retrospective, case report	1/1	3	F	No	No	Macular, maculopapular, morbiliform rash; desquamation; cracking of the lips	Generalized rash, lips, oral cavity, conjunctiva	No	> 20	RT-PCR negative	No	Fever	–1	No
Verdoni *et al.*	2020, Italy	Retrospective, observational cohort study	10/10	Median age: 7.5 (2–16)	F (*n* = 3) M (*n* = 7)	No	NR	Maculopapular rash; erythema or firm induration of hands and feet; erythema of the lips and/or oral cavity and/or cracking of the lips	Generalized rash (*n* = 8), feet and hands (*n* = 5), lips and oral cavity (*n* = 6)	NR	NR	T-PCR negative (*n* = 8) RT-PCR positive (*n* = 2)	IgM negative (*n* = 7), IgM positive (*n* = 3), IgG negative (*n* = 2), IgG positive (*n* = 8)	Fever (*n* = 10), Conjunctivitis (*n* = 9), Diarrhoea (*n* = 6), Meningeal signs (*n* = 4), Fatigue (*n* = 1)	NR	No

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Torrelo *et al.*	2020, Spain	Retrospective, case series	4/4	12	M	No	NR	Chilblain-like and erythema multiforme-like	Upper and lower extremities, face	Pruritus	7–-14	No	No	No	NR	Interface dermatitis with superficial and deep perivascular lymphocytic inflammation; Moderate exocytosis with vacuolar changes and spongiosis No necrotic keratinocytes Deep extension of the inflammatory infiltrate involving eccrine glands
				17	M	No	NR	Chilblain-like and Erythema multiforme-like	Upper and lower extremities	Pruritus	7–14	No	No	Cough, rhinitis, pharyngodynia	NR	Superficial and deep perivascular inflammation and vascular ectasia Mild exocytosis, vacuolar changes and spongiosis; No necrotic keratinocytes Mid dermal vessel showing transmural lymphocytic infiltration and plump endothelial lining
				11	F	No	NR	Chilblain-like and Erythema multiforme-like	Upper and lower extremities	No	7–14	RT-PCR positive	No	Gastrointestinal symptoms	NR	No
				15	M	No	NR	Chilblain-like and erythema multiforme-like	Upper and lower extremities	Pruritus, pain	7–14	No	No	Cough, rhinitis, pharyngodynia	NR	No

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Study	Year, country	Type of the study	Number of cases (paediatric/ total in the study)	Age [years]	Sex (F/M)	History of dermatological conditions	Other chronic disorders	Morphological features of the lesions	Anatomical location of skin lesions	Symptoms associated with skin changes	Duration of skin changes	Nasopharyngeal swab RT-PCR test result	Serological test results for COVID-19	Systemic symptoms of COVID-19	Time from the onset of non-cutaneous COVID-19 symptoms to the onset of skin lesions – days	Histopathological examination
Genovese *et al.*	2020, Italy	Retrospective, case report	1/1	8	F	No	No	Varicella-like exanthema	Trunk	No	7	No	No	Cough Fever	+3 –2	No
Durmaz *et al.*	2020, Turkey	Retrospective, case series	3/20	8 months	F	No	NR	Maculopapular rash (roseola-like)	Face, upper and lower extremities, Trunk	No	2	RT-PCR positive	No	Fever	0	No
				11	F	No	NR	Maculopapular rash	Face, upper and lower extremities, trunk	Pruritus	5	RT-PCR positive	No	No	–	No
				17	F	No	NR	Maculopapular rash (drug related)	Face, upper and lower extremities, trunk	Pruritus	After HCQ termination	RT-PCR positive	No	No	–	No
Morey-Olivé *et al.*	2020, Spain	Retrospective, case series	2/2	6	M	No	Cholestatic liver disease of unknown aetiology.	Maculopapular rash (erythematous, confluent)	Face, upper and lower extremities, trunk	No	5	RT-PCR positive	No	Fever (and worsening of the markers of cholestasis and cytolytic hepatitis)	+ > 14 days	No
				2 months	F	No	NR	Urticaria	Face, upper and lower extremities, trunk	Pruritus	9	RT-PCR positive	No	Fever	0	No

Table 2. Summary of the clinical characteristics

Parameter		General data
Total number of cases		196
Mean age [years] (range)		12.57 (2 months–18 years)
Sex	Male, *n* (%)	107 (54.6)
	Female, *n* (%)	89 (45.4)
Morphological features of the lesions – *n* (% of all cases)	Chilblain-like	173 (88.3)
	Maculopapular rash	16 (8.2)
	Erythema multiforme-like	12 (6.1)
	Varicella-like exanthema	1 (0.5)
	Urticaria	1 (0.5)
Anatomical location of skin lesions – *n* (% of all cases)	Feet	177 (91.7)
	Hands	45 (23.3)
	Trunk	16 (8.3)
	Arms, forearms	15 (7.8)
	Thighs, shins	15 (7.8)
	Face	10 (5.2)
	Lips	9 (4.7)
	Oral cavity	9 (4.7)
	Conjunctiva	3 (1.6)
Mean duration of skin lesions [days]		17.2 (2–25)
Symptoms associated with skin lesions – *n* (% of all cases)	Pruritus	62 (31.6)
	Pain	57 (29.1)
	Burning	7 (3.6)
	Coldness	1 (0.5)
	No	95 (48.5)
Nasopharyngeal swab RT-PCR test result (*n* = 69), *n* (%)	Positive	18 (26.1)
	Negative	51 (73.9)
Systemic symptoms of COVID-19 – *n* (% of all cases)	Fever	28 (14.4)
	Gastrointestinal symptoms	20 (10.3)
	Cough	18 (9.3)
	Conjunctivitis	9 (4.6)
	Rhinitis	8 (4.1)
	Dyspnoea	6 (3.1)
	Headache	4 (2.1)
	Meningeal signs	4 (2.1)
	Fatigue	3 (1.5)
	Pharyngodynia	2 (1.0)
	Muscle pain	2 (1.0)
	No	134 (68.4)
Mean time from the onset of non-cutaneous COVID-19 symptoms to the onset of skin lesions [days]		8.9 (-2–28)
Chilblain-like lesions (*n* = 173)		
Total number of cases		173
Mean age (range) [years]		13.2 (8 months –18 years)
Sex	Male, *n* (%)	79 (45.7)
	Female, *n* (%)	94 (54.3)
Anatomical location of skin lesions – *n* (% of all cases)	Only feet	143 (82.7)
	Only hands	13 (7.5)
	Both feet and hands	13 (7.5)
	Face	2 (20)
Mean duration of skin lesions (range) [days]		18.5 (4-25)
Symptoms associated with skin lesions – *n* (% of all cases)	Pruritus	57 (32.9)
	Pain	56 (32.4)
	Burning	7 (4.0)
	Coldness	1 (0.6)
	No	78 (45.1)
Nasopharyngeal swab RT-PCR test result (*n* = 49), *n* (%)	Positive	10 (20.4)
	Negative	39 (79.6)
Systemic symptoms of COVID-19 – *n* (% of all cases)	Cough	17 (9.8)
	Gastrointestinal symptoms	13 (7.5)
	Fever	11 (6.4)
	Rhinitis	7 (4.0)
	Dyspnoea	6 (3.5)
	Headache	3 (1.7)
	Fatigue	3 (1.5)
	Pharyngodynia	2 (1.2)
	Muscle pain	2 (1.2)
	No	129 (74.6)
Mean time from the onset of non-cutaneous COVID-19 symptoms to the onset of skin lesions (range) [days]		10.4 (-2–28)

Table 2. Cont.

Parameter		General data
Maculopapular rash (*n* = 16)		
Total number of cases		16
Mean age (range) [years]		7.22 (8 months – 17 years)
Sex	Male, *n* (%)	9 (56.3)
	Female, *n* (%)	7 (43.7)
Anatomical location of skin lesions – *n* (% of all cases)	Feet	16 (100)
	Hands	16 (100)
	Arms, forearms	14 (87.5)
	Thighs, shins	14 (87.5)
	Trunk	14 (87.5)
	Lips	8 (50)
	Oral cavity	8 (50)
	Face	6 (37.5)
	Conjunctiva	2 (12.5)
Mean duration of skin lesions (range) [days]		9.3 (2–25)
Symptoms associated with skin lesions – *n* (% of all cases)	Pruritus	2 (12.5)
	Burning	7 (4.0)
	No	14 (87.5)
Nasopharyngeal swab RT-PCR test result (*n* = 16) – *n* (%)	Positive	6 (37.5)
	Negative	10 (62.5)
Systemic symptoms of COVID-19 – *n* (% of all cases)	Fever	14 (87.5)
	Conjunctivitis	9 (56.3)
	Gastrointestinal symptoms	6 (37.5)
	Meningeal signs	4 (25)
	Fatigue	1 (6.3)
	No	2 (12.5)
Mean time from the onset of non-cutaneous COVID-19 symptoms to the onset of skin lesions (range) [days]		3.5 (-1–15)

Parameter		General data
Erythema multiforme-like lesions (*n* = 12)		
Total number of cases		12
Mean age (range) [years]		12.1 (6–17)
Sex	Male – *n* (% of all cases)	9 (75)
	Female – *n* (% of all cases)	3 (25)
Anatomical location of skin lesions – *n* (% of all cases)	Only feet	7 (58.3)
	Only hands	2 (16.7)
	Both feet and hands	3 (25)
	Face	2 (16.7)
	Lips	1 (8.3)
	Oral cavity	1 (8.3)
	Conjunctiva	1 (8.3)
Mean duration of skin lesions (range) [days]		16.7 (14–21)
Symptoms associated with skin lesions – *n* (% of all cases)	Pruritus	5 (41.7)
	Pain	2 (16.7)
	No	5 (41.7)
Nasopharyngeal swab RT-PCR test result (*n* = 8) – *n* (%)	Positive	2 (25)
	Negative	6 (75)
Systemic symptoms of COVID-19 – *n* (% of all cases)	Cough	1 (8.3)
	Gastrointestinal symptoms	2 (16.7)
	Fever	2 (16.7)
	Cough	1 (8.3)
	Rhinitis	1 (8.3)
	Headache	1 (8.3)
	No	7 (58.3)
Mean time from the onset of non-cutaneous COVID-19 symptoms to the onset of skin lesions [days]		21.0 (15–28)

most common symptoms were fever and gastrointestinal symptoms. RT-PCR tests from nasopharyngeal swabs were performed in majority of the patients from this group (*n* = 8), positive results for SARS-CoV-2 were found only in two children (Table 2).

Torrelo *et al.* and Andina *et al.* [19, 24] presented an interesting description of 4 children aged 11–17 years who had erythema multiforme-like lesions in addition to chilblain-like lesions on the feet (in 4 patients) and hands (in 2 patients). The subjects had never before experienced such symptoms, had not taken new medications, and had not received vaccinations during the previous 30 days, and did not have any symptoms of or exposure to herpes virus, Epstein-Barr virus, varicella, adenovirus, cytomegalovirus, or orf. RT-PCR testing for SARS-CoV-2 was positive in only 1 of the patients; another had contact with a family member with suspected infection; 3 had mild symptoms of COVID-19 a few days before the appearance of skin lesions. Histopathological examination performed in 2 patients did not show an erythema multiforme characteristic picture, but immunohistochemistry was positive for SARS-CoV/SARS-CoV-2 spike protein. Oral corticosteroids have been administered in 1 patient and topical corticosteroids were used in anoth-

er. Skin lesions disappeared without complications in all patients within one to 3 weeks [19, 24].

García-Gil *et al.* [25] in their publication presented a clinical case of a 12-year-old boy with erythema multiforme-like skin changes which presented as purple erythematous lesions and vesicular blisters.

Histopathological examination of skin lesions revealed partial epidermal necrosis and perivascular lymphoid infiltrate in superficial and deep dermis, microthrombi of the papillary dermis accompanied by extravasation of red blood cells, thickening of the vessel wall, and activation of the endothelium with nuclear enlargement. The authors of the publication emphasized the similarity of the histopathological image of erythema multiforme-like lesions (pauci-inflammatory thrombogenic vasculopathy) to vascular lesions occurring in adult patients with severe COVID-19. This suggests that SARS-CoV-2 may be an etiological factor in the development of acute vascular lesions in children despite often negative test results confirming the infection.

Maculopapular changes

The clinical picture of patients with maculopapular lesions was quite diverse. In the analysed articles, 16 cases of children with maculopapular exanthema (8.2%) were described. The average age of patients in the analysed articles was 7.22 years, the changes were more frequent in boys. In all described clinical cases, the changes concerned hands and feet. Moreover, in 14 patients a generalized rash on whole upper and lower extremities and trunk was found.

The average duration of the exanthema was 9.3 days. Only itching was described among the accompanying symptoms. The most frequently described general symptoms of COVID-19 were: fever, conjunctivitis and gastrointestinal symptoms. Extracutaneous symptoms in this group of patients appeared on average 3.5 days before the occurrence of maculopapular rash. RT-PCR tests of nasopharyngeal swabs were performed in all children in analysed clinical cases, most of the results were negative (Table 2).

Bursal Duramaz *et al.* [26] described two clinical cases of patients with confirmed SARS-CoV-2 infection who did not require systemic treatment. In an 8-month-old infant, an erythematous rash of the face and trunk resembling roseola was found. These skin changes and a fever appeared and subsided simultaneously. An 11-year-old girl presented with a pruritic, morbiliform rash on the face and back. The changes disappeared spontaneously after 5 days.

The course of COVID-19 among paediatric patients is often asymptomatic or has few symptoms [27, 28]; thus, systemic treatment is less frequently used compared to in the adult population.

However, Bursal Duramaz *et al.* [26] described a case report of a 17-year-old female patient experiencing a drug eruption on day 3 of hydroxychloroquine use. Erythematous and maculopapular changes occurred on the face and limbs with slight itching. Symptoms disappeared upon termination of hydroxychloroquine treatment.

Morey-Olivé *et al.* [29] described an interesting clinical case of a 6-year-old boy with cholestatic liver disease of unknown aetiology. Two weeks after a slight fever, elevated bilirubin and hepatic transaminases in blood, the patient had a positive result of RT-PCR smear test for the presence of SARS-CoV-2. After the next 48 h an itchy, non-smelling, generalised, dewy sediment appeared. Skin lesions persisted in the boy for a total of 5 days, were not accompanied by any symptoms associated with COVID-19 and upon their subsidence, liver parameters normalised. Interestingly, no SARS-CoV-2 was detected in the liver extract.

However, in 3 of the publications we analysed [30–32], the erythematous and papular lesions occurred in the form of a generalised rash with subsequent epidermal exfoliation with often accompanying erythema or firm induration of hands and feet, erythema of the lips or oral cavity, and cracking of the lips.

In addition, the patients were found to have additional symptoms characteristic of Kawasaki's disease, namely fever, coronary artery abnormalities, hypotension and/or elevated inflammatory markers.

Labé *et al.* [31] presented a clinical case of a 3-year-old patient hospitalized for 8 days of high fever, whose mother was diagnosed with SARS-COV-2 infection 3 weeks earlier. The patient was described as generalized exanthema with desquamation of the extremities, bilateral palmar oedema, glossitis, and cervical lymphadenopathy. Laboratory tests showed an increase in inflammation parameters.

Although the result of the RT-PCR swab test for SARS-CoV-2 was negative, the ground-glass opacities and consolidation in the right posterobasal area clearly supported the diagnosis of COVID-19. According to the authors, the clinical case presented in the publication suggests that SARS-CoV-2 infection may be the trigger for Kawasaki-like disease [31].

In April 2020, there were reports from Europe and North America about a severe form of Paediatric Inflammatory Multisystem Syndrome (PIMS) sharing common features with other paediatric inflammatory conditions including: Kawasaki disease (KD), staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndromes. A possible temporal association of PIMS with SARS-COV-2 infection has been proposed as some paediatric patients have tested positively for SARS-CoV-2 infection using either polymerase chain reaction (PCR) or serological testing [30–34].

The initial definition of the Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 infection [35, 36] based on a document published by the WHO on 15 May 2020 [37] covers children and

adolescents under 19 years of age with a fever lasting 3 days or more, presenting at least two of the following symptoms:
– rash or non-purulent, bilateral conjunctivitis or symptoms of mucocutaneous inflammation signs (oral, hands, or feet),
– hypotension or shock,
– features of myocardial dysfunction, pericarditis, valvular inflammation, or coronary artery abnormalities,
– coagulopathy,
– acute gastrointestinal symptoms.

Additionally, diagnosis requires elevated inflammatory markers, exclusion of other infectious causes of presented symptoms, and either confirmation of COVID-19 or probable contact with an infected individual [37].

PIMS-TS symptoms are similar to those of KD, including persistent fever and coronary artery damage; however, relatively older children are typically affected [38, 39].

Verdoni *et al.* pointed out a significant increase in the incidence of KD symptoms in the Italian Bergamo area since the beginning of the SARS-COV-2-related pandemic, particularly a 30-fold increase in the incidence of Kawasaki-like disease between 18.02.2020 and 20.04.2020. Compared to patients admitted before February 2020, only in the group of children hospitalized after the beginning of coronavirus epidemic, KD shock syndrome and features of macrophage activation syndrome were reported [30].

While the aetiology of KD is still not fully understood, available studies suggest that the disease may be due to abnormal regulation of the immune system in response to the infectious agent. This inappropriate immune response is most probably genetic as indicated by the limited number of cases of children with KD in the course of infectious diseases. A hypothesis to explain the aetiology of PIMS-TS has yet been put forward [40, 41].

Patients with PIMS-TS symptoms require immediate hospitalization. Treatment of this disease is similar to that of KD. First-line treatment is high-dose intravenous immunoglobulin (IVIG) (2g/kg) to reduce the risk of coronary artery damage. Additionally, acetylsalicylic acid, corticosteroids, and anti-TNF monoclonal antibodies may be used to reduce inflammation [42].

Other skin lesions

Among the analysed publications, single clinical cases of children with papulovesicular skin changes and urticaria were presented.

Varicella-like exanthema

Genovese *et al.* [43] presented a description of an 8-year-old girl, hospitalized due to varicella-like exanthema lasting for 3 days and a positive RT-PCR result from nasopharyngeal swabs for SARS-CoV-2 (in the patient and her closest family). In the history, the patient had smallpox a year earlier.

On admission, disseminated papular, papular-bladder lesions with a tendency to crack and scab formation in the area of the torso skin were found. The skin lesions were accompanied by only a slight cough, which occurred 3 days before the onset of the skin lesions, and a fever, which occurred on the 2nd day of dermatosis. Laboratory tests were all within normal range except for slight thrombocytopenia. Skin lesions and general ailments disappeared without any treatment within 7 days.

Urticaria

Urticaria is a rare disease in childhood (3.4% UK, 4.4% Germany, 5.4% Denmark) and the risk of transformation into a chronic form is negligible (0.1–0.3%) [44–46]. Scientific studies show that viral infections can also be an etiological factor in urticaria [47, 48].

Morey-Olivé *et al.* [29] described a clinical case of a 2-month-old girl with itchy acute urticaria skin lesions lasting 4 days and accompanied by a slight fever. The girl had contact with two people with confirmed SARS-CoV-2 infection. The urticaria initially occurred on the face and upper limbs and subsequently spread to the trunk and lower limbs. The palms and soles remained free of lesions and no angioedema was found. After oral symptomatic treatment, all symptoms disappeared within 5 days.

Conclusions

An increasing number of publications regarding skin lesions in the course of COVID-19 are describing skin lesions occurring in children. The preceding examples show that both the morphology and prevalence of particular dermatoses in the course of COVID-19 is different in children compared to these found in adults.

In many cases, skin lesions are the only visible manifestation of the disease in the paediatric population, and RT-PCR tests from nasopharyngeal swabs and serological tests confirming SARS-CoV-2 infection may be negative.

However, the histopathological picture of acute chilblain-like lesions and erythema multiforme-like lesions in children shows similarity to vascular lesions in adult patients with severe COVID-19.

While symptoms in the paediatric population are typically mild, there is an increasing number of reports of severe COVID-19 in the form of multi-systemic inflammatory disease resembling an incomplete picture of Kawasaki disease, most probably related to SARS-CoV-2 infection.

Case reports of clinical skin lesions in the course of COVID-19 in children indicates that there is a need for large, comprehensive studies confirming the characteristics and prevalence of dermatoses associated with SARS-CoV-2 infection. Precise and rapid diagnosis, includ-

ing skin lesions, may prove to be crucial for rapid medical intervention to prevent further spread of the disease, especially in the paediatric population, where skin lesions may be the only manifestation of COVID-19.

Conflict of interest

The authors declare no conflict of interest.

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