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REVIEW ARTICLE

DERMATOLOGIC THERAPY WILEY

Cutaneous and histopathological features of coronavirus disease 2019 in pediatrics: A review article

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Abstract

Prevalence of dermatological manifestations of coronavirus disease 2019 (COVID-19) is estimated between 0.25% and 3% in children and adolescents. In this review article, we decided to describe the cutaneous and histopathological manifestations of COVID-19 infection in pediatrics. We searched published articles in PubMed database for key words of "children" or "pediatric" and "cutaneous" or "dermatology" or "skin" and "COVID-19" or "SARS-CoV-2" or "Coronavirus disease 2019" in abstract or title from December of 2019 until September 2020. Finally, 38 articles were selected. The majority of patients were between 11 and 17 years old with predominantly male gender. Most of the patients were either asymptomatic or had a few general symptoms. The latency time from appearance of general symptoms to cutaneous ones was between 1 day and weeks. Skin lesions faded between 3 and 88 days without any sequelae, spontaneously or with either topical or systemic corticosteroids. Skin manifestations were chilblain-like (pseudochilblain), erythema multiforme-like, dactylitis, acral erythema, acute urticaria, livedo reticularis, mottling, acro-ischemia, generalized maculopapular lesions, eyelid dermatitis, miliaria-like, varicelliform lesions, and petechiae and/or purpura. Kawa-COVID-19 patients were presented more frequently with cardiogenic shock, neurological symptoms, lymphocytopenia, and thrombocytopenia as compared to classic Kawasaki's disease. Furthermore, more number of cases were resistant to the first-line treatments.

KEYWORDS

COVID-19, cutaneous, pathology, pediatric

1 | INTRODUCTION

Coronavirus disease 2019 or COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). At the beginning of the COVID-19 pandemic, dermatological manifestations were rarely reported. Since dermatologists participation in triage of the patients, wide spectrum of skin manifestations were reported including erythema multiforme (EM)-like, chilblain-like, pityriasis rosea-like, urticaria, varicelliform, mottling, livedo-like, symmetrical drug-related intertriginous and flexural exanthema, acro-ischemia, palmar erythema, perifollicular, maculopapular, and rash with petechiae and purpura.[1-4]

Children infected with the virus are usually asymptomatic or oligosymptomatic. Thus, many of the infected children are overlooked that leads to more spreading of the disease. Since the COVID-19 pandemic, there are several case reports and case series characterizing skin manifestations in children with mild respiratory and gastrointestinal (GI) symptoms or in asymptomatic ones who had household contact with COVID-19.[5] In one systematic review by Hoang et al, the prevalence of dermatological manifestations of COVID-19 was

TABLE 1 Cutaneous features of COVID-19 in pediatrics

First author name	Age	Sex (M/F)	Clinical feature	Cutaneous symptom	Site	Mean duration until visit	Time from general symptoms	General sign and symptom
Rosés-Gibert[8]	3–13 (11.1) y	M = 23, F = 13	CLL: erythematous papules (66.67%), purpuric macules (44.44%), both (11.11%), erosion (13.8%), swelling (16.67%)	Pruritus (38.89%), pain (22.22%), asymptomatic (50%)	Hand (5.55%), feet (97.22%), both (2.78%)	NS	After (12.62 d), coincided (27.27%)	Respiratory (7), nonrespiratory (4)
Mohan[9]	10 y	M	CLL: erythema, swelling	Burning, itching	Toes	NS	2 wk	Fever, fatigue, myalgia, dry cough
Maniaci[10]	15 y	M	Erythematous skin lesion	NS	Lower limb	NS	2 d	Asthenia, loss of appetite, mild fever, flu-like symptom, metallic taste
García-Gil[11]	12 y	M	EM-like, hemorrhagic purpuric eruption and vesicular blister	Itching	Heel	NS	—	—
Papa[12]	11 y	F	Ischemic hemorrhagic vasculitis, nonblanching erythematous CLL, ulceration	Pain, itching	Feet, nail	NS	NA	—
Olisova[13]	12 y	F	Purpuric eruption, erythematous macules, slightly swollen tongue with pronounced lingual papilla	—	Upper eyelid, upper eyebrow, temporal region, tongue	3 d	3 d	Fever, fatigue, headache
Chen[14]	2 d	M	Small miliary-like red papules	—	Forehead	At 2 d after birth	1 d	Dyspnea, edema,
Chen[14]	3 d	M	Maculopapular, ulceration	—	Diffuse, forehead	At birth	Before (3 d)	Edema in lateral thigh
Romani[15]	17 y	F	Purpuric papules, vesicles	NS	Fingers	3 wk	NA	—
Romani[15]	11 y	F	CLL	NS	Hand, feet	2 wk	NA	—
Romani[15]	17 y	M	CLL, blister	NS	Hand, feet	NS	NA	—
Romani[15]	14 y	F	CCL, erythromelalgia, edema, blistering	NS	Feet	NS	NA	—
Romani[15]	14 y	F	CLL	Itching, burning	Feet	3 wk	NA	—
Romani[15]	12 y	M	CLL	Itching	NS	NS	NA	—

TABLE 1 (Continued)

First author name	Age	Sex (M/F)	Clinical feature	Cutaneous symptom	Site	Mean duration until visit	Time from general symptoms	General sign and symptom
Romani[15]	15 y	F	CLL	Itching	Feet	3 wk	NA	—
Romani[15]	7 y	F	CLL	NS	Hand, feet, palmar	1 wk	NA	—
Romani[15]	14 y	M	Purpuric papules	NS	Heel	2 wk	NA	—
Romani[15]	12 y	M	CLL, purpuric papules	NS	Feet, heel	3 wk	NA	—
Licciardi[16]	7 y	M	Kawasaki-like: erythema, petechiae, deepithelialized tongue		Eyelid, scrotum, palm, sole, limb, back, lip, tongue	Same day	5 d	Fever, nausea, vomiting, diarrhea, abdominal pain, tachypnea, tachycardia
Licciardi[16]	12 y	M	Kawasaki-like, skin rash, erythema and edema, fissured lips, petechiae	—	Generalized, hand and feet, lip	—	3 d	Fever, abdominal pain, conjunctivitis, diarrhea, vomiting
Cordoro[17]	12-17 y	M = 5, F = 1	Red violaceous macules, edematous dusky purpuric plaques, superficial bullae, focal hemorrhagic crust, periungual erythema, livedo reticularis	Pruritus, tenderness	Toe, heel, sole, distal and lateral surfaces of feet, flexure of forearm, dorsal hand and feet	NS	1-2 wk	Rhinorrhea, congestion, sore throat, fever (in two siblings)
Genovese[18]	8 y	F	Papulovesicular, crust	—	Trunk	3 d	6 d	Fever, cough
Kamali Aghdam[19]	15 d	M	Mottling	—	NS	1 d	Same day	Fever, lethargy, respiratory distress, tachycardia, tachypnea
Verdoni[20]	2.9-16 (7.5) y	M = 7, F = 3	Classic Kawasaki-like (50%), incomplete Kawasaki-like (50%), polymorph rash , hand and feet erythema and firm induration	NS	NS	NS	NS	Fever, LAP, diarrhea, meningeal signs, nonexudative conjunctivitis
Wu[21]	34 mo	M	Eye lid dermatitis	—	Eye lid	Same day	7 d after positive test	Conjunctivitis

(Continues)

TABLE 1 (Continued)

First author name	Age	Sex (M/F)	Clinical feature	Cutaneous symptom	Site	Mean duration until visit	Time from general symptoms	General sign and symptom
Schnapp[22]	16 y	M	Kawasaki: migratory mild erythematous edematous plaques, dusky erythematous plaque	Truck, extremities, posterior scalp	Pain	Same day	3 d	Abdominal pain, fever
Magro[23]	16 y	M	CLL, bilateral purpuric-like plaques	Pain	Toe	NS	NA	—
Riphagen[24]	4-14 y	M = 5, F = 3	Kawasaki-like maculopapular rush (50%)	NS	NS	NS	NS	Fever, diarrhea, abdominal pain, head each, conjunctivitis, vomiting, myalgia, odynophagia
Andina[25]	6-17 (12) y	M = 13, F = 9	CLL: erythematous-purpuric dusky, violaceous lesions, dark ischemic areas with superficial blister	Pruritus (9), pain and tenderness (7)	Toe, lateral feet, heel	1-28 (7) d	1-28 (14) d	Respiratory (cough, rhinorrhea): 9, GI (diarrhea, abdominal pain): 2
Colonna[26]	11 y	F	CLL: dusky erythematous cyanotic macules with blurred edges, slightly atrophic	Mild pain and coldness	Lat. foot, dorsal toe, plantar surface	2 wk	Weeks	Mild flu-like, headache, rhinitis
Colonna[26]	6 y	F	CLL: erythematous, edematous rounded macules, blurred edge, central erythematous-cyanotic area	Itchy, moderately painful	Plantar	2 d	10 d	Mild intermittent fever
Colonna[26]	5 y	M	CLL: edema, chilblain-like (round macules with blurred edge)	Pain	Feet and hand	NS	2 mo, 1 mo, few days	Pneumonia, cough, fever
Colonna[26]	11 y	F	CLL: swelling, asymmetric erythematous dusky macules	Pain	Margin foot and dorsal toe	20 d	10 d	Intermittent fever
El Hachem[27]	11-17 (14) y	F = 5, M = 14	CLL: erythema, swelling, purpuric macules, crust, violaceous macules, pustule, erosion	Pain (5), itching (7), burning (2), asymptomatic (8)	Toe, heel, lateral margin sole	12-40 (22.2) d	1-2 mo Before (1 wk)	Fever, headache, sore throat, cough, diarrhea

TABLE 1 (Continued)

First author name	Age	Sex (M/F)	Clinical feature	Cutaneous symptom	Site	Mean duration until visit	Time from general symptoms	General sign and symptom
Roca-Ginés[28]	12.3 ± 4.3 y	M = 13, F = 7	Acral erythema, dactylitis, purpuric maculopapular, mixed pattern	NS	Feet, hand	7-30 d	NA	—
Raut[29]	5 mo	M	Incomplete Kawasaki: nonpruritic maculopapular rush	—	Upper limb, trunk	2 d	5 d	Bilateral conjunctivitis, irritability, fever
Mastrolonardo[30]	10.6 y	M = 25, F = 13	CLL: asymmetrical, purpuric-ecchymotic, pernio-like, red-bluish erythematous patch, superficial vesiculo-bullous swelling and erosion	Feet, occasionally (hand, sole, heel, plantar surface of toe)	Asymptomatic	NS	NA	—
Caselli[31]	7-18 (13.5) y	M = 22, F = 16	CLL: pseudo-chilblain, asymmetric purpuric-ecchymotic patch occasionally: superficial vesicle and bulla, erosion, swelling	—	Sole, heel, plan tar Few: hand	3-88 (25) d	1 mo	Fever, diarrhea (2.1%)
Colmenero[32]	11-17 y	F = 3, M = 4	CLL, EM	Pain, pruritus	Feet, hand, heel, toe-knee, elbow	4-30 d	NS	Respiratory (5), GI (1)
Klimach[33]	13 y	M	Erythematous papular eruption, tender, erythematous papules, erythematous macules and scattered petechiae	Pain	Axilla, plantar, distal L/Ex	10-14 d	1 d	Fever, myalgia, headache, axillary and cervical LAP
Torrelo[34]	11-17 y	M = 3, F = 1	CLL + EM, classic target, atypical target, confluent macules and papules, plaques, hemorrhage, crust in center	Pain, pruritus	Arm, thighs, ears, hand, feet, ankle, forearm, knee, elbow	1-3 wk	Few days	Mild respiratory (2), mild GI (1)
Neri[35]	11-15 y	3 = M, 5 = F	CLL: symmetrical red-purple macules and patches, nodules, bullae	Pain, itching, tingling	Toe, sole, heel, finger	9-30 (19.6) d	NA	—
Pouletty[36]	4-12.5 (10) y	M = 8, F = 8	Kawasaki's disease, skin rush (81%), erythema and edema in hand and feet (68%), conjunctivitis (94%), dry cracked lip (87%)	NS	NS	NS	NS	Fever (100%), respiratory (12%), GI (81%)

(Continues)

TABLE 1 (Continued)

First author name	Age	Sex (M/F)	Clinical feature	Cutaneous symptom	Site	Mean duration until visit	Time from general symptoms	General sign and symptom
Mazzotta[37]	13 y	M	Erythematous-violet lesions with blurred borders, purpura, tense blister, blackish crust	Itching and burning	Foot, dorsal toe	NS	Before (2 d)	Fever, muscle pain, headache
Morey-Olivé[38]	6 y	M	Erythematous, confluent, maculopapular	Asymptomatic	U/E, L/E, trunk, neck, cheek, plantar	5 d	2 wk	Fever, impaired liver function test and coagulation test
Morey-Olivé[38]	2 mo	F	Acute urticaria	Pruritus	Face, U/E, trunk, L/E	4 d	NA	—
Garcia-Lara[39]	<16 (14.4) y	M = 18, F = 9	CLL (92.6%), EM-like (7.4%)	Pruritus (11%), mild pain (22%)	Hand (22%), feet (74%), both (14%)	14.6 d	Same day	Diarrhea (1)
Jones[40]	6 mo	F	Erythematous, blanching rush, polymorphous maculopapular, dry cracked lip, swelling hand and L/E	Asymptomatic	NS	Same day	2 d	Fever, fussiness, conjunctivitis, mild congestion, tachypnea
Landa[41]	15 y	M	CLL	Mild itchy	Toe, heel	NS	NA	—
Landa[41]	15 y	F	Reddish, palpable purpura	Mild pain	Finger, heel	NS	1 wk	Nasal congestion,, diarrhea
Recalcati[42]	13-18 (14.4) y	F = 8, M = 6	CLL: erythematous-violaceous papules and macules, bullous, digital swelling EM: erythematous papular targetoid	Mild itch	Feet, hand, elbow	NS	3 wk	Cough, fever
Piccolo[43]	12-16 (14) y	F = 36, M = 30	CLL: erythematous-edematous lesions (31), blister (23)	Pain: 27% Itch: 27% Pain + itch: 20.6%	Feet: 85.7% Feet/hand: 7% Hand: 6%	6-15 (10)	1-10 d	GI(11.1%), fever (4.8%), respiratory (7.9%)
Locatelli[44]	16 y	M	CLL: erythematous edematous eroded macules and plaques	—	Dorsal finger and toe	Several weeks	20 d	Dysgeusia, diarrhea
Grimaud[45]	2.9-15 (10) y	F = 10, M = 10	Cheilitis (25%), skin rash (50%)	NS	NS	1-10 (6)	NS	Fever (100%), abdominal pain (100%), hypotension (100%), conjunctivitis (30%)

First author name	History in other family members	RT-PCR (swab)	RT-PCR skin biopsy	Serology test	Laboratory and para clinic	Treatment	Out come
Rosés-Gibert[8]	Suspected or confirmed (33.33%)	— (7)	NP	— (1)	NS	Topical steroid, topical antibiotics (16.66%)	NS
Mohan[9]	—	—	NP	—	NP	Topical steroid	Improved after 2 mo
Maniaci[10]	+	+	NP	NP	Mild leukocytosis, lymphocytosis	Acetaminophen, azithromycin	Resolved after 16 d
García-Gil[11]	—	—	NP	Negative for SARS-CoV-2 and other virus and bacteria	NL	—	Improved
Papa[12]	NS	—	NP	IgG+, IgM+	NL	Paracetamol, mupirocin	Resolved after 15 d
Olisova[13]	Positive in mother	+	NP	NP	Increased levels of CRP, ESR	—	Resolved after 3 d
Chen[14]	Positive in mother	—	NP	NP	Leukocytosis	Oxygen therapy, nasal continuous positive airway pressure	Improvement after 10 d
Chen[14]	Positive in mother	NP	NP	NP	Hypoalbuminemia, lymphopenia	—	Improvement after 1 d
Romani[15]	NS	—	—	NS	NL	Topical steroid	Improvement within 3 wk
Romani[15]	NS	—	—	NS	NL	—	Improvement within 2 wk
Romani[15]	NS	—	—	NS	NS	NS	NS
Romani[15]	NS	—	—	NS	NL	ASA, gabapentin	NS
Romani[15]	NS	—	—	NS	NL	Topical steroid	Improvement within 3 wk
Romani[15]	NS	—	—	NS	NL	Topical	Improvement
Romani[15]	NS	—	—	NS	NS	—	Improvement within 3 wk
Romani[15]		—	NP	—	NL	Topical antibiotic	Improvement within 1 wk
Romani[15]	NS	—	NP	—	NL	Topical steroid	Improvement within 2 wk
Romani[15]	NS	—	NP	—	NL	Topical steroid, antibiotic	Improvement within 3 wk

(Continues)

TABLE 1 (Continued)

First author name	History in other family members	RT-PCR (swab)	RT-PCR skin biopsy	Serology test	Laboratory and para clinic	Treatment	Out come
Licciardi[16]	Suspected in mother (anosmia, taste dysfunction)	—	NP	Positive IgG	Lymphocytopenia, thrombocytopenia, complement consumption, hypoalbuminemia, hyperferritinemia, increased D-dimer, increased level of troponin,, pro-brain natriuretic peptide	IVIG, methylprednisolone, antibiotic therapy	Improvement
Licciardi[16]	NS	—	NP	Positive IgG	Lymphocytopenia, thrombocytopenia, complement consumption, hypoalbuminemia, proteinuria, hyperferritinemia, pleural effusion, increased level of troponin T, CK MB	Methylprednisolone	Improved within 2 wk
Cordoro[17]	Mild URI	—	NP	—	Subtle reduction in fibrinogen	NS	NS
Genovese[18]	RT-PCR: positive (father, mother, grandmother)	+	NP	NP	Thrombocytopenia	—	Subsided within 7 d
Kamali Aghdam[19]	Suspected (mother)	+	NP	NP	Laboratory: NL CXR: NL Echocardiography: PFO	Vancomycin, amikacin	Resolved after 2 d, discharged after 6 d
Verdoni[20]	+ (50%)	+ (20%)	NP	IgG+ (80%) IgM+ (30%) 20% (both negative)	Leukopenia, lymphopenia, thrombocytopenia, increased levels of CRP, ESR, ALT, TG, ferritin, abnormal echocardiography (60%)	IVIG, ASA corticosteroid (80%)	Complete remission (100%), KDSS (50%), MAS (50%)
Wu[21]	Positive RT-PCR (father and grandmother)	+	NP	IgG+ IgM−	Lymphocytosis, increased levels of myoglobin, CK MB, LDH	Chinese national protocol	Resolved after 5 d

TABLE 1 (Continued)

First author name	History in other family members	RT-PCR (swab)	RT-PCR skin biopsy	Serology test	Laboratory and para clinic	Treatment	Out come
Schnapp[22]	NS	—	—	IgG+	Significant lymphopenia, mild neutrophilia, increased levels of creatinine, CRP, D-dimer, hyperferritinemia, elevation in fibrinogen, TG, echocardiography: impaired LV function with dilatation	IV methylprednisolone	Complete improvement
Magro[23]	Fever, cough (brother): several weeks before	—	NP	NP	NP	—	Self-improvement
Riphagen[24]	Confirmed in four	2: positive	NP	NP	Increased levels of CRP, troponin, D-dimer, procalcitonin, hypoalbuminemia, thrombocytopenia, hyperferitenimea, positive PCR for adenovirus and retrovirus: 1	IVIG, systemic corticosteroid, clindamycin, ceftriaxone, dopamine, noradrenalin, milrinone	1: Death, discharged from PICU after 3-7 d
Andina[25]	Confirmed: 1, suspected: 12	Positive: 1	NP	NP	Increased D-dimer: 1	Topical steroid: 1, oral steroid: 1, oral analgesics, oral antihistamines	Complete improvement
Colonna[26]	Cough in both parents	—	NP	NP	NL	—	Subside within 5 d
Colonna[26]	Fever in mother, positive exposure in father	—	NP	NP	Increased D-dimer	—	Subsided within 3 d
Colonna[26]	Cough (grandfather and parents)	—	NP	NP	Mild thrombocytosis and monocytosis	—	Subsided in 3 d
Colonna[26]	—	—	NP	NP	NL	—	Self-limited

(Continues)

TABLE 1 (Continued)

First author name	History in other family members	RT-PCR (swab)	RT-PCR skin biopsy	Serology test	Laboratory and para clinic	Treatment	Out come
El Hachem[27]	Suspected (47%)	– (19)	– (3)	Ig G for nucleus capsid: negative IgG against S1 domain of spike protein (1), borderline (3), Ig A+ (6), borderline (3)	NL	—	Pain subsided within 7-10 d After 2 wk asymptomatic mild erythema, swelling, brown macules, crust
Roca-Ginés[28]	Similar symptoms in skin of other family members (6)	NP	NP	—	NL, serology for other virus: negative	—	NS
Raut[29]	+	+	NP	NP	Elevate ESR, CRP, hyperferritinemia, hypoalbuminemia, hypernatremia CXR: mild opacity in the right middle lung zone Echocardiography: dilated left main coronary artery and left descending artery	IVIG (2 g/kg) + ASA + azithromycin, cephalosporin, paracetamol	Improvement after 2 d
Mastrolonardo[30]	Similar skin lesions in sibling in two cases in 2-3 wk	—	NP	NP	NL	Topical steroid + antibiotic	Improvement in 2 wk with mild dyschromia
Caselli[31]	—	—	NP	-	NL, – (PCR for other virus), + (mycoplasma [1])	—	NS
Colmenero[32]	Suspected contact (4)	—	+ (100%)	NP	Minimally increasing in D-dimer: 1	—	Self-improvement in 8 wk
Klimach[33]	Cough, flu-like in mother	+	NP	NP	NL, – (PCR for other virus and mycoplasma)	—	Improvement in 10-14 d

TABLE 1 (Continued)

First author name	History in other family members	RT-PCR (swab)	RT-PCR skin biopsy	Serology test	Laboratory and para clinic	Treatment	Out come
Torrelo[34]	+ (1)	+ (1) – (3)	+	NP	NL	Top steroid (1), oral steroid (1)	Improvement: 1-3 wk
Neri[35]	—	—	– (1)	—	Slightly lymphocytosis (37.5%) – (other virus and mycoplasma)	Topical steroid	Improvement in 4-5 wk
Pouletty[36]	+ (75%)	+ (69%)	NP	+ (87%)	Abnormal echocardiography (69%), abnormal CXR (31%)	IVIG (93%), oral steroid (25%), anti-IL-1 (6%), IL-6 (6%), hydroxychloroquine: 6%	
Mazzotta[37]	Suspected (mother and sister)	NP	NP	NP	NP	Oral macrolide, topical therapy	Regress after few days
Morey-Olivé[38]	NS	+	NP	NP	Elevate liver enzymes, impaired coagulation tests	—	Improvement after 5 d
Morey-Olivé[38]	+ (2)	+	NP	NP	NP	Symptomatic oral treatment	Improvement after 5 d
Garcia-Lara[39]	—	—	NP	—	NP	—	Self-limited after 14.6 d
Jones[40]	URT in sibling: 3 wk before	+	NP	NP	Increased ESR, CRP, left-shifted leukocytosis, hypernatremia, hypoalbuminemia, CXR: opacity in the left mid lung zone, echocardiography: normal	Single dose IVIG + ASA	Complete remission
Landa[41]	NS	—	NP	NP	CXR: mild bilateral pneumonia	Heparin, azithromycin, hydroxychloroquine	
Landa[41]	+ (father)	NP	NP	NP	NP	—	Improved
Recalcati[42]	—	—	NP	– (for SARS-CoV-2 and other virus and bacteria)	NL	—	Resolve after 2–4 wk

(Continues)

TABLE 1 (Continued)

First author name	History in other family members	RT-PCR (swab)	RT-PCR skin biopsy	Serology test	Laboratory and para clinic	Treatment	Out come
Piccolo[43]	+ (2), suspected (8)	+ (3.2%)	NP	+ (3.2%), + for mycoplasma (1)	NP	—	Resolved (6.3%), relapsing course (14.3%), stable (79.4%)
Locatelli[44]	+	+	NP	NP	NL	—	Self-limited after several weeks
Grimaud[45]	NS	+ (10)	NP	+ (15)	Increased CRP, procalcitonin Typical CT with negative serology and PCR: 1	Epinephrine, milrinone, dobutamine, norepinephrine (19) Intubated (18) IVIG (19) Systemic steroid (2) Anti-IL-6 (1)	Discharged after 1-8 (4) d

Abbreviations: ALT, Alanine aminotransferase; ASA, acetylsalicylic acid; CK MB, Creatine kinase-MB; CLL, chilblain-like lesion; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography scan; CXR, chest X-ray; EM, erythema multiforme; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; Ig, immunoglobulin; IL, interleukin; IV, intravenous; IVIG, intravenous immunoglobulin; KDSS, Kawasaki's disease shock syndrome; L/E, Lower extremity; L/Ex, Lower extremity; LAP, lymphadenopathy; LDH, lactate dehydrogenase; LV, left ventricular; MAS, macrophage activation syndrome; NA, Not applicable; NL, normal; NP, not performed; NS, Not stated; PFO, patent foramen ovale; PICU, pediatric intensive care unit; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TG, Triglyceride; U/E, Upper extremity; URI, upper respiratory infection; URT, upper respiratory tract.

estimated as 0.25% in 2445 children with confirmed COVID-19 and the prevalence of skin manifestations was reported as 3% in 100 children in another study by Parri et al in Italy.[6,7] Review articles about cutaneous manifestation of COVID-19 mostly focused on adults and only a few pediatric cases have been discussed. There is only one systematic review by Shah et al evaluating cutaneous manifestations in 149 children, with acral lesions being the most common (43%), which reported systemic manifestations in 43.6% of cases. This study reported other cutaneous manifestations such as EM-like, varicella-like, Kawasaki-like, and nonacral erythematous maculopapular rash.[1-4] As COVID-19 infection in children and adults shows different clinical pictures, in this review article, we decided to reveal cutaneous and histopathological manifestations of COVID-19 infection in pediatrics.

2 | METHODS

We searched published articles in PubMed database for key words "children" or "pediatric" and "cutaneous" or "dermatology" or "skin" and "COVID-19" or "SARS-CoV-2" or "Coronavirus disease 2019" in abstract or title from December of 2019 until September 2020. Furthermore, articles' references were searched for related articles. Review articles and opinion articles were excluded.

3 | RESULTS

Finally 38 articles including 353 patients (58.35% boys and 41.64% girls) were selected, after omitting duplicate articles or literature in languages other than English. The results of literature are summarized in Table 1.

Skin manifestations included chilblain-like (pseudochilblain), EM-like, dactylitis, acral erythema, acute urticaria, livedo reticularis, mottling, acro-ischemia, generalized maculopapular lesions, eyelid dermatitis, miliaria-like, varicelliform lesions, and rash with petechiae and purpura. The majority of patients were between 11 and 17 years old with predominantly male gender. Preschool and school-aged children constituted less number of cases. Only three neonatal cases and three infantile cases were reported. In symptomatic cases, the latency time from appearance of general symptoms (respiratory or GI) to cutaneous ones was between 1 day and weeks. In three cases, general symptoms appeared after cutaneous manifestations and in two cases they appeared simultaneously.[2,8,14,27,39] Skin lesions improved between 3 and 88 days without any sequelae.

4 | DISCUSSION

Angiotensin-converting enzyme (ACE)-2 is known to be the receptor of glycoprotein spikes of SARS-CoV-2. In addition to epithelial cells of lung (pneumocytes type 2), other organs such as liver, GI, urinary system, conjunctiva and cornea, endothelial of blood vessels, epithelial cells of sweet glands, and keratinocytes of basal layer of skin have ACE-2 receptors for SARS-CoV-2. Therefore, in addition to respiratory and GI manifestations, dermatological manifestations, cutaneous vessel vasculitis, and conjunctivitis can be expected with this infection. Infected children are usually asymptomatic or have a few general symptoms that can be due to innate immune system with higher number of T, B and NK cells; lower number of ACE-2 receptor with less affinity to SARS-CoV-2; less pro-inflammatory cytokine response; and possible role of Bacillus Calmette–Guérin vaccination in protection against virus.[4-6]

4.1 | Chilblain-like (COVID toe)

The most common reported cutaneous manifestation in children was chilblain-like lesions. This usually presents as dusky round erythematous or violet macules with blurred borders, cyanotic or crusted centers, and atrophy in some areas. Sometimes, superficial vesiculobullous lesions, erosion, pustules, ecchymotic or purpuric areas with edema, and swelling of fingers and toes might be revealed. These lesions appeared most commonly in acral areas including dorsal and plantar surfaces of toes, feet, ankles, ears, distal of lower extremities, and periungual areas. The most common sites of involvement are feet and toes. Distribution of the lesions can be symmetric or asymmetric. Lesions were either asymptomatic or had pruritus, tenderness, pain during walking, burning sensation, tingling, or coldness. Most of the children were generally healthy or only had mild respiratory or GI symptoms. The latency period from appearance of general symptoms to cutaneous lesions was between 0 days and weeks.

Overall, sudden increase in incidence of chilblain-like lesions simultaneously with COVID-19 pandemic, onset of the lesions in warm and cool weather, positive history of contact with suspected or confirmed cases of COVID-19, mild respiratory or GI symptoms in children, similar skin lesions in siblings in some cases and occasionally detection of virus by reverse transcriptase polymerase chain reaction (RT-PCR), serological test or electron microscopy within endothelial cells of vessels in some cases increased the possible role of SARS-COV-2 as a culprit cause. One possible explanation for negative RT-PCR test in most of the cases can be due to appearance of chilblain lesions at the end of the course of the disease. Negative RT-PCR test in most of the cases might be due to rapid clearance of virus by innate immune system. Therefore, especially in children who are usually asymptomatic or oligosymptomatic and have low viral load, serological test combined with RT-PCR can be helpful in the detection of virus. In the reported cases, cutaneous lesions usually resolved without treatment after 7 to 10 days (between 5 days and 8 weeks) with no sequelae, except mild dyschromia in some cases. The most important differential diagnoses of chilblain-like lesions were perniosis, lupus chilblain, and blue toe syndrome secondary to drugs, especially those that are used in the treatment of "attention-deficit hyperactivity disorder", such as methylphenidate hydrochloride.[9,10,12,15,17,23,25,26,28,30-35,41-44]

4.2 | Kawasaki-like disease (Kawa-COVID-19)

Concurrent with the COVID-19 pandemic, a sudden increase (up to 30 times) in the prevalence of Kawasaki-like disease (Kawa-COVID-19), Kawasaki's disease shock syndrome, macrophage activation syndrome, and multisystem inflammatory syndrome in children, especially around adolescence were reported. The majority of cases were from Afro-Caribbean background and presented with GI symptoms (abdominal pain, diarrhea, and vomiting) and fever. Most of the cases were older than 5 years (older than classic cases of Kawasaki's disease). Diffuse asymptomatic maculopapular rash were observed in approximately 50% of pediatric and adolescent cases with Kawasaki-like disease. Myocarditis, pericarditis, cardiogenic shock, neurological symptoms, lymphocytopenia, and thrombocytopenia were observed more frequently in COVID-19 suspected cases than cases with classic Kawasaki's disease. More number of patients were resistant to single dose of IVIG and required additional doses of IVIG as compared with the classic form of the disease. High ferritin level (over 1400 mg/L) and older age (especially over 5 years old) were predictable risk factors for additional required treatment modalities such as systemic corticosteroids and biologics including anti-interleukin (IL)-6 monoclonal antibody (tocilizumab), anti-IL-1 antagonist (anakinra), or additional doses of IVIG. It is proposed that delayed activation of immune system (2-4 weeks after infection) with SARS-CoV-2 can lead to dramatic rise in the production of pro-inflammatory cytokines (IL-1, IL-6, and tumor necrosis factor-alpha), known as cytokine storm or burst, which may lead to multiorgan failure. It is recommended that every child and adolescent (0-19 years old) presenting with fever for more than 5 days with mucocutaneous lesions (generalized maculopapular rash, nonpurulent conjunctivitis, dry and chapped lip, and acral erythema and edema) be examined for other symptoms or sings of Kawasaki's disease in order to be diagnosed and treated early to decrease the adverse effects (coronary artery aneurysm and cardiac dysfunction). If there are two or three other clinical features of the disease, echocardiography and electrocardiography should be performed immediately. Furthermore, myocardial markers (troponin and N-terminal pro b-type natriuretic peptide), acute inflammatory reactants (CRP, ESR, procalcitonin, and ferritin), coagulative markers (prothrombin time, partial thromboplastin time, and D-dimer), renal function test (urea, creatinine, and proteinuria), and RT-PCR for SARS-CoV-2 from nasopharyngeal and stool and serology tests should be performed to assess the involvement of other organs and detection of the culprit cause.[16,20,22,24,29,36,40,45]

4.3 | EM-like lesions

EM-like lesions appear as erythematous macules, papules, and plaques with crusted center that consists of two (atypical types) or three (typical target) circles. Petechiae and purpura can be seen in proximity of the lesions. Lesions were most frequently observed in forearm, thigh, knee, elbow, arm, and dorsal surface of hands and feet. Patients had no history of vaccination, herpes simplex infection, or taking drugs since 1 month ago. Latency phase (since the appearance of general symptoms to cutaneous manifestations) lasted only a few days. Skin lesions were usually improved in 1 to 3 weeks without treatment, or with either topical or oral corticosteroids. EM-like lesions should be differentiated from EM secondary to other viral or bacterial infections.[11,32,34]

4.4 | Acute urticaria

A 2-month-old girl with a history of 4 days of acute urticaria involving face, trunk, and upper and lower extremities with sparing of mucosa, palm, and sole was referred to the emergency room. Lesions were pruritic and with no history of angioedema. The patient had no other symptoms, but because of positive confirmed infection with COVID-19 in two other family members, RT-PCR from nasopharyngeal swab was performed, with a positive result. Oral symptomatic therapy led to improvement of the lesions after 5 days. Other types of urticaria including idiopathic/secondary to other infections or drug reactions should be considered in the differential diagnosis.[38]

4.5 | Acro-ischemic lesions

Acro-ischemic lesions are most frequently seen in adults with severe infection and hypercoagulable states. Development of these lesions in children is rare. There is only one report in a 13-year-old boy who complained of pruritus and burning pain with erythematous-violet round macules and plaques and tense blisters in feet and dorsal surface of toes evolving to purpuric lesions and blackish scar after 7 days, and responded to oral erythromycin and topical therapy. Fever, myalgia, and headache developed 2 days after the appearance of skin lesions in the patient. Two other family members had suspected signs of fever, cough, and dyspnea few days ago. RT-PCR test was not performed in the patient, but suspected contact and respiratory symptoms support the possible role of SARS-CoV-2. Microthrombosis, endothelial cell damage, and apoptosis have essential role in the pathogenesis of acro-ischemic skin lesions. Severe cases in adults can lead to gangrene and massive necrosis but this is usually not an issue in children. Differential diagnoses include other causes of acral ischemia including cryoglobulinemia and vascular and drug-induced coagulopathies.[37]

4.6 | Chickenpox-like or varicelliform lesions

There is only one report in an 8-year-old girl with a history of mild cough since 6 days ago and development of asymptomatic papulovesicular lesions in trunk with sparing of face, limbs, and mucosal surfaces. After 2 days, fever developed and RT-PCR test demonstrated positive result for COVID-19. Patient had a history of varicella 1 year ago. Skin lesions improved without treatment after 7 days.

Differential diagnoses of varicelliform lesion related to SARS-CoV-2 are bite reaction and viral exanthema, especially chickenpox. Lack of pruritus and positive RT-PCR test for SARS-CoV-2 ruled out bite reaction. Previous history of varicella and absence of enanthem ruled out chickenpox or other viral exanthema.[18]

4.7 | Mottling

A 15-day-old neonate presented with fever and mottling of the skin and referred to the emergency room with lethargy, respiratory distress, tachycardia, and tachypnea. RT-PCR was performed for SARS-CoV-2, with a positive result. The neonate was treated with vancomycin and amykacin and discharged with good general health after 6 days. Mottling and respiratory symptoms improved after 2 days of admission.[19]

4.8 | Eyelid dermatitis

A 2-year and 10-month-old boy presented with asymptomatic conjunctivitis and eyelid dermatitis 1 week after positive COVID-19 test. Laboratory tests revealed lymphocytosis and elevated myocardial enzymes without any other systemic symptoms. Serological tests demonstrated negative immunoglobulin (Ig) M and positive IgG for SARS-CoV-2. The patient was treated according to Chinese national protocol, and skin lesions and conjunctivitis improved after 5 days.[21]

4.9 | Livedo-like lesions

Cordoro et al reported livedo-like lesions that presented with pruritic-tender, net-like reticulated erythema at dorsal surface of hands and feet and flexor of the forearm in three adolescents. Patients had mild respiratory symptoms (fever, sore throat, congestion, and rhinorrhea) 1 week before the appearance of skin lesions and positive history of upper respiratory infection in other family members. RT-PCR and serological tests for COVID-19 were negative and laboratory tests were normal, except for mild decrease in fibrinogen level. Livedo reticularis secondary to vasospasm, vasculitis, and coagulopathies should be considered in the differential diagnosis of livedo-like lesions due to COVID-19.[17]

4.10 | Acral erythema and dactylitis

In one study, 20% of cases had dactylitis presenting as erythematous inflamed digits. Both fingers and toes were involved with females being slightly more affected (female to male ratio of 3:2).[28]

Acral erythema was detected in 30% of cases in one study with female to male ratio of 4:2. Lesions presented with erythematous digit without any inflammation or purpura or other skin lesions.[28]

4.11 | Generalized maculopapular rash

A 6-year-old boy admitted with fever, elevated liver enzyme tests, and impaired coagulation tests since 2 weeks ago. He developed asymptomatic generalized erythematous maculopapular rash involving cheeks, neck, trunk, plantar surface, and upper and lower extremities with sparing of mucosal surface. RT-PCR for COVID-19 was positive and skin lesions improved without treatment after 5 days.[38]

A male neonate whose mother had a positive history of COVID-19 during pregnancy developed generalized maculopapular rash on all body surfaces along with an ulcerated lesion on forehead at birth. Localized edema in the lateral surface of thighs developed after 3 days and laboratory test revealed hypoalbuminemia. No other general symptoms or signs developed. Swab from nasopharyngeal showed negative result for SARS-CoV-2. Skin lesions disappeared after 1 day without any treatment.[14]

4.12 | Rash with petechiae and purpura

A 12-year-old female whose mother had a history of positive SARS-CoV-2 PCR test presented with fever, fatigue, and headache. After 3 days, erythematous macules with purpuric eruption developed on upper eyelid, upper eyebrow, and temporal regions. Oral examination showed swollen tongue with prominent red papillae and hairy tongue. RT-PCR test for COVID-19 was positive. Lesions were resolved after 3 days without any treatment.[13]

Another case was a 13-year-old boy complaining of fever, myalgia, headache, and axillary and cervical lymphadenopathy that developed into annular erythematous macule and scattered petechiae in the lower extremities after 1 day. In addition, axillary erythematous papular eruption and plantar tender erythematous papules were observed. PCR test for SARS-CoV-2 was positive. Lesions resolved without treatment after 10 to 14 days.[33]

4.13 | Miliaria-like lesion

One male neonate whose mother had a positive history of COVID-19 during the third trimester of pregnancy developed dyspnea at birth. The neonate developed miliaria-like red papules on the forehead on the second day after birth that resolved without treatment after 10 days. RT-PCR for COVID-19 was negative.[14]

4.14 | Histopathology and dermoscopic features

Skin biopsy from the chilblain-like lesions demonstrated spongiosis; exocytosis; necrotic keratinocytes; vacuolar degeneration of basal layer; papillary dermal edema; perivascular, perieccrine, and periadnexal lymphocytic infiltration; mucin deposition; and lymphocytic vasculitis with focal fibrin thrombi. Immunohistochemical (IHC) evaluation demonstrated increased number of $CD3^+$ T lymphocytes

with increased ratio of $CD4^+/CD8^+$ T cells, scattered numbers of B cell lymphocytes, and a few number of $CD30^+$ T cells. In one study, SARS-CoV-2 was detected by electron microscopy of the skin biopsy.[23,26,27]

Dermoscopy of the lesions demonstrated decreased density in dermal capillary, pericapillary edema, dilated capillaries with abnormal morphology, microhemorrhage, ischemic areas, violaceous erythema, and pigmented dots. Dermoscopic manifestations of COVID-19 were more prominent than idiopathic form of chilblain lesions. Furthermore, microhemorrhage is only seen in COVID-19-related chilblain lesions.[25,27]

Skin biopsy from EM-like lesions demonstrated mild exocytosis; spongiosis; hydropic degeneration of basal layer without necrotic keratinocytes; superficial, deep, and subcutaneous lymphocytic infiltration; endothelial cell swelling; and intramural and perivascular lymphocytic infiltration with vascular dilation without fibrinoid necrosis in one study, and with microthrombosis in papillary dermis vessels in another study. IHC demonstrated spike protein of SARS-CoV-2 in endothelial cell of vessels and epithelial cells of eccrine glands. Lack of necrotic keratinocytes, deep inflammation of lymphocytes, and vascular involvement are differentiating features of EM-like lesions related to COVID-19 than classic EM lesions.[34]

Skin biopsy from skin lesions of patients with Kawasaki-like disease demonstrated necrosis of epidermis and dermis, leukocytoclastic vasculitis, infiltration of neutrophils, and nuclear dust within vessels wall and extravasation of red blood cells. Direct immunofluorescence from skin showed deposition of complement (C3) and IgA within vessels' wall.[22]

5 | CONCLUSION

Skin manifestations of COVID-19 were chilblain-like, EM-like, dactylitis, acral erythema, acute urticaria, livedo reticularis, mottling, acro-ischemia, generalized maculopapular lesions, eyelid dermatitis, miliaria-like, varicelliform lesions, and rash with petechiae and purpura. Most of the dermatological manifestations of COVID-19 present in healthy children without general symptoms or with mild respiratory or GI symptoms. In most of the cases, RT-PCR or serological tests were negative.

Kawa-COVID-19 patients presented more frequently with fever, GI symptoms, cardiogenic shock, neurological symptoms, lymphocytopenia, and thrombocytopenia compared with classic Kawasaki's disease. Generalized maculopapular rashes were observed in approximately half of the cases. Furthermore, more number of cases were resistant to single dose of IVIG treatment and required additional treatments including systemic corticosteroids, biologic therapy, or additional doses of IVIG.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Behzad Iranmanesh, Maryam Khalili, and Mahin Aflatoonian contributed to the study conception and design. Material preparation and data collection were performed by Behzad Iranmanesh, Maryam Khalili, Mahin Aflatoonian, and Saman Mohammadi. The first draft of the manuscript was written by Maryam Khalili and Mahin Aflatoonian, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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