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Chilblains-like lesions in children following suspected Covid-19 infection

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ABSTRACT

During the COVID-19 pandemic, chilblains-like lesions have been reported in mildly symptomatic children and adolescents. We present four children investigated for suspected COVID-19 infection with who presented with acral skin findings and mild systemic symptoms. Histology from one case showed signs of vasculitis with evident fibrin thrombus.

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Introduction

Novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19).

Since the first reports of cases from Wuhan (Hubei Province, China) at the end of 2019, a pandemic of COVID-19 cases has spread worldwide. The clinical spectrum of infection ranges from mild to critical but many cases are asymptomatic or minimally symptomatic, the so-called “invisible” patient (1). Joob et al. (2) and Recalcati (3) have reported several non-specific cutaneous manifestations, from maculopapular rash to urticaria, in adults affected by COVID-19 with no recent history of drug intake, excluding possible drug reaction phenomena. Acro- ischemic lesions have been reported in adult COVID-19 patients hospitalized in emergency units (4).

Mazzotta et al. (5) reported a pediatric patient with similar findings and summarized that, the lesions often occur in asymptomatic or mildly symptomatic children and adolescents and mainly affect the feet (more) and hands (less), especially toes and fingers and also the plantar region and the heel. Cases are reported mainly by family pediatricians. First brought to our attention by professor of dermatology Ernesto Bonifazi, in a European pediatric dermatology blog . The number of reports is increasing continuously in Italy and in many European countries and seems to overlap the COVID-19 pandemic spread.

CASE 1

On April 10, 2020, an 11-year-old girl from Milan (Lombardy region, Italy) was referred to Pediatric Dermatology Department by her pediatrician for a 14-day history of lesions on the feet. Skin examination demonstrated several macules, 5-10 mm in diameter, dusky erythematous, with blurred edges located on the lateral margin of the feet and the dorsal surface of the right first, second and third toes. On the plantar surface of the left first and fourth toes, the lesions appeared erythematous-cyanotic and slightly atrophic. Dorsal surface the third and fourth toes are affected with erythematous plaque (**Figure 1**). Upper limbs, face, trunk, genitals and mucous membranes were spared. The lesions, initially faint, had become marked in a few days preceded by edema. They were associated with a feeling of coldness and mild pain. Medical history revealed that the patient was in good health except for mild flu-like symptoms with headache and rhinitis in the previous weeks that did not require any treatment. During the same time, both parents had a cough. Based on the clinical findings and literature reports, an acro-ischemia due to COVID-19 infection was suspected. The girl and her father were tested for COVID-19 with nasopharyngeal swab and aspirate. Both were negative. Antibody tests against COVID-19 were not available. No biopsy was performed. Laboratory testing, including blood count, liver and kidney function tests and C-reactive protein, coagulation profile, ferritin and fibrinogen, showed no abnormalities (D-dimer test was not available because of in vitro hemolysis). Antiphospholipid antibodies (anti-cardiolipin IgG and IgM), interleukin 6 (IL-6) and anti-nuclear antibody (ANA) were in the normal range. Cytomegalovirus (CMV), Epstein-Barr virus (EBV), parvovirus B19 and serology for *Mycoplasma pneumoniae* did not show recent infection. The skin lesions subsided without any therapy within 5 days, leaving no sequelae. The child remains under home isolation with no systemic or skin manifestations.

CASE 2

On the same day as case 1, a 6-year-old girl from Monza (Lombardy region, Italy) was admitted to our Pediatric Emergency Department with a 2-day history of vascular lesions on the feet.

Erythematous, edematous 8-10 mm rounded macular lesions with blurred edges and a central erythematous-cyanotic area were located on the bilateral plantar surfaces only (**Figure 2**). The lesions were itchy and moderately painful. Systemic symptoms had begun 10 days prior and included mild intermittent fever and localized pain on soles. Her mother also reported fever during the previous month; her father had worked closely with a positive COVID-19 individual but had remained asymptomatic. Both the girl and her mother were negative for COVID-19 by nasopharyngeal swab and aspirate. Blood tests (blood count, C-reactive protein, coagulation panel, fibrinogen, ferritin, IL-6, lupus anticoagulant, antinuclear antibody, and viral titers for CMV, EBV and parvovirus B19 showed no abnormalities except for an elevated D-dimer at 723 µg/L (<500 µg/L normal range). Due to the isolation restrictions, no biopsy was performed. Symptoms subsided without any therapy within 3 days, leaving no sequelae. The child remains under home isolation with her family.

CASE 3

Four days later, on April 14, 2020, a 5-year-old boy from Milan (Lombardy region, Italy) was examined for similar vascular lesions on the feet and right hand, preceded by edema. On February 10, 2020, the child experienced fever and cough with radiographic evidence of pneumonia and was treated with systemic antibiotics. Five days later, the boy's grandfather developed the same symptoms. No hospitalizations were required, nor were they tested for COVID-19. On March 20, 2020, the boy developed fever and, in a few days, edema and localized pain of the right hand and feet were evident, leading to difficulty walking. Four days later chilblain-like lesions appeared. On

examination, there were several rounded macules with blurred edges, 5-20 mm in diameter, on the plantar surface of both feet, as well as the right hand (**Figure 3**). The child's parents also reported having had coughs for the last 20 days. The boy and his mother were tested for COVID-19 with nasopharyngeal swab and aspirate and the results were negative. Blood tests showed no abnormalities except for mild thrombocytosis and monocytosis. No treatments or biopsy were performed and within 3 days the lesions subsided leaving no sequelae.

CASE 4

On April 18, 2020, an 11-year-old girl from Milan (Lombardy region, Italy) was referred to our department by her pediatrician for a 20-day history of foot lesions, swelling and difficulty walking. Skin examination demonstrated erythematous and dusky 5-15 mm plaques on the lateral margin of the left foot and the dorsal surface of the left second, third and fifth toes (**Figure 4**). The patient also reported intermittent fever and localized pain during the previous ten days. The girl and her mother (present at the visit) were tested for COVID-19 with nasopharyngeal swab and aspirate and the results were negative. Blood tests showed no abnormalities. A skin biopsy was performed. Histology revealed 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 vessels (**Figure 5**). No treatments were necessary and the lesions are still present to date.

DISCUSSION

Herein we describe the chilblain-like lesions and to further explore their correlations with COVID-19. In our patients, the cutaneous manifestation appeared several days after systemic symptoms and all tests for COVID-19 were negative at the first clinical evaluation. However, the accuracy and predictive values of COVID-19 testing have not been systematically evaluated. Serologic tests might be able to clarify a previous COVID-19 infection linked to the cutaneous manifestations but reliable test were not available at the time these cases were evaluated (6). Vasculitis-like manifestations have been reported in association with viral infections or use of drug; as seen in Parvovirus B19 atypical acrosyndrome (7) with an eruption that differs from the classic "gloves and socks syndrome" because of the presence of plantar painful erythrocyanosis. However, infection with several typical viruses was ruled out in these cases. As reported by Zhang et al. (4), COVID-19 could be responsible for coagulation disorders, increasing the D-dimer and fibrinogen degradation products and leading to acro-ischemia with finger and toe cyanosis. The finding of an elevated D-dimer in one of our patients, along with the clinical features suggestive of a vaso-occlusive phenomenon, supports consideration of laboratory evaluation for coagulation defects in asymptomatic or mildly symptomatic children with acro-vasculitis-like findings. Up to now, thrombosis have been described mainly in the lung and kidney in small autopsy series (8, 9,10). The finding of acro-ischemia appears to be a not unusual manifestation (4), however very little has been published describing the histological aspect of this skin finding (11). It is known that chilblains-like lesions could be seen in other circumstances (e.g. infectious diseases, interferon disorders) but the nature of the phenomenon among COVID19 infection is still under evaluation. Some autaptic findings showed IL6 is significantly elevated and associated with adverse clinical outcomes, suggesting a sure relation between inflammation and severity and a predictable relation between autoimmune reaction and intensity.

Given the fact that the sensitivity and specificity of both nasopharyngeal swabs and antibody tests for COVID-19 (when available) are not 100% reliable, the question of the origin of these strange chilblain-like lesions is still elusive (12). Until our observation can be further validated by larger studies, clinicians should be alert to the presentation of chilblains-like findings in paucisymptomatic pediatric patients as a possible sign of Covid-19 infection.

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FIGURE LEGENDS

Figure 1. Case 1, chilblains-like lesions on the toes in an 11-year-old girl.

Figure 2. Case 2, moderately painful chilblains-like lesions localized on plantar surface of the first metatarsus in a 6-year-old girl.

Figure 3. Case 3, diffuse chilblain-like lesions on plantar surface of the left foot in a 5-year-old boy.

Figure 4. Case 4, chilblain-like lesion on lateral surface of the left foot in an 11-year-old girl.

Figure 5. Case 4, Punch biopsy from the lateral surface of the left foot of Case 4. Dense lymphocytic perivascular and periadnexal infiltrates extending to the subcutis. Inset: higher magnification of a small thrombus in a capillary vessel in the upper part of the dermis (arrow).









