

## CUTANEOUS MANIFESTATIONS AMONG COVID-19 AFFECTED HEALTHCARE WORKERS

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### ABSTRACT

**Introduction:** Cutaneous manifestations have been associated with the COVID-19 infection with two different patterns: inflammatory/exanthematous eruptions and vasculopathic/vasculitic patterns.

**Materials and method:** We considered 126 healthcare workers who tested positive for Sars-CoV2 in the period between March 2020 and January 2021. Those subjects were asked to fulfill a telephonic questionnaire regarding the presence and characteristics of skin symptoms that happened during the period of positivity.

**Conclusion:** The present article aims to demonstrate a causal connection between the appearance of cutaneous and vasculitic manifestations and the positivity of the nasopharynx swab and the title of the antibodies generated after the infection.

**Keywords:** COVID19, cutaneous manifestations, vasculitis, serological test.

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### Introduction

COVID-19 infection has been associated with a large spectrum of clinical manifestations, including variable and heterogeneous skin symptoms that can appear before, during, and after the disease<sup>(1)</sup>. A Chinese study of 1099 patients with SARS-Cov-2 infection found 2 patients showing a skin rash<sup>(2)</sup>, but other groups have described skin manifestations in a substantial rate of COVID patients<sup>(3)</sup>.

Most of these manifestations have been classified in inflammatory/exanthematous eruptions (urticaria, erythematous/maculopapular/morbilliform rash, papulovesicular exanthem) and in vasculopathic/vasculitic patterns, including chilblain-like acral lesions, livedo reticularis-like lesions, and purpuric "vasculitic" rash. Chilblain-like and livedo reticularis-like lesions can be defined by an occlusive thrombotic microvasculopathy and a procoagulant state.

In a recently published study, skin manifestations were described as pauci-inflammatory thrombogenic vasculopathy with complement deposition in 3 patients with a purpuric skin rash. According to Marzano et al, the vasculitic pattern was considered extremely rare<sup>(4)</sup>.

Healthcare workers are considered to be at higher risk for COVID-19 infection due to their daily activities that involve close contact with affected patients<sup>(5-8)</sup>.

During the COVID pandemic, Italy was one of the most involved countries, and in our hospital, we registered over 380 cases of covid infection among healthcare personnel.

The aim of our study was to identify the presence and the most frequent symptoms found in COVID-19 affected operators who underwent clinical follow-up at the occupational health service of Policlinic Tor Vergata. Since the hypothetical genesis of skin and vasculitic manifestation is supposed to be mediated

by the immunological response to viral infection, we also aimed also to evaluate the association between cutaneous and vasculitic manifestations and the anti-N antibodies for Sars-Cov-2 found after the infection.

The study was made analyzing the population of healthcare professionals who have contracted COVID-19 infection. It also aimed to examine the possibility that these manifestations may be premature and helpful markers in the diagnosis of SARS-CoV2 infection or signals of possible sequelae.

Particularly, it was evaluated the presence of a causal connection between the appearance of cutaneous and vasculitic manifestations correlated to the positivity of the nasopharynx swab and the title of the antibodies generated after the infection or the onset and persistence of these manifestations after the negativization.

## Materials and method

In this study, we collected data through a questionnaire that was submitted to 126 healthcare workers who tested positive for Sars-CoV in the period between March 2020 and January 2021.

During this period ,the nasopharyngeal swabs were performed by the Occupational Medicine Department of the Tor Vergata hospital on health workers exposed to COVID-19 risk. The swabs were performed on the operators who were in direct contact with positive patients and as screening for health surveillance in order to control the spread of the Sars-CoV2 infection in the different departments. All subjects who tested positive at nasopharyngeal swab (350) were asked to fulfill a telephonic questionnaire regarding the presence and characteristics of skin symptoms that happened during the 15 days following the first positivity. Among those operators, 126 (36%) accepted to participate in the study.

For data collection, we used a standardized questionnaire; study participants were asked to reportage, gender, job task, absence or presence, and type of symptoms that have arisen during the study period. In details, subjects were asked to refer regarding any changes in the skin or vascular plan in the period before, during, and after the acute infection (the period between the first positive swab and the final negative result).

Operators symptomatic for skin manifestations were asked whether these injuries were subjected to

specialist evaluation and to refer, in this case, the diagnosis made by the specialist.

At the time of return to work after negativization, all subjects were asked to undergo serological screening for N-Covid IgG.

Occupational exposure to ionizing radiation and previous dermatological diseases were set as exclusion criteria for the study.

We performed the statistical analysis. All data were processed using Stata software, version 11.0 (StataCorp LP, 4905 Lakeway Drive, College Station, TX, USA). The data on demographics (age class, gender), work-related factors, the type and the localization of the cutaneous lesions, the serological levels of N-Covid IgG were reported as descriptive statistics.

The image shows a screenshot of a web-based questionnaire titled "Questionario COVID19 Operatori Sanitari". The form is divided into several sections with checkboxes for responses:

- Header:** "Questionario COVID19 Operatori Sanitari" with a subtitle "Recupero dati per: Area di Scienze di Medicina e Chirurgia".
- Professional Information:**
  - Indirizzo email? (Free text)
  - professione:  medico,  infermiere,  assistente sociale,  altro
  - setore:  pronto soccorso,  altro
- Clinical and Symptom Information:**
  - È risultato positivo al test serologico? (Yes/No/Non fu effettuato)
  - Avvicina della positività al tempo:  meno di 2 settimane,  più di 2 settimane,  più di 4 settimane
  - Ha avuto manifestazioni cutanee? (Yes/No)
  - Ha avuto manifestazioni vasculitiche (tipo grossi)? (Yes/No)
  - età:  18-24,  25-34,  35-44,  45-54,  55-64,  65+
  - È esposto a radiazioni ionizzanti? (Yes/No)
  - come ha scoperto di essere positivo a COVID19? (Infermiere, assistente sociale, medico, altro)
  - Le manifestazioni cutanee e vasculitiche, rispetto alla diagnosi di positività, sono comparse? (prima, durante, dopo)
  - Le manifestazioni cutanee e vasculitiche, si sono prolungate anche dopo la negativizzazione? (Yes/No)
  - Le manifestazioni cutanee vasculitiche, sono state sottoposte a valutazione dermatologica? (Yes/No)
  - Leggibilità è stata confermata al tempo nasofaringeo (in PCR)? (Yes/No)

## Results

Sample specification: We enrolled 126 healthcare workers (85 female and 41 male) who tested positive for COVID-19 in the period between March 2020 and January 2021.

The mean age of the population was 39 years (22 ds 67). Most skin manifestations occurred in the age group 31-40 yrs.

The main characteristics of the study population are reported in table 1.

		N (%)
Gender	Male	68%
	female	32%
Age class	18-30	21%
	30-40	36%
	40-50	25%
	>50	18%
Job task	Nurse	61%
	Structured doctor	10%
	Trainees doctor	21%
	Technician	2%
	Oss	2%
	Others	4%

**Table 1:** The main characteristics of the study population.

The professions investigated and most involved are represented in the graph below and concern 61% of our sample category of nurses, followed by 21% of trainees and 10% of structured doctors.

Regarding the presence of systemic symptoms at the time of the swab, 30% of operators resulted positive for one or more manifestations.

Anosmia was found as a symptom of onset in 22 cases, always associated with other symptoms such as fever, asthenia, and ageusia, while only in 1 case was found as the only symptom. It showed up with a frequency of 17.5%. Ageusia presented a frequency of 14%. The diarrheal alvus showed a frequency of 11.9%, while the dyspnea 7.9%.

The dry and irritating cough occurred in 33 cases as a symptom of onset, even before the confirmation of positivity, manifesting itself as a symptom with a frequency of 26.2%.

As for the fever, it showed up with a prevalence of 32.5%. More particularly, 41 subjects presented fever, 8 as the only symptom and 33 associated with other symptoms, most frequently asthenia, anosmia, and diarrhea.

Fatigue is the one symptom that has accompanied more frequently than the other symptoms (49.2% of cases), even if not characteristic of the COVID19 infection but as an indicator of a stressful condition for the organism. It was present as an isolated symptom in 17 cases.

Concerning the duration of the positive swab, the meantime of viral shedding was 23 days (12 ds 35). We classified the population, according to symptoms duration in 3 groups: <3 weeks; > 3 <4 weeks; > 4 weeks.

The lowest number of asymptomatic workers was found in health workers who have tested

positive for over 4 weeks (4 out of 30), while the greatest number of asymptomatic is found in those who have tested positive for less than three weeks (18 out of 50).

Skin and vasculitic manifestations occurred in 20% of our sample. Among the 25 subjects, we observed 13 cases with exclusively skin lesions and in 7 exclusively vasculitic, while 5 patients showed the simultaneous presence of both manifestations.

The main findings are shown in table 2.

		N (%)
Skin Manifestation	Vasculitic lesions	6 %
	Cutaneous lesions	10 %
	Vasculitic and cutaneous lesions	4%
	None	80 %
Localization	Arms	28%
	Legs	20%
	Hands	28 %
	Feet	28%
	Torso	28%
	Face	44%

**Table 2:** The main findings.

The lesions were localized more frequently to the face and hands, particularly in the acral area with vasculitic lesions like perniosis. In 4 cases, there was only involvement of the face, while the presentations on the trunk have always been associated with the involvement of other districts as legs and arms.

When undergone specialist evaluation, all the skin lesions were classified as exfoliative-type dermatitis or eczema. Regarding the time of presentation of the manifestation in relation to the confirmation of positivity to the swab: 3 interviewees noticed the alterations of the skin days before the confirmation of positivity, the remaining 22 noticed its appearance during the period of infection: 10 cases as transitory lesions of short duration, while the remaining 12 have complained these problems even after the negativization.

The antibody titer (n-CoV IgG) was evaluated in 67.7% of the sample, and the remaining 32.3% had never performed a serological test. Among antibodies tested subjects (21/85; 24.7 %) did not develop antibodies after the infection, while the remaining subjects (64/85; 75.3 %) showed an antibody titer greater than 1.4, considered as a cut-off value. In relation to the antibody titer, 93.3% of the operators who had skin manifestations tested positive at serological evaluation.

We found a statistically significant association (chi2 test) between dyspnea and vasculitic lesions while evaluating the correlation between systemic and skin symptoms.

Protective antibody level, tested after the infection, resulted related to the presence of cutaneous manifestations was obtained from the analysis of 15 subjects.

In the study population, 12 patients reported vasculitic lesions, described as pivotal-like in the acral area, especially in the upper limbs. In 5 patients, they came out with associated skin manifestations.

In contrast with the skin manifestations, the presence of vasculitic manifestations was not statistically related to anti-N Sars-Cov-2 IgG.

Vasculitic changes in our population resulted related to dyspnea that was reported by 25% of those subjects (Table 3).

	Cutaneous lesions	Vasculitic lesions	n-Cov IgG
Subject 1	x	x	16.57
Subject 2	x		5.84
Subject 3			1.03
Subject 4			1.65
Subject 5			0.12
Subject 6	x	x	13.93
Subject 7	x		4.54
Subject 8			0.95
Subject 9	x		4.06
Subject 10			1.01
Subject 11	x		3.20
Subject 12			0.04
Subject 13	x	x	7.42
Subject 14	x		5.83
Subject 15			0.06
Subject 16	x		6.13
Subject 17	x	x	3.98
Subject 18			0.54
Subject 19	x		4.48
Subject 20			1.54
Subject 21	x		6.34
Subject 22			0.09
Subject 23			0.87
Subject 24	x	x	7.34
Subject 25	x		5.52
Subject 26	x		8.93
Subject 27			1.12
Subject 28			0.53
Subject 29			0.31
Subject 30			0.03

**Table 3:** Occurrence of cutaneous or vasculitic manifestations related to n-Cov IgG titre.

## Discussion

Our study showed that, in the study population, both dermatological lesions and vasculitic alterations frequently occurred. This is consistent with other studies that have reported the presence of these manifestations in patients affected by SARS-CoV2<sup>(9-10)</sup>.

A study of 552 hospitals in China, reported a prevalence of 0.2% of skin symptoms among covid-19 patients. However, in other recently published studies from France and Italy, a prevalence between 4.9% and 20.4% were reported<sup>(8-11)</sup>.

Regarding the pathogenesis of the skin lesions, the link between Sars-cov-2 to the ACE2 receptors, widely expressed in different tissues (including epithelial and endothelial cells), has been considered to be the key mechanism that justifies the involvement of these issues.

Female gender showed, in our study, a greater frequency of cutaneous manifestations when compared to male subjects. Those findings are in line with similar results from the literature<sup>(12-16)</sup>.

The most frequently reported site of location was the face and, in most cases, simultaneous involvement of other districts was observed, confirming the systemic nature of skin involvement during COVID-19 infection. Moreover, most acral lesions, like perniosis, happened in subjects lacking a previous history of Raynaud's disease or exposure to cold.

Compared to the positivity confirmed by nasopharyngeal swab (rt-PCR), most of the lesions occurred after the onset of the other non-cutaneous symptoms and, in any case, during the isolation period, making a specialist dermatological evaluation difficult to achieve.

In order to justify the presence of these manifestations, we refer to the De Perosanz-Lobo et al., in which two COVID19 patients with urticarial vasculitis, a form of small vessel leukocytoclastic vasculitis associated with urticaria, were described (17-20).

In three cases, these manifestations appeared before the positive of nasopharyngeal swab; of positivity and among these, the only operator who underwent dermatological evaluation was recognized as affected by dyshidrosis.

Considering the actual knowledge on COVID-19 related dermatoses, this lesion could be better classified as a vesicular lesion due to SARS-CoV2 infection<sup>(21-23)</sup>.

Among the cases in which the lesions continued after the negative swab test, two were identified as COVID-19 related exfoliative dermatitis at the specialistic dermatological visit.

The subjects who reported the presence of such manifestations specified that they had never previously suffered from such disorders. Therefore, having all been previously tested positive for COVID-19, this supports the hypothesis that these lesions are closely related to the infection.

In the literature, such acral lesions reported as perniosis-like lesions have been observed mainly in children rather than in adults subjects.

Colmenero et. al<sup>(24)</sup> confirmed the correlation with COVID-19 through a biopsy examination by observing the presence of superficial and deep perivascular lymphocytic inflammation and positive immunohistochemistry for SARS-CoV2, in the endothelial and epithelial cells of the eccrine glands.

Bouaziz et. al<sup>(25)</sup> hypothesize that the finding of these lesions, in the absence of exposure to low temperatures, is due to a dysregulation of the immune system, thrombosis of small vessels, or neo-angiogenesis. Our sample, despite being representative of adulthood, reported the presence of such lesions that occurred during the infection and prolonged beyond the negativization time.

In order to achieve a correlation, even in these cases, it would therefore be necessary to verify these lesions through skin biopsies.

Our study shows that vasculitic lesions intended as micro-angiopathic, appeared after the swab positivity and after the onset of systemic and respiratory symptoms, so they cannot help to improve early diagnosis of infection.

Moreover, among subjects who developed skin manifestations during the course of covid-19 infection, we have observed a higher positive n-CoV IgG antibody titer than that found in those who did not present the skin injuries, accounting for a causal role of immune response in the genesis and enhancement of skin inflammation<sup>(26-28)</sup>.

Our data also showed a clear correlation between vasculitis and dyspnea: 25% of those who showed vasculitic manifestations also had dyspnea at anamnestic recall. In an autopsy study by Yan et. al<sup>(29)</sup>, the presence of an extensive and widespread perivascular lymphocyte aggregate in the lungs was observed for the first time, with few focal points of infiltration within the vessel walls, in the absence of fibrinoid necrosis, compatible with non-necrotizing lymphocytic vasculitis.

The same inflammatory condition was observed in the study by Colmenero et. al in the biopsy of the acral lesions.

Dyspnea could otherwise be explained as a symptom of lung damage like angiogenic pulmonary edema in the context of systemic vasculitis, as suggested by the Kubanov study<sup>(30-31)</sup>.

It is also true that in the autopsy study conducted by Yan et. al, an accurate ultrastructural analysis was verified for the presence of fibrin aggregates inside the blood vessels, which suggested a greater propensity for clot formation, as hypothesized by Bouaziz et al. to the. in the acral vasculitic manifestations.

Therefore, in the presence of acral vasculitic lesions and dyspnea, greater attention should be paid to these patients to understand the relationship between these two phenomena and to understand if the acral lesions may be suggestive of the alterations present in the lungs.

The most common symptoms at onset were fever and cough. This matches the results found from the observation of our sample: these were present in a higher percentage (fever 32.5%, cough 26.2%), compared to other manifestations.

It is also necessary to consider that 49.2% of our population of health-care workers reported a condition of marked asthenia. Considering the enormous efforts required of all the operators employed in the health sector, the grueling working hours and the limited time available to devote to rest, this data should be considered noteworthy.

Dyspnea was reported in a lower percentage than all the other symptoms (7.9%); It can be considered as the least frequent manifestation in the analyzed sample. That finding doesn't exclude the presence of hypoxemia in patients who have not manifested dyspnea.

In fact, the literature hypothesizes that the condition identified as silent hypoxia is related to the direct invasion of the nervous tissue by the virus or the effect of the cytokine storm that affects the meso-corticolimbic system.

Dyspnea is a relatively infrequent symptom in patients suffering from COVID-19 related pneumonia because, in parallel with a deterioration of respiratory function, a high patient respiratory compliance is accompanied. Lack of this symptom is associated with worse outcomes<sup>(32-34)</sup>.

Anosmia and ageusia were reported respectively in 17.5% and 13.5% in our population.

These disfunctions are present in other respiratory tract infections, that cause damage to the olfactory epithelium or involve the olfactory nerve, but in SARS-CoV2 infection, transmission through the olfactory bulb to the SNC seems easier<sup>(35)</sup>.

According to the Lee et. al<sup>(36)</sup>, the prevalence of these symptoms seems to be present in 15% of COVID-19 subjects in the initial stages of infection; this appears consistent with our research.

## Conclusions

Our study adds significant knowledge on the epidemiology of skin manifestations among COVID-19 patients. Since health-care professionals

are occupationally exposed to a higher risk of Sars-Cov2 infection, COVID-19 related skin manifestation should be carefully addressed among those subjects in order to evaluate the possible impact on fitness for work. Cutaneous and vasculitic manifestations can both alter the integrity of the skin barrier and be the consequence of systemic and pulmonary involvement during COVID disease.

The knowledge of the mentioned COVID-19 lesions allows to adding further details to the classification of the pathology with respect to the most common symptoms. Identifying a statistically significant correlation between vasculitic manifestations and dyspnea is only a first step towards a clearer understanding of the pathophysiology of COVID-19 disease. which requires further investigation.

The identification of vasculitic lesions as a prognostic marker of the disease could be helpful, needing further investigations to confirm the results obtained so far.

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