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EDITOR in CHIEF
Antonino Di Pietro

Cutaneous manifestations associated with COVID-19 The experience of the **Dermatological Clinic** of Milan

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Cari amici, cari colleghi,
mi fa molto piacere potervi presentare il primo “speciale monotematico” JPD. Esso affronta una problematica attualissima: le manifestazioni cutanee associate a COVID-19. Viene riportata l’esperienza della Clinica Dermatologica di Milano, sicuramente una delle casistiche più significative a livello internazionale, considerando che Milano e la Lombardia sono state tra le zone più colpite al mondo. Ci sarà ancora molto da studiare e da capire su questo terribile virus e spero che questa monografia possa essere utile per aggiungere un importante tassello alle nostre conoscenze.

Uno speciale ringraziamento va ai colleghi che hanno reso possibile questo lavoro: Francesca Barei, Valentina Benzecry, Lucia Brambilla, Giovanni Fellegara, Serena Giacalone, Raffaele Gianotti, Carlo Alberto Maronese, Sebastiano Recalcati, Davide Riva, Maurizio Romagnuolo, Cristina Beatrice Spigariolo, Stefano Veraldi.
Buona lettura.

Dear friends, dear colleagues,
I am very pleased to be able to present the first JPD “monothematic special” to you. It addresses a very topical issue: cutaneous manifestations associated with COVID-19. The experience of the Dermatological Clinic of Milan is reported, certainly one of the most significant internationally, considering that Milan and Lombardy were among the most affected areas in the world. There will still be much to study and understand about this terrible virus and I hope this monograph will be useful to add an important piece to our knowledge. Special thanks go to the colleagues who made this work possible: Francesca Barei, Valentina Benzecry, Lucia Brambilla, Giovanni Fellegara, Serena Giacalone, Raffaele Gianotti, Carlo Alberto Maronese, Sebastiano Recalcati, Davide Riva, Maurizio Romagnuolo, Cristina Beatrice Spigariolo, Stefano Veraldi.
Enjoy the reading.

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CONTENTS

- pag. 5** *Cutaneous manifestations associated with
Coronavirus Disease 2019*
*Stefano Veraldi, Valentina Benzecry, Maurizio Romagnuolo,
Cristina Beatrice Spigariolo*
- pag. 11** *Does Sars-CoV-2 accelerate skin aging?*
Lucia Brambilla, Francesca Barei
- pag. 15** *Clinical-pathological correlation of COVID-19
cutaneous manifestations*
*C.B. Spigariolo, S. Giacalone, D. Riva, C. A. Maronese,
G. Fellegara, R. Gianotti*
- pag. 21** *COVID-19 skin manifestations: a first
classification*
Sebastiano Recalcati

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Cutaneous manifestations associated with Coronavirus Disease 2019



STEFANO VERALDI

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SUMMARY

The incidence of cutaneous involvement associated with Coronavirus Disease 2019 (COVID-19) differs highly from country to country. Several different cutaneous manifestations have been associated with COVID-19. In our experience, the most frequent of them are erythematous exanthem, erythematous-papular-vesicular eruption, acute urticaria, acrodermatitis, pityriasis rosea and pityriasis rosea-like eruption, and herpes zoster. Furthermore, seborrhoeic dermatitis, acne, rosacea and perioral dermatitis worsen in patients who wear anti-COVID-19 face masks for several hours per day.

KEYWORDS

Severe acute respiratory syndrome-coronavirus-2, SARS-CoV-2, Coronavirus Disease 2019, COVID-19, cutaneous manifestations

INTRODUCTION

Milan and the region of Lombardy have been struck down in March and April 2020 by a dramatic outbreak caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), with a very high number of infected patients and deaths. Some reasons have been hypothesized: a) the high density of the population: more than ten millions of inhabitants live in Lombardy and 3.300.000 inhabitants in the metropolitan area of Milan; b) the high number of elderly people and, consequently, the high median age of the population;

c) the high number of infected patients in rest homes; d) wrong and bad approach and management of the outbreak by politicians of Lombardy. This outbreak occurred despite of: a) the high gross domestic product (HDP) of Milan: in June 2019, HDP was the third highest in Europe, after London and Paris; b) the quality of life: Milan, in 2018 and 2019, was the Italian city with the best quality of life: Rome was 18th out of 107 cities, Naples was at position 81 and Palermo was at number 98; c) a good level of the public health. However, this outbreak allowed us to observe many patients with cutaneous manifestations.

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Epidemiology of cutaneous manifestations associated with COVID-19

The incidence of cutaneous involvement associated with COVID-19 differs highly from country to country. In China, cutaneous involvement was observed in 2/1.099 patients (0.2%) [1]. In a Lombardy hospital, 18/88 patients (20.4%) developed cutaneous manifestations [2]. In Thailand, “almost all patients have no significant dermatological presentation”[3]. In France, 103 patients [32 men and 71 women, with an age ranging from 20 to 88 years (mean age: 47 years)], were followed at their homes (n. 76) or admitted to hospital (n. 23) or admitted to intensive care (n. 4): 5/103 patients (4.9%) showed cutaneous manifestations [4]. In Rome, 2/130 patients (1.5%) had skin lesions [5]. It is very difficult to explain these results. In the metropolitan area of Milan, it is possible that approximately 10% of patients with COVID-19 shows skin lesions.

Cutaneous manifestations associated with COVID-19

Several different cutaneous manifestations have been associated with COVID-19 [6-8].

→ **Erythematous exanthem** occurs mainly in elderly patients with a severe clinical picture. It is characterized by widespread erythematous lesions, mildly or no infiltrated, of different morphology and size, pink to red in colour (**Figure 1**), symptomless or accompanied by mild pruritus. Healing occurs within 1-3 weeks with fine desquamation. Some clinical varieties have been described: erythematous macules, morbilliform exanthem, and annular and circinate erythematous lesions. Furthermore, an erythematous exanthem may appear 3-6 weeks after the first positive nasopharyngeal swab for SARS-CoV-2. In these patients, an etiopathogenetic role of previously administered drugs must be excluded.



Figure 1

Figure 1.
Erythematous exanthem.

Figures 2-4.
Acrodermatitis.

→ **Erythematous-papular-vesicular eruption** will be discussed in the chapter by Marzano et al.

→ **Acute urticaria** is often the first clinical manifestation of COVID-19, in absence of other symptoms and signs of the disease [9-12]. The problem is that these patients can unknowingly infect other persons and contribute to the spread of the infection: their isolation is therefore necessary [10]. Urticaria involves mainly the limbs and face [9,11,12]. Itching is often mild or absent [2,11,12]. Apparently no correlation with COVID-19 severity exists. It would be helpful (or necessary?) to test for SARS-CoV-2 all patients with urticaria living in endemic regions for COVID-19.

→ **Acrodermatitis** occurs mainly in young patients with mild COVID-19. Erythematous-papular lesions are more common, sometimes with thin scales (**Figures 2-4**). Other clinical presentations are lichen planus-like or erythematous-papular-purpuric lesions. Itching is mild or absent [13-17].

→ **Pityriasis rosea and pityriasis rosea-like eruption** is sometimes the first clinical manifestation of COVID-19, in absence of other symptoms and signs of the disease [18]. It occurs mainly in young patients with mild COVID-19. The clinical picture is characterized by widespread erythematous lesions, of different morphology and size, accompanied by mild itching. Healing occurs with fine desquamation [18]. Furthermore, pityriasis rosea may appear some weeks (six weeks in two patients of ours) following the first clinical manifestations of COVID-19. In these cases, it is possible that chronic lymphopenia induces a reactivation of human herpes virus HHV-6 and HHV-7. It was demonstrated that SARS-CoV-2 induces a reactivation of several viruses, such as HHV-6, HHV-7, varicella zoster virus (VZV) and Epstein-Barr virus [19-22]. In a Turkish study, it was observed that the number of patients with pityriasis rosea

Figure 2



Figure 3



Figure 4



and Kawasaki disease increased significantly during the COVID-19 pandemic. The authors put forward the hypothesis that this increase was related to HHV-6 reactivation by SARS-CoV-2 [23].

→ **Herpes zoster** has been rarely observed in patients with COVID-19 [21,24-28]. It may be the first clinical presentation of the disease [25]. In most cases, herpes zoster is characterized by a severe clinical picture [24-28]. It is due to a reactivation of latent VZV infection. Furthermore, herpes zoster may develop 8-10 weeks after COVID-19 recovery, supporting the hypothesis that persistent impaired immunity may be the mechanism underlying this association. In fact, in several reported cases, as well as in our patients, both chronic lymphopenia and decrease in CD4+/CD8+ ratio were observed [21].

→ **Seborrhoeic dermatitis, acne, rosacea and perioral dermatitis.** In the period December 2019 - February 2020 we examined 43 adult patients with seborrhoeic dermatitis. In the period March - April 2020 we observed a worsening of the disease in 20/43 patients (46.5%). They were 15 males (75%) and 5 females (25%), with an age ranging from 23 to 48 years (mean age: 36.7 years). All patients used anti-COVID-19 face masks for 6-10 hours/day. Seven/20 patients (35%) were physicians, obstetricians or nurses. Worsening was characterized by increased erythema and desquamation; furthermore, 14/20 patients (70%) stated that also itching worsened. It is possible that high temperature of the face induces abnormalities of microbiota (proliferation of *Malassezia* spp.?) and permeability of skin barrier, and increases sweating with irritant action and worsening of itching [29].

Some articles have been published on cases of dermatitis of the face associated with the use of anti-COVID-19 masks [30-34]. In a Chinese study, it was observed that 49% of subjects reported skin reactions on the face related to mask. Itch (14.9% of patients), erythema (12.6%) and dryness (11.6%) were the most frequent manifestations. Furthermore, 43.6% of patients with acne, 100% of patients with rosacea and 37.5% of patients with seborrhoeic dermatitis reported worsening of their diseases [30]. A Polish study demonstrated that itching associated with the use of face mask was present in 19.6% of subjects. In particular, subjects with acne, atopic dermatitis and seborrhoeic dermatitis were at higher risk of itching development. Furthermore, subjects who wore masks for many hours per day reported itching more frequently [31]. A case of occupational allergic contact dermatitis caused by formaldehyde and 2-bromo-2-nitropropane-1,3-diol (bronopol) contained in a polypropylene surgical mask was published [32]. In another Chinese study, it was observed a significant increased flare of acne in subjects who wore face mask for more than four hours per day over two months. The authors hypothesized that this condition is due to the high temperature of the face covered by the mask, that induces an increased sebum excretion rate: the latter increased by 10% for each 1°C rise [33]. Also in our experience, acne, rosacea and perioral dermatitis worsen in patients who wore face masks for several hours per day [34].

Conclusions

It is possible that other skin manifestations will be reported in the next future... but we do not hope it...

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, et al: Clinical characteristics of Coronavirus Disease 19 in China. *N Engl J Med.* 2020; 382, 1708-1720.
2. Recalcati S: Cutaneous manifestations in COVID-19: a first perspective. *J EADV.* 2020; 34: e212-213.
3. Mungmungpantipantip R, Wiwanitkit V: COVID-19 and cutaneous manifestations. *J EADV.* 2020; 34, e246.
4. Hedou M, Carsuzaa F, Chary E, et al: Comment on "Cutaneous manifestations in COVID-19: a first perspective " by Recalcati S. *J EADV.* 2020; 34, e299-300.
5. Tammaro A, Adebanjo GAR, Parisella FR, et al: Cutaneous manifestations in COVID-19: the experiences of Barcelona and Rome. *J EADV.* 2020; 34, e306-307.
6. Gianotti R, Veraldi S, Recalcati S, et al. Cutaneous clinico-pathological findings in three COVID-19-positive patients observed in the metropolitan area of Milan, Italy. *Acta Derm Venereol.* 2020 Apr 23;100(8):adv 00124.
7. Sachdeva M, Gianotti R, Shah M, et al. Cutaneous manifestations of COVID-19: report of three cases and a review of literature. *J Dermatol Sci.* 2020; 98, 75-81.
8. Galvan Casas C, Catala A, Carretero Hernandez G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 Cases. *Br J Dermatol.* 2020; 183, 71-77.
9. Henry D, Ackerman M, Sancelme E, et al. Urticarial eruption in COVID-19 infection. *J EADV.* 2020; 34, e244-245.
10. van Damme C, Berlingin E, Saussez S, et al. Acute urticaria with pyrexia as the first manifestations of a COVID-19 infection. *J EADV.* 2020; 34, e300-301.
11. Quintana-Castanedo L, Feito-Rodriguez M, Valero-Lopez I, et al. Urticarial exanthem as early diagnostic clue for COVID-19 infection. *JAAD Case Rep.* 2020; 6, 498-499.
12. Veraldi S, Romagnuolo M, Benzecry V: Urticaria as first clinical manifestation of COVID-19. *Eur J Dermatol.* 2020 (in press).
13. Garca-Gil MF, Monte Serrano J, Garca Garca M, et al. Acral purpuric lesions associated with coagulation disorders during the COVID-19 pandemic. *Int J Dermatol* 2020; 59 :1151-1152.
14. Aghazadeh N, Homayouni M, Sartori-Valinotti JC. Oral vesicles and acral erythema: report of a cutaneous manifestation of COVID-19. *Int J Dermatol* 2020; 59: 1153-1154.
15. Valtuena J, Ruiz-Sanchez D, Volo V, et al Acral edema during the COVID-19 pandemic. *Int J Dermatol* 2020; 59: 1155-1157.
16. Brin C, Sohier P, L'honneur AS, et al. An isolated peculiar Gianotti-Crosti rash in the course of a COVID-19 episode. *Acta Derm Venereol* 2020 Sep 30;100(16):adv 00276.doi:10.2340/00015555-3641.
17. Mahieu R, Tillard L, Le Guillou-Guillemette H, et al. No antibody response in acral cutaneous manifestations associated with COVID-19? *J EADV* 2020;34: e546-548.
18. Veraldi S, Romagnuolo M, Benzecry V: Pityriasis rosea-like eruptions revealing COVID-19. *Aust J Dermatol.* 2020 (in press).
19. Ciccarese G, Parodi A, Drago F. SARS-CoV-2 as possible inducer of viral reactivations. *Dermatol Ther.* 2020 Jun 19;e13878.doi:10.1111/dth.13878.



20. Drago F, Ciccarese G, Rebora A, et al. Human herpesvirus-6, -7, and Epstein-Barr virus reactivation in pityriasis rosea during COVID-19. *J Med Virol.* 2020 Sep 24; 10.1002/jmv.26549.doi:10.1002/jmv.26549.
21. Brambilla L, Maronese CA, Tournalaki A, et al. Herpes Zoster following COVID-19: a report of three cases. *Acta Derm Venereol.* 2020 (in press).
22. Veraldi S, Spigariolo CB. Pityriasis rosea and COVID-19. *J Med Virol.* 2020 (in press).
23. Dursun R, Temiz SA. The clinics of HHV-6 infection in COVID-19 pandemic: pityriasis rosea and Kawasaki disease. *Dermatol Ther.* 2020; 33, e13730.
24. Andorinho de Freitas Ferreira AC, Taynan Romão T, Silva Macedo Y, et al. COVID-19 and herpes zoster co-infection presenting with trigeminal neuropathy. *Eur J Neurol.* 2020 May 24;10.1111/ene.14361.
25. Shors AR. Herpes zoster and severe acute herpetic neuralgia as a complication of COVID-19 infection. *JAAD Case Reports.* 2020; 6, 656-657.
26. Elsaie ML, Youssef EA, Nada HA. Herpes zoster might be an indicator for latent COVID 19 infection. *Dermatol Ther.* 2020; 33: e13666.
27. Tartari F, Spadotto A, Zengarini C, et al. Herpes zoster in COVID-19-positive patients. *Int J Dermatol.* 2020; 59, 1028-1029.
28. Elsaie ML, Nada HA. Herpes zoster (shingles) complicating the course of COVID19 infection. *J Dermatol Treat.* 2020 Oct 12; 1-3 doi:10.1080/09546634.2020.1782823.
29. Veraldi S, Angileri L, Barbareschi M. Seborrheic dermatitis and anti-COVID-19 masks. *J Cosmet Dermatol.* 2020 Aug 13;10.1111/jocd.13669. doi:10.1111/jocd. 1366.
30. Zuo Y, Hua W, Luo Y, et al. Skin reactions of N95 masks and medial masks among health-care personnel: A self-report questionnaire survey in China. *Contact Dermatitis.* 2020 Apr 16;10.1111/cod.13555.doi:10.1111/cod.13555.
31. Szepietowski JC, Matusiak Ł, Szepietowska M, et al. Face mask-induced itch: a self-questionnaire study of 2.315 responders during the COVID-19 pandemic. *Acta Derm Venereol.* 2020 May 28;100(10):adv00152.doi:10.2340/00015555-3536.
32. Aerts O, Dendooven E, Foubert K, et al. Surgical mask dermatitis caused by formaldehyde (releasers) during the COVID-19 pandemic. *Contact Dermatitis.* 2020 May 28.doi:10.1111/cod.13626.
33. Han C, Shi J, Chen Y, et al. Increased flare of acne caused by long-time mask wearing during COVID-19 pandemic among general population. *Dermatol Ther.* 2020; May 29;e13704.doi:10.1111/dth.13704.
34. Giacalone S, Minuti A, Spigariolo CB, et al. Facial dermatoses in general population due to personal protective masks: first observations after lockdown. *Clin Exp Dermatol.* 2020 Jul 13.doi:10.1111/ced.14376.

Does Sars-CoV-2 accelerate skin aging?



LUCIA BRAMBILLA

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SUMMARY

Since the beginning of the pandemic, numerous COVID-19-related skin manifestations have been described but little is known about skin aging during this viral infection. It is possible, in fact, that COVID-19 might induce premature aging through a dysregulation of the immune response. Herein, we report a number of skin manifestations such as skin xerosis, cherry angiomas, solar lentigos, seborrheic keratoses, herpes zoster, nail changes and telogen effluvium, some of them being related to aging after Sars-CoV2 infection.

KEYWORDS

Aging, COVID-19, Sars-CoV-2

INTRODUCTION

Since the beginning of the pandemic, numerous COVID-19-related skin manifestations have been described but little is known about skin aging during and after this viral infection. It has been suggested, in fact, that COVID-19 might induce premature aging through a dysregulation of the immune response and a decrease in the skin immune surveillance [1].

The aging process might be accelerated during chronic viral infections through a genetic mechanism involving telomeres shortening [2]. Telomeres are protein-DNA complexes, located at the ends of chromosomes, that protect the end of the chromosome from illicit ligation and resection. Due to the inherent limitations of DNA replication and telomerase suppression in most somatic cells, telomeres undergo age-dependent incremental attrition. The progressive shortening of telomeres leads to inhibition of cell growth in a pro-

cess called replicative senescence [2].

Telomere shortening is influenced by oxidative damage and replicative stress caused by genetic and environmental factors. In fact, a faster and earlier shortening of telomeres is associated with certain lifestyles such as smoking, obesity, sedentary lifestyle and incorrect diet. Excessive sun exposure, some drugs and infectious diseases might have some influence, too. Furthermore, the speed of shortening is different for both sexes, usually being lower in females [2].

Telomeres shortening is associated with aging and age-related diseases such as cancer, diabetes, cardiovascular diseases and neurodegenerative diseases. Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death.

In addition, telomere dynamics might also play a role in the senescence of the immune system. Indeed, immune senescence [1,2] is the mechanism by

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which the shortening of the telomeres of the cells of the immune system causes a reduction in its proliferative capacity. This phenomenon underlies the reduction of the immune response associated with aging. Growing evidence suggests that this phenomenon happens during chronic viral infections, too. The antigenic volume imposed by persistent and latent viruses leads to host T-cell exhaustion, characterized by impaired T-cell function. Enduring antigen stimulations favor telomere attrition, consequently enhancing T-cell senescence [2].

It's possible then that COVID-19 might induce a dysregulation skin immune system. Herein, we report some skin manifestations we observed in patient affected by COVID-19, some of them being related to aging.

Patients and methods

We report 10 patients (7 females and 3 males; median age 61, range 40-73 yrs) with laboratory confirmed COVID-19, who were clinically observed by a dermatologist (L.B.) for 8 months. Seven of them had mild COVID-19 symptoms, while 3 patients presented severe disease requiring hospitalization.

Results

In this group, we detected the occurrence of skin xerosis and cherry angiomas in all of them, solar lentigos in 8, seborrheic keratoses and herpes zoster in 3 [Figure 1]. We also observed appendages alterations such as nail changes in 1 pa-



Fig 1.



Fig 2.

Fig 1.
The metamer Herpes Zoster detected in our group of 3 patients.

Fig 2.
The case of nail alterations of the thumbs we detected in our group of patients. The photos were taken respectively 3 weeks (a-b) and 5 months (c-d) after the beginning of the COVID-19 symptoms. Notice the retraction of the proximal nail fold with disappearance of the cuticula (a-b). Over the months, the nails appear brittle and prone to break (c-d).

tient [Figure 2] and diffuse hair loss clinically compatible with telogen effluvium (TE) in 9 patients [3]. Besides COVID-19, the patients did not report any disease, drugs intake or lifestyle modifications.

Discussion

Some of the skin manifestation detected in our group of patients are related to aging. Given the absence of this type of lesions in our group of patients before the pandemic and the “subacute” occurrence of these latter, we believe COVID-19 might had a pathogenic role in their appearance.

Thirty skin biopsies of a group of patients seen at our Department with a confirmed COVID-19 diagnosis and from a group of patients highly suspicious for being infected were recently examined [4]. This study analyzed the histological and immunohistochemical characteristics of the two groups and identified four histopathological patterns. In the most frequent pattern, the mini-chilblain-like one, the authors reported a mild peri-glandular lymphoid infiltrate surrounding the dermal ducts and eccrine glands. We believe that this finding might justify the skin xerosis we found in our group of patients.

As cherry angiomas are concerned, they mostly occurred in an eruptive form in patients aged 50-60 and their number tended to increase with time. The etiology of cherry angiomas is not well-known and different hypotheses have been suggested over the years. Among them, it has been supposed that immunosuppression, both iatrogenic and age-related, might play a role in the pathogenesis [5]. Therefore, once again an imbalance of skin immune system might underlie several COVID-19 skin manifestations.

Interestingly, the possible in-

volvement of herpes virus 8 (HHV8) in eruptive cherry angiomas [6], particularly in immunosuppressive status, is similar to what has been recognized for the major HHV8-induced pathologies. Similarly, one could hypothesize that also the varicella-zoster virus might be reactivated during the COVID-19 infection. In this respect, some authors reported the occurrence of vesicular eruptions (chickenpox-like) during the course of COVID-19 [7-9]. It has been suggested that leukopenia and lymphopenia often described in COVID-19 patients [10] might have triggered the varicella-zoster reactivation.

Regarding the nail changes, we observed a case of retraction of the proximal nail fold with disappearance of the cuticula associated with brittle nail syndrome in one patient having suffered from a multiorgan SARS-CoV-2 infection. One can suppose that the possible pathogenic role was played by a nail blood vessels injury, with a consequent transitory matrix injury, possibly due to the COVID-19 procoagulant state causing microvascular occlusion [11].

Concerning the telogen effluvium (TE) observed in about all our COVID-19 patients, different explanations have been hypothesized. The defluvium might be caused by the psychophysical stress induced by COVID-19 or as a consequence of the Sars-CoV-2 infection in an acute telogen effluvium-like pattern. As to the first hypothesis, it is known that TE is often secondary to an acute systemic stressful event such as emotional stress and severe febrile illness [12]. Moreover, a worsening of TE has been observed in a group of female patients during the Italian national quarantine [13]. Besides, a study that aimed to investigate the change

profiles of dermatologic diseases during COVID-19 pandemic reported that the percentage of patients with TE was statistically significantly increased about 2 months after the occurrence of the pandemic [14].

As concerns the hypothesis of TE as a consequence of the virus Sars-CoV-2, a paper reported 10 cases of newly diagnosed acute TE in a group of females with neither previous history nor other causes of hair loss, within weeks to months after Sars-CoV-2 infection [15].

In addition, there is the possibility of a TE due to lymphocytotoxicity (“autoimmune” TE) with circulating anti-thyroperoxidase antibodies and Hashimoto’s thyroiditis [16, 17]. This hypothesis could be linked to the observation that the defluvium might be caused by an atypical subacute thyroiditis (characterized by thyrotoxicosis followed by hypothyroidism with final restoration of euthyroidism) induced by Sars-CoV-2 [18]. Indeed, patients with COVID-19 who required high intensity care showed low or suppressed serum thyroid stimulating hormone, with and without elevated free thyroxine concentrations, which suggests thyrotoxicosis. Patients who are critically ill can have alterations of thyroid function tests, known as non-thyroidal illness syndrome. Alternatively, thyrotoxicosis could result from SARS-CoV-2 directly infecting the thyroid gland, as described in other viral infections [1, 18].

In conclusion, it has been shown that Sars-CoV-2 can cause different skin disorders, including skin aging and some related manifestations. For this reason, dermatologists could recommend the regular use of moisturizers, sun protection and thyroid gland control in all patients during Sars-CoV-2 infection.

REFERENCES

1. Vardhana, S. A., & Wolchok, J. D. (2020). *The many faces of the anti-COVID immune response*. *Journal of Experimental Medicine*.
2. Bellon M, Nicot C. *Telomere dynamics in immune senescence and exhaustion triggered by chronic viral infection*. *Viruses* 2017;9,289.
3. Rebora A. *Telogen effluvium: a comprehensive review*. *Clin Cosmet Invest Dermatol* 2019;12,583-590.
4. Gianotti R, Coggi A, Boggio F, et al. *Similarities in Cutaneous Histopathological Patterns between COVID-19-positive and COVID-19 High-risk Patients with Skin Dermatoses*. *Acta Derm Venereol*. 2020 Aug 19;100(15):adv00249. doi: 10.2340/00015555-3612. PMID: 32812055.
5. Borghi A, Minghetti S, Battaglia Y, Corazza M. *Predisposing factors for eruptive cherry angiomas: New insights from an observational study*. *Int J Dermatol*. 2016 Nov;55(11):e598-e600. doi: 10.1111/ijd.13330. PMID: 27229271.
6. Borghi A, Benedetti S, Corazza M, et al. *Detection of human herpes virus 8 sequences in cutaneous cherry angiomas*. *Arch Dermatol Res* 2013;305:659-664.
7. Marzano, A. V., Genovese, G., Fabbrocini, G., et al. 2020. *Varicella-like exanthem as a specific COVID-19-associated skin manifestation: Multicenter case series of 22 patients*. *Journal of the American Academy of Dermatology*.
8. Brambilla L., Maronese C.A., Tourlaki A., Veraldi S.; *Herpes Zoster following COVID-19: a report of three cases*. *Eur J Dermatol* 2020 (epub ahead of print) DOI: 10.1684/ejd.2020.3924.
9. Shors AR. *Herpes zoster and severe acute herpetic neuralgia as a complication of COVID-19 infection*. *JAAD Case Rep*. 2020 Jul;6(7):656-657. doi: 10.1016/j.jacr.2020.05.012. Epub 2020 May 20. PMID: 32572380; PMCID: PMC7238983.
10. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Cao, B. (2020). *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China*. *The Lancet*.
11. Magro, C., Mulvey, J. J., Berlin, D., Nuovo, G., Salvatore, S., Harp, J., Laurence, J. (2020). *Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases*. *Translational Research*.
12. Malkud, S. (2015). *Telogen effluvium: A review*. *Journal of Clinical and Diagnostic Research*.
13. Rivetti, N., & Barruscotti, S. (2020). *Management of telogen effluvium during the COVID-19 emergency: Psychological implications*. *Dermatologic Therapy*.
14. Kutlu Ö, Metin A. *Relative changes in the pattern of diseases presenting in dermatology outpatient clinic in the era of the COVID-19 pandemic*. *Dermatol Ther*. 2020 Jul 28:e14096. doi: 10.1111/dth.14096. Epub ahead of print. PMID: 32869938.
15. Mieczkowska K, Deutsch A, Borok J et al. *Telogen effluvium: a sequel of COVID-19*. *International Journal of Dermatology* 202; Correspondence 1,3.
16. Baldari M, Guarrera M, Rebora A. *Thyroid peroxidase antibodies in patients with telogen effluvium*. *J Eur Acad Dermal Venereol*. 2010;24:980-982.
17. Sinclair R. *Chronic telogen effluvium: a study of 5 patients over 7 years*. *J Am Acad Dermatol*. 2005;52:S12-S16.
18. Muller, I., Cannavaro, D., Dazzi, D., Covelli, D., Mantovani, G., Muscatello, A., Salvi, M. (2020). *SARS-CoV-2-related atypical thyroiditis*. *The Lancet Diabetes and Endocrinology*.

Clinical-pathological correlation of COVID-19 cutaneous manifestations



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SUMMARY

Various cutaneous manifestations have been observed in patients affected by COVID-19. What appeared to be constant in all skin biopsies was alteration on acrosyringium and dermal duct of eccrine glands, peri-glandular lymphoid infiltrate, coat perivascular lymphoid infiltrate, consisting mainly of cytotoxic CD8+ lymphocytes and eosinophils along with verticalized and engulfed vessels with red blood cells. The four main histological patterns resulted from the combination of the above mentioned characteristics. In particular mini-chilblain-like, chilblain-like, erythema multiforme-like and livedoid-like patterns were described. Mini-chilblain-like pattern associated to a dermatitis resembling pityriasis lichenoides et varioliformis acuta was called papulo-necro-hemorrhagic dermatitis of childhood (PNH 19 Dermatitis of Childhood). Immunohistochemical positivity for SARS-CoV-2 nucleocapsid antibody on cuticular staining of the glomerular part of the eccrine glands appeared to be a cutaneous specific clue of SARS-CoV-2 infection. The presence of erythematous, maculopapular morbilliform rash, chickenpox-like eruption, urticarial presentation, livedo reticularis, chilblain-like lesions and vasculitis together with those histopathological features induce the clinical suspect of SARS-CoV-2 infection.

KEYWORDS

SARS-CoV-2; COVID-19; histopathological patterns; mini-chilblain-like pattern; chilblain-like pattern; erythema multiforme-like pattern; livedoid-like pattern; PNH 19 Dermatitis of Childhood

INTRODUCTION

From February 2020, Northern Italy, especially Lombardy had to face a virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coming from Whuan (China). The clinical spectrum of disease varied from asymptomatic/minimally symptomatic to critical and severe forms. In addition to classic symptoms (fever, respiratory symptoms, conjunctivitis, gastrointestinal manifestations, change of taste and smell) [1], Recalcati et al. [2] had first described in Italy classical well known dermatosis associated with SARS-CoV-2 infection as erythematous rash, urticaria and chickenpox-like vesicles. Specifically, of 80 patients collected, 18 developed

skin lesions. By increasing the number of reports of skin involvement, Marzano et al. [3] made a clinical classification of cutaneous manifestations distinguishing exanthems and other inflammatory eruptions from vasculopathic/vasculitic lesions. The first group included confluent erythematous, maculopapular morbilliform rash, chickenpox-like eruption and urticarial presentations, similar to aspecific rashes in the course of common viral infections. These manifestations should be differentiated from drug reaction, often difficult to discriminate in hospitalized multidrug-treated patients. The second one encompassed livedo reticularis/racemosa, chilblain-like lesions, especially in pediatric population, and vasculitis, resembling leukocytoclastic vasculitis.

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In literature there are reports of Varicella Zoster [4], Pityriasis Rosea [5, 6] and Pityriasis Rosea-like eruption [7] after 5-6 weeks from first clinical manifestations of COVID-19 (Coronavirus disease 19), probably due to lymphopenia [8].

Finally, it was recorded an increase of seborrheic dermatitis, acne, rosacea and perioral dermatitis [9] because of daily mask using and hand eczema [10] due to the frequent use of alcohol sanitizing gel and hand-washing.

Dermatology Unit of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, was directly hit [11]. Inevitable consequences of the phenomenon were: on one hand the re-organization of daily activity in order to face the pandemic [12, 13], on the other hand, the possibility to evaluate and perform skin biopsies of SARS-CoV-2 patients with cutaneous signs [14, 15, 16]. This allowed to describe the four main histopathological patterns and run immunohistochemical analysis on paraffin sections using the SARS-CoV-2 nucleocapsid antibody [17].

Histologic patterns

→ Mini-chilblain-like pattern [17]

In the first 2-3 days after developing SARS-CoV-2 symptoms, biopsies showed edematous dermis with dilated and vertically arranged vessels associated to a collections of perivascular lymphocytes. Mild interstitial infiltration of eosinophils was also seen. The fully developed lesion was characterized by a dense coat perivascular lymphoid infiltrate, greatly dilated and vertically arranged vessels and engorged capillaries with red blood cells (Fig. 1a, b). Very characteristic were the elongated and hyperplastic dermal excretory ducts and acrosyringium of eccrine glands, alongside verticalized vessels, mild peri-glandular lymphoid infiltrate and vacuolized serum. Numerous interstitial eosinophils, extravasated erythrocytes

and nets of Langherans in the epidermis were frequently reported. In all the tested specimens immunohistochemical for SARS-CoV-2 nucleocapsid antibody marked a cuticular staining of the glomerular part of the eccrine glands (Fig. 1c).

Clinical manifestations related to this histopathological pattern were heterogeneous, ranging from erythematous-urticarial lesions, erythema multiforme to pigmented purpuric dermatitis and pityriasis lichenoides et varioliformis acuta (Mucha-Habermann disease).

In young patients the presence of lesions consistent with pityriasis lichenoides et varioliformis acuta associated to histologically mini-chilblaine-like pattern was defined by an author of us (RG) as papulo-necro-hemorrhagic dermatitis of childhood (PNH 19 Dermatitis of Childhood) (Fig. 2). In all the cases immunohistochemistry demonstrated positivity for nucleocapsid antigens in the lumina of eccrine glands. RT-PCR (reverse transcription PCR) swab was negative and lesions recovered leaving macular hypopigmentation.

→ Chilblain-like pattern [17]

Chilblain-like pattern reflected acro-ischemic lesions [18, 19] which often occurred in asymptomatic or minimally symptomatic children and adolescent. Histology was characterized by lymphocytes around medium- and small caliber vessels associated with a dense peri-glandular lymphocytic distribution (Fig. 3). The main difference from the classical chilblain non-COVID-19-related was the severity of vasculitis, so intense to induce dermo-epidermal separation and necrosis of the epidermis. Occasionally dense lymphoid infiltrate around acrosyringial ducts and the almost constant presence of eosinophils among the infiltration were observed. Sporadic micro-thromboses of small deep dermal vessels were reported. Immunohistochemical stained the cuticula of glomerular part of the eccrine glands.

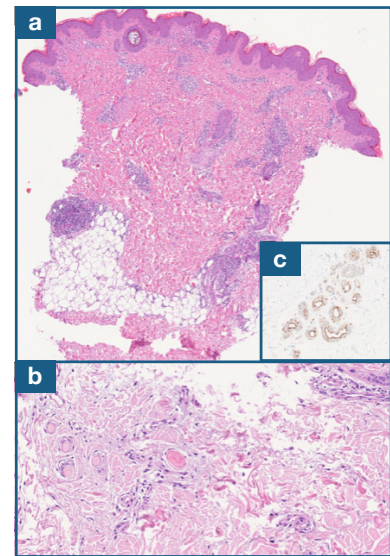


Fig. 1a

Mini-chilblain-like pattern. Diffuse edema of the dermis, dense lymphocytic perivascular and periadnexal infiltrates extending to the subcutis associated to elongated and hyperplastic dermal excretory ducts.

Fig. 1b

Mini-chilblain-like pattern. High magnification of a small thrombosed vessels.

Fig. 1c

Immunohistochemical staining. Cuticular staining of the glomerular part of the eccrine glands using SARS-CoV-2 nucleocapsid antibody.

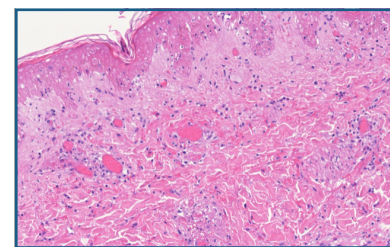


Fig. 2

Papulo-necro-hemorrhagic dermatitis of childhood (PNH 19 Dermatitis of Childhood). Diffuse microthrombi in the upper dermis.

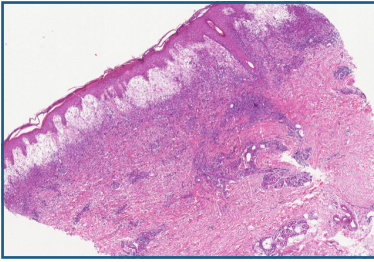


Fig. 3
Chilblain-like pattern. Lymphocytes around medium- and small caliber vessels associated with a dense periglandular lymphocytic distribution. Dramatic dermo-epidermal detachment and necrosis of some keratinocytes.

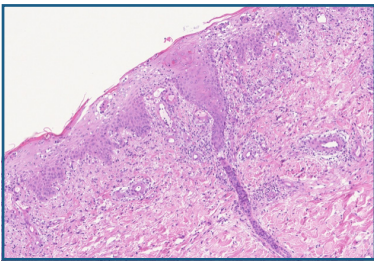


Fig. 4
Erythema multiforme-like pattern. Lichenoid dermatitis characterized by lymphocytes localized at dermo-epidermal junction which diffusely infiltrated the epithelium inducing necrosis of keratinocytes. Elongated and enlarged acrosyringal with peri-glandular lymphoid infiltration is evident.

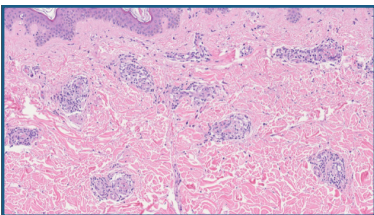


Fig. 5
Livedoid-like pattern. Lymphocytic perivascular cuff. Hyperplastic endothelia with early stage of microthrombi formation.

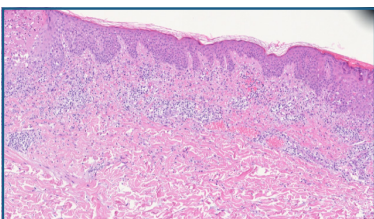


Fig. 6
Grover-like pattern. Patchy band-like infiltration, focal acantholytic suprabasal clefts, perivascular lymphoid infiltration and dilated vessels engulfed by red blood cells.

→ Erythema multiforme-like pattern [17]

Clinically it appeared as erythematous-targetoid lesions similar to the classical erythema multiforme. The specimens showed a lichenoid dermatitis consisting of cytotoxic CD8+ lymphocytes localized at dermo-epidermal junction which diffusely infiltrated the epithelium inducing necrosis of keratinocytes. Specifically, lymphocytes were grouped around the acrosyringal ducts and along the dermal eccrine gland ducts (Fig. 4). In addition, abnormally dilated capillaries engorged with red blood cells, together to microthrombi in the deep dermis and nests of Langerhans cells in the epidermis were reported. Even in these cases, immunohistochemical stained the glomerular part of the eccrine glands.

Compared to non-SARS-CoV-2-related erythema multiforme, there are erythrocytes cells extravasation, microthrombi, verticalized dermal vessels and peri-glandular leucocyte infiltrations.

→ Livedoid-like pattern [17]

Patients were clinically characterized by purpuric target-like lesions. Diffuse livedoid eruption appeared to be related to multi-organ involvement in COVID-positive patients. Histologically, microthrombi were evident in the superficial and deep dermis (Fig. 5). The epidermis was characterized by spongiosis, minimal lymphocytic exocytosis and intraepidermal Langerhans nests.

→ Other aspects: Grover's disease related to SARS-CoV-2 [15, 20]

Histologic specimens were characterized by focal acantholytic suprabasal clefts, dyskeratotic keratinocytes and patchy band-like infiltration with occasional necrotic keratinocytes and minimal lymphocytic satellitosis. In the dermis clusters of dilated ducts of eccrine glands associated to engorged vessels with microthromboses, vacuolated serum and dense lymphocyte perivascular infiltrate, mixed with rare eosinophils, were observed (Fig.

6). It differed from the classic Grover's disease for the so great perivascular infiltrate, microthromboses and hyperplastic eccrine ducts.

What we know about the etiopathogenesis of COVID-19 disease

Since the outbreak begin, the mechanisms by which COVID-19 create a multi-organs damage has been the main topic of dedicated research. Despite the absence of detailed explanation, many progresses have been done from February 2020. In these months, cutaneous histopathology has played a pivotal role. The high incidence of infection in Milan and the co-occurrence of cutaneous manifestations, created the opportunity to perform skin biopsies obtaining a large sample of histopathologic analysis. Accumulating data had supported the idea of a comprehensive theory, previously described by one of the authors (RG), of how COVID-19 arrives in the skin creating a multi-step process that goes from inflammatory to prothrombotic state [21]. Moreover, some of these etiopathogenetic processes, with high probability, can be translated from skin to other organs. The main features are summarized below.

Entrance and early inflammation

In 2004 the angiotensin-converting enzyme 2 (ACE2) has been identified as the functional receptor for SARS-CoV [22]. In the skin, COVID-19 probably use ACE-2 expressed in the basal layer of the epidermis, in the endothelial cells of the dermis vessels and in the eccrine adnexal glands as main gateway. This correlate with two main findings: the presence of lymphocytic infiltration around verticalized dermal vessels and eccrine excretory ducts and the cuticular staining of the latter to the immunohistochemistry technique [15]. The presence of COVID-19 in

the cutaneous vascular system stimulate the immune system mobilizing resident Langerhans cells and lymphocytes. At initial stage, the rapid passage of the virus and the creation of immunocomplex could be responsible for urticarial and exanthematous manifestations, that are self-healing [21].

Maintenance phase and prothrombotic state

When natural course of disease progress, CD4+ T helper lymphocytes produce cytokines (e.g IL-1, IFN- γ , and TNF- α) that recruit eosinophils, CD8+ cytotoxic T cells, B cells, and natural killer cells.

This process has been previously demonstrated to explain the histopathologic findings of lymphocytic vasculitis associated with thrombi in vessel lumina [23]. Clinically, this histopathological stage correlate with severe symptoms and vasculopathic/vasculitic lesions (e.g as livedo racemosa) [3]. However, what stimulate a prothrombotic state is still debated.

On the one hand, the widely presence of eosinophils in the inflammatory perivascular infiltrated suggest a possible involvement. These cells could be responsible of coagulative cascade activation through tissue factor release. This is not a mere speculative mechanism: the association of hypereosinophilia and thrombosis have been documented in Churg-Strauss syndrome [24], bullous pemphigoid disease [25] and scabies lesions [26]. On the other hand, Magro et al. investigated the interaction of complement cascade and COVID-19 spike glycoprotein on the endothelium [27].

However, it is important to remember that between the initial and final stage there are numerous shades of clinical and histopathological correlations. In fact young people are frequently affected by chill-blain like pattern [17] and most of them have RT-PCR swab

and serology test negative.

Cytopathic actions of the virus

It is well known that a virus can affect skin via different strategies: direct or immune-mediated cytopathic effect on keratinocytes is one of that. For example, in case of erythema multiforme herpes simplex virus is supposed to activate a mechanism of autoimmune cross-reactivity against keratinocytes itself. Histopathologic evidence of that damage is represented by ballooning keratinocytes detached from the spinous layer [28]. It turned out that similar floating cells have been observed in the alveolar space examining lung biopsy of COVID-19 pneumonia [29]. Moreover, in one case described by one of the authors (RG), histology showed diffused necrotic

keratinocytes with large ballooned and multinucleated cells in the epithelium of a hair follicle [20]. There are other examples of inflammatory dermatoses probably elicited by virus infection. In mini-chillblain-like pattern the presence of Langerhans nest resemble histology of lichen striatus; the keratinocytes are destroyed by lymphocyte satellitosis organized in a band like dermatitis [30]. As previous described in this paper, in people with dermatoses that resemble Grover's disease have been documented the presence of necrotic keratinocytes, micro-thrombi and dilatated eccrine ducts [15, 20]. Evidence of histopathological changes in epithelium of hair follicles and acrosyringium are present in literature also among Zika [31] and measles [32] infections.

Conclusions

At the beginning of the pandemic it turned out to be essential understanding the pathogenesis of "strange interstitial pneumonia" caused by SARS-CoV-2. In fact, when microthromboses were evident on cutaneous specimens, it was

assumed that thrombosis might be present in other organs, as in lungs, causing that interstitial involvement.

Curiously excision of cutaneous lesions in healthy patients showed occasionally multiple microthrombi in the deep dermis. This might suggest the presence of SARS-CoV-2 infection in asymptomatic carriers.

Furthermore, one co-author of this paper (RG) re-examined skin biopsies of patients with atypical histopathological patterns observed at the end of year 2019. Histopathology, immunohistochemistry and RNA-FISH analysis demonstrated the presence of SARS-CoV-2 RNA in paraffin sections of a young woman. In addition, the serological test conducted on April 2020 was positive for SARS-CoV-2 specific antibody. This finding suggests the virus had been circulating since winter 2019. As a confirmation of this, two Italian papers respectively reveal the presence of SARS-CoV-2 antibodies in asymptomatic individuals who underwent blood screening for lung cancer [33] and positive RT-PCR for SARS-CoV-2 RNA in wastewater from Milan, Turin and Bologna [34]. Both data have been collected from September-October 2019.

REMINDER

- Alteration on acrosyringium and dermal duct of eccrine glands
- Peri-glandular lymphoid infiltrate
- Coat perivascular lymphoid infiltrate
- Verticalized vessels
- Vacuolized serum
- Microthromboses

REFERENCES

- Pascarella G, Strumia A, Piliago C, Bruno F, Del Buono R, Costa F, Scarlata S, Agrò FE. COVID-19 diagnosis and management: a comprehensive review. *J Intern Med*. 2020 Aug;288(2):192-206. doi: 10.1111/joim.13091. Epub 2020 May 13. PMID: 32348588; PMCID: PMC7267177.
- Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol*. 2020 May;34(5):e212-e213. doi: 10.1111/jdv.16387. PMID: 32215952.
- Marzano AV, Cassano N, Genovese G, Moltrasio C, Vena GA. Cutaneous manifestations in patients with COVID-19: a preliminary review of an emerging issue. *Br J Dermatol*. 2020 Sep;183(3):431-442. doi: 10.1111/bjd.19264. Epub 2020 Jul 5. PMID: 32479680; PMCID: PMC7300648.
- Brambilla L, Maronese CA, Tournalaki A, et al. Herpes Zoster following COVID-19: a report of three cases. *Acta Derm Venereol*. 2020 (in press).
- Drago F, Ciccarese G, Rebora A, et al. Human herpesvirus-6, -7, and Epstein-Barr virus reactivation in pityriasis rosea during COVID-19. *J Med Virol*. 2020 Sep 24; 10.1002/jmv.26549. doi:10.1002/jmv.26549.
- Veraldi S, Spigariolo CB. Pityriasis rosea and COVID-19. *J Med Virol*. 2020 Nov 18. doi: 10.1002/jmv.26679. Epub ahead of print. PMID: 33205836.
- Veraldi S, Romagnuolo M, Benzecry V: Pityriasis rosea-like eruptions revealing COVID-19. *Aust J Dermatol*. 2020 (in press).
- Ciccarese G, Parodi A, Drago F. SARS-CoV-2 as possible inducer of viral reactivations. *Dermatol Ther*. 2020 Jun 19;e13878. doi:10.1111/dth.13878.
- Giacalone S, Minuti A, Spigariolo CB, Passoni E, Nazzaro G. Facial dermatoses in the general population due to wearing of personal protective masks during the COVID-19 pandemic: first observations after lockdown. *Clin Exp Dermatol*. 2020 Jul 13;10.1111/ced.14376. doi: 10.1111/ced.14376. Epub ahead of print. PMID: 32658350; PMCID: PMC7404647.
- Giacalone S, Bortoluzzi P, Nazzaro G. The fear of COVID-19 infection is the main cause of the new diagnoses of hand eczema: Report from the frontline in Milan. *Dermatol Ther*. 2020 Jul;33(4):e13630. doi: 10.1111/dth.13630. Epub 2020 Jun 9. PMID: 32436317; PMCID: PMC7267079.
- Nazzaro G, Marzano AV, Berti E. What is the role of a dermatologist in the battle against COVID-19? The experience from a hospital on the frontline in Milan. *Int J Dermatol*. 2020 Jul;59(7):e238-e239. doi: 10.1111/ijd.14926. Epub 2020 May 7. PMID: 32378731.
- Spigariolo CB, Piccinno R. Phototherapy and dermatologic Radiotherapy during the COVID-19 emergency: the experience from the frontline of Milan, *Photodermatology Photoimmunology & Photomedicine* 2020 (in press).
- Giacalone S, Bortoluzzi P, Nazzaro G. Which are the "emergent" dermatologic practices during COVID-19 pandemic? Report from the lockdown in Milan, Italy. *Int J Dermatol*. 2020 Aug;59(8):e269-e270. doi: 10.1111/ijd.15005. Epub 2020 Jun 5. PMID: 32501536; PMCID: PMC7300752.
- Gianotti R, Zerbi P, Dodiuk-Gad RP. Clinical and histopathological study of skin dermatoses in patients affected by COVID-19 infection in the Northern part of Italy. *J Dermatol Sci*. 2020 May;98(2):141-143. doi: 10.1016/j.jdermsci.2020.04.007. Epub 2020 Apr 30. PMID: 32381428; PMCID: PMC7190511.
- Gianotti R, Veraldi S, Recalcati S, Cusini M, Ghislanzoni M, Boggio F, Fox LP. Cutaneous Clinico-Pathological Findings in three COVID-19-Positive Patients Observed in the Metropolitan Area of Milan, Italy. *Acta Derm Venereol*. 2020 Apr 23;100(8):adv00124. doi: 10.2340/00015555-3490. PMID: 32315073.
- Gianotti R, SARS-CoV-2 and the skin, a hidden treasure, *Dermatology Reports* 2020; volume 12:8881, pag 26-27.
- Gianotti R, Coggi A, Boggio F, Fellegara G. Similarities in Cutaneous Histopathological Patterns between COVID-19-positive and COVID-19 High-risk Patients with Skin Dermatoses. *Acta Derm Venereol*. 2020 Aug 19;100(15):adv00249. doi: 10.2340/00015555-3612. PMID: 32812055.
- Colonna C, Monzani NA, Rocchi A, Gianotti R, Boggio F, Gelmetti C. Chilblain-like lesions in children following suspected COVID-19 infection. *Pediatr Dermatol*. 2020 May;37(3):437-440. doi: 10.1111/pde.14210. Epub 2020 Jun 1. PMID: 32374033; PMCID: PMC7267284.
- Recalcati S, Barbagallo T, Frasin LA, Prestinari F, Cogliardi A, Provero MC, Dainese E, Vanzati A, Fantini F. Acral cutaneous lesions in the time of COVID-19. *J Eur Acad Dermatol Venereol*. 2020 Aug;34(8):e346-e347. doi: 10.1111/jdv.16533. Epub 2020 May 27. PMID: 32330324; PMCID: PMC7267354.
- Boix-Vilanova J, Gracia-Darder I, Saus C, Ramos D, Llull A, Santonja C, Del Pozo LJ, Martín-Santiago A. Grover-like skin eruption: another cutaneous manifestation in a COVID-19 patient. *Int J Dermatol*. 2020 Aug 9;10.1111/ijd.15104 doi:

- 10.1111/ijd.15104. Epub ahead of print. PMID: 32880914; PMCID: PMC7436884.
21. Gianotti R, Recalcatti S, Fantini F, Riva C, Milani M, Dainese E, Boggio F. Histopathological Study of a Broad Spectrum of Skin Dermatoses in Patients Affected or Highly Suspected of Infection by COVID-19 in the Northern Part of Italy: Analysis of the Many Faces of the Viral-Induced Skin Diseases in Previous and New Reported Cases. *Am J Dermatopathol.* 2020 Aug;42(8):564-570. doi: 10.1097/DAD.0000000000001707. PMID: 32701690; PMCID: PMC7368844.
 22. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* 2004 Jun;203(2):631-7. doi: 10.1002/path.1570. PMID: 15141377; PMCID: PMC7167720.
 23. Lee JS, Kossard S, McGrath MA. Lymphocytic thrombophilic arteritis: a newly described medium-sized vessel arteritis of the skin. *Arch Dermatol.* 2008 Sep;144(9):1175-82. doi: 10.1001/archderm.144.9.1175. PMID: 18794463.
 24. Maino A, Rossio R, Cugno M, Marzano AV, Tedeschi A. Hypereosinophilic syndrome, Churg-Strauss syndrome and parasitic diseases: possible links between eosinophilia and thrombosis. *Curr Vasc Pharmacol.* 2012 Sep;10(5):670-5. doi: 10.2174/157016112801784594. PMID: 22272911.
 25. Marzano AV, Tedeschi A, Fanoni D, Bonanni E, Venegoni L, Berti E, Cugno M. Activation of blood coagulation in bullous pemphigoid: role of eosinophils, and local and systemic implications. *Br J Dermatol.* 2009 Feb;160(2):266-72. doi: 10.1111/j.1365-2133.2008.08880.x. Epub 2008 Oct 20. PMID: 18945300.
 26. Elwood H, Berry RS, Gardner JM, Shalin SC. Superficial fibrin thrombi ... and other findings: a review of the histopathology of human scabietic infections. *J Cutan Pathol.* 2015 May;42(5):346-52. doi: 10.1111/cup.12482. Epub 2015 Apr 8. PMID: 25754497.
 27. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res.* 2020 Jun;220:1-13. doi: 10.1016/j.trsl.2020.04.007. Epub 2020 Apr 15. PMID: 32299776; PMCID: PMC7158248.
 28. Lucchese A. From HSV infection to erythema multiforme through autoimmune crossreactivity. *Autoimmun Rev.* 2018 Jun;17(6):576-581. doi: 10.1016/j.autrev.2017.12.009. Epub 2018 Apr 7. PMID: 29635075.
 29. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, Mou HM, Wang LH, Zhang HR, Fu WJ, Luo T, Liu F, Guo QN, Chen C, Xiao HL, Guo HT, Lin S, Xiang DF, Shi Y, Pan GQ, Li QR, Huang X, Cui Y, Liu XZ, Tang W, Pan PF, Huang XQ, Ding YQ, Bian XW. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. *Zhonghua Bing Li Xue Za Zhi.* 2020 May 8;49(5):411-417. Chinese. doi: 10.3760/cma.j.cn112151-20200312-00193. PMID: 32172546.
 30. Gianotti R, Restano L, Grimalt R, et al. Lichen striatus - a chameleon: an histopathological and immunohistological study of forty-one cases. *J Cutan Pathol.* 1995;22:18-22.
 31. Paniz-Mondolfi AE, Blohm GM, Hernandez-Perez M, Larrazabal A, Moya D, Marquez M, Talamo A, Carrillo A, Rothe de Arocha J, Lednicky J, Morris JG Jr. Cutaneous features of Zika virus infection: a clinicopathological overview. *Clin Exp Dermatol.* 2019 Jan;44(1):13-19. doi: 10.1111/ced.13793. Epub 2018 Sep 28. PMID: 30267436.
 32. Santana MF, Ferreira LCL, Oliveira JGN, Francesconi F. Histopathological changes in epithelium of hair follicles and acrosyringium caused by measles in child. *An Bras Dermatol.* 2020;95(2):238-240. doi:10.1016/j.abd.2019.02.015.
 33. Apolone G, Montomoli E, Manenti A, Boeri M, Sabia F, Hyseni I, Mazzini L, Martinuzzi D, Cantone L, Milanese G, Sestini S, Suatoni P, Marchianò A, Bollati V, Sozzi G, Pastorino U. Unexpected detection of SARS-CoV-2 antibodies in the pre-pandemic period in Italy. *Tumori.* 2020 Nov 11:300891620974755. doi: 10.1177/0300891620974755. Epub ahead of print. PMID: 33176598.
 34. La Rosa G, Mancini P, Bonanno Ferraro G, Veneri C, Iaconelli M, Bonadonna L, Lucentini L, Suffredini E. SARS-CoV-2 has been circulating in northern Italy since December 2019: Evidence from environmental monitoring. *Sci Total Environ.* 2021 Jan 1;750:141711. doi: 10.1016/j.scitotenv.2020.141711. Epub 2020 Aug 15. PMID: 32835962; PMCID: PMC7428442.

COVID-19 skin manifestations: a first classification



SEBASTIANO RECALCATI

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SUMMARY

A wide range of cutaneous signs were observed in COVID-19 patients. This retrospective study assessed the presence and impact of dermatologic manifestations related to COVID-19 spread in Lombardy, the geographic district with the most important outbreak in Italy. We observed 7 major cutaneous clinical patterns, merged under three main groups: exanthems, vascular lesions and other cutaneous manifestations. Cutaneous findings can lead to suspect COVID-19 infection and identify potentially contagious cases with indolent course.

KEYWORDS

COVID-19, SARS-CoV-2, cutaneous manifestations, chilblain-like lesions

INTRODUCTION

In December 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was isolated from samples from the lower respiratory tract of infected patients, and the resulting disease was termed Coronavirus Disease 2019 (COVID-19) [1-2]. Since then, SARS-CoV-2 has rapidly spread, reaching the level of a pandemic disease. Recent reports from several countries have indicated that this novel coronavirus may be associated with cutaneous manifestations. These

may be useful in identifying otherwise asymptomatic COVID-19 carriers, in order to slow down the viral transmission. We report our experience from Lombardy, Italy, one of the region with the earliest outbreak.

Patients and methods

In the period between February 1 and July 31, 2020 we investigated the epidemiologic and clinical features of COVID-19 cutaneous manifestations. Patients with laboratory confirmation of SARS-CoV-2 infection, according to the definitions created by the European

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Centre for Disease Control, were included.³ Cutaneous signs, epidemiologic, clinical, therapeutic, and outcome data were recorded on admission. A complete dermatologic history was recorded, in order to discriminate between newly-occurred COVID-19 related pathologies and persistence/reactivation of pre-existing dermatologic conditions. Some patients of this case series have been published in our previous articles [4-11].

Results

We observed 54 patients with confirmed COVID-19, aged 7 to 94 years, having new-onset dermatologic conditions. There was no gender prevalence. We documented 7 major clinical patterns merged in 3 main groups: exanthems, vascular lesions and miscellaneous cutaneous manifestations.

1) Exanthems (69%): maculo-papular lesions were the most common manifestations in SARS-CoV-2 infection, frequently impacting middle-aged adults. Lesions frequently appeared early on and lasted for an average of 7 days. In our experience, this setting was associated with a more severe course of COVID-19: these patients were often hospitalized and many placed on the intensive care units. Urticarial, vesicular and erythema multiforme eruptions were less frequent compared to maculo-papular rash. Urticarial lesions appeared in adults, typically presenting at the beginning of a SARS-CoV-2 infection. Itching was often reported. These lesions were usually associated with a good prognosis. Vesicular lesions, characterized by small monomorphic vesicles, appeared in middle aged patients, often early in the course of the disease. They commonly affected the trunk, and about half of the patients complained of pruritis. The appearance of vesicular eruptions occurred with variable

severity and often required hospitalization. Erythema multiforme eruptions were observed in few patients, occurring on an average of 6 days after the COVID-19 infection onset and lasted for about 10 days. Clinically, there were infiltrated papules with targetoid lesions on the extremities, sometimes with central vesiculation. The patients were considered to have a mild or moderate level of disease severity.

2) Vascular lesions group (20%) included vasculitic lesions (livedo reticularis, thrombosis, acro-ischemia, and vasculitis), and chilblain-like lesions (CLL). CLL appeared late over the disease course and affected typically children and young adults. The cutaneous manifestations of this setting ranged from an acral eruption of erythematous-violaceous papules and macules, to possible bullous evolution or digital swelling. Lesions were localized predominantly on the feet, but hands were often involved. Lesions were usually asymptomatic, occasionally painful. In most cases CLL were the only manifestation of the disease, rarely mild systemic symptoms preceded the onset of the lesions from 1 to 8 weeks. Most lesions resolved in 3-4 weeks without treatment, while some patients experienced a prolonged course till 2 months. CLL were associated with a good prognosis.

3) Between miscellaneous cutaneous manifestations we observed alopecia (11%) (mainly telogen effluvium) and indirect cutaneous manifestations (reactivation of other skin diseases, cutaneous manifestations following therapies or hospitalization, aggravation of pre-existing skin conditions).

Discussion

SARS-CoV-2 infection has been demonstrated to affect the skin; gender prevalence was uniform and middle-aged adults was the

most involved group, even if disease can affect age transversely.

An uncommon aspect of SARS-CoV-2 compared to other viruses, is its ability to determine a wide spectrum of cutaneous manifestations. We described 7 major cutaneous clinical patterns associated with COVID-19, under 3 main groups. Exanthems were the most commonly reported skin manifestations. They are characteristic of an early viremic phase, similarly to rashes occurring in the course of other common viral infections. In the group of vascular lesions, likely due to a delayed vasculopathic mechanism, a distinction was made between vasculitic lesions and CLL subset, because the latter was related to a well-defined setting of young patients, with reproducible lesions and always good prognosis. Treatment of skin involvement was based mostly on administering antihistamines and sometimes topical or systemic corticosteroids. Patients developing thromboses required proper low molecular weight heparin therapy, while patients with livedo reticularis and CLL underwent complete resolution without systemic therapy. Maculo-papular eruptions were associated with a worse prognosis for COVID-19 infection, while urticarial and vesicular eruptions usually portended good outcome. In the vascular lesions group, a diagnosis of CLL was related to a good prognosis, while the other vascular manifestations (livedo reticularis, thrombosis, acro-ischemia, vasculitis), which typically involved the elderly, were linked to a worse outcome. The recognition of cutaneous manifestations in asymptomatic patients could be helpful for epidemiologic control, especially in areas where diagnostic tests are scarce.

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REFERENCES

1. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382:1199-1207.
2. Wang T, Du Z, Zhu F, et al. Comorbidities and multi-organ injuries in the treatment of COVID-19. *Lancet* 2020;395:e52.
3. European Centre for Disease Prevention and Control. Case definition and European surveillance for COVID-19, as of 2 March 2020. Available at: <https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov>.
4. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol* 2020;34:e212-e213.
5. De Giorgi V, Recalcati S, Jia Z, et al. Cutaneous manifestations related to coronavirus disease 2019 (COVID-19): A prospective study from China and Italy. *J Am Acad Dermatol* 2020;83:674-675.
6. Recalcati S, Barbagallo T, Frasin LA, et al. Acral cutaneous lesions in the Time of COVID-19. *J Eur Acad Dermatol Venereol*. 2020;34:e346-e347.
7. Recalcati S, Piconi S, Franzetti M, et al. Colchicin Treatment of Covid-19 Presenting With Cutaneous Rash and Myopericarditis. *Dermatol Ther* 2020. doi: 10.1111/dth.13891. Online ahead of print.
8. Recalcati S, Fantini F. Chilblain-like lesions during the COVID-19 pandemic: early or late sign? *Int J Dermatol* 2020;59:e268-e269.
9. Gianotti R, Recalcati S, Fantini F, et al. Histopathological Study of a Broad Spectrum of Skin Dermatoses in Patients Affected or Highly Suspected of Infection by COVID-19 in the Northern Part of Italy: Analysis of the Many Faces of the Viral-Induced Skin Diseases in Previous and New Reported Cases. *Am J Dermatopathol*. 2020;42:564-570.
10. Gianotti R, Veraldi S, Recalcati S, et al. Cutaneous Clinico-Pathological Findings in three COVID-19-Positive Patients Observed in the Metropolitan Area of Milan, Italy. *Acta Derm Venereol* 2020. doi: 10.2340/00015555-3490. Online ahead of print.
11. Recalcati S, Tonolo S, Luzzaro F, Fantini F. Response to "No evidence of SARS-CoV-2 infection by PCR or serology in children with pseudochilblain". *Br J Dermatol*. 2020. doi: 10.1111/bjd.19493. Online ahead of print.

L'ESPERIENZA TEDESCA CON LE MICROONDE CHE PORTANO ALLA BELLEZZA

Il Dr. Klaus Hoffmann, tra i massimi esperti di adiposità, analizza i trend e le opzioni terapeutiche nel body contouring

I Dr. Klaus Hoffmann, membro senior del dipartimento di dermatologia dell'Università della Ruhr di Bochum, è dermatologo e chirurgo estetico, tiene regolarmente lezioni all'università di chirurgia plastica estetica e di laser terapia ed è anche presidente del Dipartimento di Medicina e Chirurgia estetica presso il St. Josef-Hospital oltre che membro di un gran numero di società scientifiche, a cominciare dalla Società Dermatologica tedesca e l'Accademia Europea e Americana di Dermatologia.

Il Dr. Hoffmann è un professionista molto attivo sia in Germania che in ambito internazionale, uno dei massimi esperti di adiposità. Gli interventi maggiormente richiesti nel suo dipartimento universitario presso la Dermatologische Klinik riguardano liposuzione, lifting, chirurgia delle palpebre superiori e inferiori. "In questo periodo, soprattutto con i vari lockdown, stiamo assistendo a un numero particolarmente elevato di richieste di interventi di chirurgia

plastica. Ciò è probabilmente dovuto al fatto che i pazienti possono affrontare questo approccio clinico impegnativo perché hanno più tempo libero, e preferiscono utilizzarlo per le operazioni di chirurgia che richiedono un periodo di convalescenza a casa, dove gestiscono il post intervento con più attenzione e lontano da occhi estranei", afferma il Dr. Hoffmann. Oltre ai trattamenti prima elencati, la struttura tedesca di cui si occupa il Dr. Hoffmann è anche uno dei più grandi centri laser dell'Europa occidentale, in cui l'individuo è al centro delle procedure cliniche, che vengono proposte a seconda delle aspettative e delle necessità che i medici riscontrano. Nel complesso viene coperta e soddisfatta la totalità di richieste dei trattamenti di dermatologia, medicina estetica e body contouring, di cui circa 1/3 delle richieste sono per il miglioramento della cellulite e delle adiposità e per cui utilizziamo più o meno tutti gli strumenti e i sistemi disponibili sul mercato.

Parlando dei trattamenti corpo il Dr. Hoffmann ci racconta che sul mercato esistono moltissime tecnologie a radiofrequenza (RF). Come sappiamo, la tecnologia a RF, sfrutta il principio della generazione di calore, che si sviluppa all'interno dei tessuti cutanei propagandosi in profondità raggiungendo il derma, il grasso sottocutaneo dell'ipoderma fino ad arrivare allo strato adiposo. Recentemente il Dr. Hoffmann ha adottato il sistema Onda Coolwaves, che dimostra il costante ed ulteriore sviluppo della tecnologia verso le microonde, in particolare nell'ordine dei Ghz. Onda rappresenta un arricchimento speciale per l'offerta di trattamenti corpo non invasivi. Onda, infatti, agisce particolarmente bene nella riduzione delle adiposità localizzate e per trattare eventuali piccoli inestetismi che si possono formare dopo la liposuzione. Con questo dispositivo stiamo ottenendo risultati molto buoni anche nel rassodamento della pelle e nel miglioramento della cellulite.



Dr. Klaus Hoffmann

Onda è particolarmente efficace perché raggiunge la temperatura necessaria all'interazione con il target. "Con le microonde, andiamo a colpire direttamente gli adipociti e ne distruggiamo le membrane. Il lisato che fuoriesce dalla membrana va nel tessuto interstiziale e viene poi processato nel fegato oppure dai macrofagi. Questo processo richiede circa 6 settimane.

Solitamente facciamo un trattamento al mese e sono necessarie dalle 3 alle 5 sedute.

Utilizziamo Onda anche nel trattamento del sottointento e abbiamo un numero relativamente elevato di richieste di interventi in questo distretto. Devo dire però che la domanda di trattamenti nella zona del collo è significativamente inferiore in Europa occidentale rispetto agli USA. Molti colleghi in Europa fanno ricorso all'acido desossicolico, spesso in combinazione con altre apparecchiature, ma io sono piuttosto critico nei confronti di questo approccio e per questo motivo, a seconda della natura della pelle e del collo, utilizzo dispositivi non invasivi come Onda", specifica il Dr. Hoffmann.

Onda viene utilizzato anche in modo combinato. "In clinica la usiamo, per esempio, insieme

a un sistema di massaggio per coadiuvare il processo di drenaggio linfatico, oppure con tecnologie che sfruttano i campi elettromagnetici e agiscono direttamente sul muscolo, con risultati molto soddisfacenti", continua il Dottore, specificando che in tutti i trattamenti viene prestata particolare attenzione alla gestione del paziente con una corretta anamnesi e l'acquisizione fotografica dell'area trattata. "Per noi è particolarmente importante mantenere i pazienti informati per lungo tempo. Durante ogni consulto, investiamo almeno 30 minuti per consigliare il paziente sul percorso terapeutico migliore.

Molti pazienti credono che abbiamo macchine miracolose che possono fare tutto. Ma è importante portare le aspettative a un livello ragionevole e spiegare bene ciò che è fattibile, rispetto a quello che il paziente desidera. La documentazione fotografica pre e post è essenziale perché sono necessarie immagini particolarmente accurate e standardizzate in cui il prima e dopo permettano di apprezzare e confrontare in modo inequivocabile i miglioramenti clinici. Mi piace segnalare che con Onda Coolwaves il grado di soddisfazione dei pazienti è molto alto, non abbiamo pazienti con effetti collaterali e stiamo

ottenendo risultati sulla cellulite, ma anche sul rassodamento cutaneo. Abbiamo iniziato a utilizzare Onda per trattare i casi più difficili, tuttavia anche in questo caso è indispensabile avvisare i pazienti sulle reali possibilità sul raggiungimento di determinati risultati. Insisto, è assolutamente importante. In alcuni casi, infatti, è meglio rifiutare un paziente che intraprendere un percorso clinico con chi ha aspettative esagerate. Alla fine, questo porterebbe a una delusione per entrambe le parti. Solo con queste premesse e con risultati concreti è possibile migliorare la qualità della vita dei pazienti, sia che vengano trattati con Onda che con altre metodiche. Quello che ripeto sempre, non solo ai miei pazienti ma anche agli studenti di medicina, è di non dimenticare mai che, per un medico, il successo è importante ma va visto, in sé, sempre come l'aver contribuito al miglioramento della vita del paziente. E questo è possibile solo se il dispositivo giusto viene utilizzato nella giusta indicazione", conclude il Dr. Hoffmann.

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