

## Original paper

# COVID-19 Dermatological manifestations. Presentation of two cases

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### Abstract

The coronavirus (COVID-19) is an emerging disease that was first reported in the city of Wuhan, China, last December 2020, which continues to spread throughout the world and has become an international public health alarm. COVID-19 was characterized as a "pandemic" by the World Health Organization (WHO) which has officially recognized that "there are currently no specific vaccines or pharmaceutical treatments available for COVID-19".<sup>1</sup>

The authors submit two cases of COVID-19 that debuted with skin lesions and that were treated in an adjuvant way; the first with rectal insufflations and the second with ozonized saline solution (O<sub>3</sub>SS). Ozone therapy was chosen as a complementary treatment, as it has an anti-inflammatory, antithrombotic and antihypoxic character. Three characteristics with which the disease occurs.<sup>2</sup>

The evolution of the patients was managed on an outpatient basis without complications and took place in a short period (5 to 7 days), which was accompanied by the improvement of clinical, immunological, biochemical and hematological indicators. No adverse events were observed during treatment. This case report is indicative of the likely efficacy of these complementary treatments and it is recommended that larger clinical studies be conducted that can demonstrate the benefits of these treatments

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## Introduction

There are currently no specific vaccines or pharmaceutical treatments available for COVID-19.<sup>1</sup> However, the FDA decided on March 27, 2020, the emergency authorization to use drugs and biologics during the COVID-19 pandemic. On this basis, it decided on May 1, by means of a letter to Gilead, to authorize the use of Remdesivir for the treatment of COVID-19. This despite the fact that the same FDA, in the same letter of May 1, recognizes that Remdesivir "is an investigational drug and is currently not approved for any indication"<sup>3</sup>

In Spain, today (07/09/2020) sources from the Ministry of Health and regional Ministries of Health reveal that the number of those infected by coronavirus amounts in Spain to 253,056 and 11,841,326 in the world. Spain currently faces 73 outbreaks across the country.<sup>4</sup>

Publications on cutaneous manifestations in COVID-19 are very few. Three dermatologists from different hospitals in Spain have decided to launch the COVID-Skin study, which already has the approval of the Spanish and European health authorities for its development and which has the advice of the Research Unit of the Healthy skin Foundation of the AEDV (Spanish Academy of Dermatology and Venerology).<sup>5</sup> It has been suggested that ozone therapy could be useful in the treatment of this type of patients.<sup>6</sup>

From the clinical point of view, COVID-19 presents with an acute respiratory distress syndrome (ARDS), with a hemophagocytic lymphohistiocytosis that activates a fatal hypercytokinemia, due to the phagocytosis of blood cells that it supposes. The main clinical signs are: fever, fatigue, dry cough, dyspnea, anorexia, ageusia and anosmia. Analytically stand out: elevated blood ferritin, plateletpenia and increased interleukin 6 (IL-6) as indicators of the onset of the process leading to a phase of hyperinflammation and potential death from heart failure.<sup>6</sup> In severe cases prothrombin time is elevated, the thromboplastin part-time, D-dimer, lactate dehydrogenase, procalcitonin, albumin, C-reactive protein, and aspartate aminotransferase.<sup>7</sup>

The nasopharyngeal and oropharyngeal swab, which allows virus isolation, confirms the diagnosis.

The expression of the disease at the cutaneous level is very nonspecific and varied. So far, the following changes have been described with the characteristics listed below: <sup>8</sup>

1. Erythematous/petechial/morbilliform rash:
  - a. Trunk dominance.
  - b. Scarcely itchy.
  - c. May appear before or after the onset of respiratory symptoms.
2. Urticarial rash:
  - a. Hives and erythema.
  - b. It has been described in up to 1.4% of patients.
3. Vesicular eruption:
  - a. Chickenpox-like.
  - b. Only one case described.
4. Acro-ischemic lesions:
  - a. Pernosis-like.
  - b. Erythematous-violet macules.
  - c. Very typical of paucisymptomatic young patients.
5. Lateral Side face/back/fingertip.
  - a. Of millimeters in diameter.
  - b. Well defined.
  - c. They evolve in two weeks becoming purpuric. Possibly due to the prothrombotic effects secondary to COVID-19 infection.

The treatment of these lesions is symptomatic: antihistamines in case of itching and emollients. On the other hand, situations that increase vasoconstriction should be avoided, such as the application of cold due to the possible relationship of dermal lesions with prothrombotic phenomena. It should be noted that if acro-ischemic lesions appear in hospitalized patients, anticoagulation with low molecular weight heparin should be started. <sup>9</sup>

Ozone therapy represents a useful complementary therapy. The objective of using it in these cases is to analyze the potential use of the oxygen-ozone mixture (95% oxygen-5% ozone) as complementary therapy in the compassionate treatment of COVID-19, using a systemic administration route of the oxygen mixture- ozone, through Ozonized Saline Solution and rectal insufflation. The clinical protocol complies with the standard doses and procedures defined in the Madrid Declaration on Ozone Therapy. <sup>10</sup>

The mechanism of action of ozone points to the main complications of COVID-19:<sup>11</sup>

1. It improves the metabolism of oxygen.
2. Restore the rebalancing of the cellular redox state.
3. Increases the synthesis of antioxidant proteins through Nrf2.
4. It has anti-inflammatory and antithrombotic effects.

### **Systemic routes of administration chosen**

#### *Ozonized saline solution (O<sub>3</sub>SS)*

This method was formalized by the Ministry of Health of the Russian Federation in the early 1980s and has been officially implemented in public health hospitals, specifically for the specialties of orthopedics, dermatology, gynecology, and obstetrics.<sup>12,13</sup> In 2004, it was also officially recognized in Ukraine.<sup>14</sup> The method is supported by a large number of scientific papers and solid clinical experience on the benefits of this therapy.<sup>15,16</sup>

The method consists of bubbling and saturating a physiological solution (0.9%) with a mixture of ozone and oxygen at concentrations that are calculated according to the weight of the patient. Its administration takes about 20-30 min. Unlike major autohemotherapy (MAH), ozonized saline solution has been shown to be especially effective in viral diseases such as Epstein Barr, cytomegalovirus, papilloma virus, HIV, herpes zoster, herpes simplex, etc. Compared to MAH and taking into account that the saline solution is a plasma expander, it ozonizes a larger amount of blood, so it is possible to reduce the number of sessions.

### **Materials and Method**

Two clinical cases with skin involvement are submitted.

Before proceeding to treatment, the procedure was explained verbally and in writing to both the patient in the 2nd case, and the legal guardian of the 1st. both approved it with the signing of the informed consent. They also authorized the publication of clinical data for research purposes.

#### **First case**

It is a 4-year-old girl. From her onset, she debuted with 38 degrees centigrade fever of 5 days of evolution; it subsided slightly with acetaminophen, moderate dyspnea, agitation, fatigue and itchy skin rashes distributed on the cheeks, trunk, abdomen, buttocks, thighs, arms and hands.

Fig. 1

Laboratories: rapid COVID-19 test with positive IgM and IgG results. Leukocytes with lymphocytosis, normal platelets, normal coagulation, D-Dimer 1310, PCR 10.2 mg / L, normal ferritin and CPK, liver and kidney tests, normal. Normal blood gas. Electrocardiogram, normal.



**Figure 1.** Itchy rash skin lesions distributed on the cheeks, trunk, abdomen, buttocks, thighs, arms and hands prior to the start of treatment.

### **Protocol applied to the girl: rectal insufflation**

The Ozonobaric P Sedecal® ozone generator with CE0120 class IIb was used, UL. CSA. Silicone cannula for rectal insufflation and Dual Kit Device for ozonized saline solution CE 0318 class IIb.

A rectal ozone therapy protocol is established with one session per day, as per the guidelines of the Madrid Declaration on Ozone Therapy <sup>11</sup>, 10 sessions in total:

- 25 µg / NmL and 50 mL 2 sessions
- 30 µg / NmL and 50 mL 2 sessions
- 30 µg / NmL and 75 mL 3 sessions
- 30 µg / NmL and 100 mL 3 sessions

In addition, it was administered N-Acetylcysteine 300 mg/day orally + VitC 1 gr orally, for 10 days.

Application of Oxionid® 600 IP ozonated oil throughout the body, twice a day, until the rashes disappear.

## Evolution

**At 24 h**, the fever subsided at 36.5°C and she remained afebrile. **At 72 h** fatigue and dyspnea subsided in their entirety. **At the fifth day** the skin eruptions went into clear remission, as did the itching. Fig. 2 **Towards the 10th day** of treatment the girl was completely asymptomatic and free of skin lesions. Completely normal analytics. Rapid COVID-19 test, negative on the 10th day. The girl is discharged with a recommendation for isolation for 15 days.



**Figure 2.** Skin rashes in frank remission 5 days after treatment. Without itching.

## Second Case

A 70-year-old man made his debut with cutaneous lesions of the erythematous rash type pruriginiform, a dermatitis type of 20 days of evolution that was worsened by administration of corticosteroids. The distribution of skin lesions included the arms, lower back, arm, back of the hands and legs. Fig. 3 Additionally, he had a light, subfebrile dry cough and moderate fatigue.

Laboratories: COVID-19 test with positive IgM and IgG results. Hb 15.2 g / dL, platelets  $150 \times 10^3 / \mu\text{L}$ , lymphocytes  $0.82 \times 10^3 / \mu\text{L}$ , leukocytes  $8.88 \times 10^3 / \mu\text{L}$ , fibrinogen 835 mg / dL, D-dimer 2,330 mg / L , ferritin 628 ng / L, PCR 27.2 mg / L

### Protocol applied to the adult: Ozonized Saline Solution (O<sub>3</sub>SS)

Previous saturation of the physiological saline solution 0.9% at 5  $\mu\text{g} / \text{NmL}$  for 10 min at a continuous flow of 200 mL/min. This already saturated solution was administered to the patient under continuous bubbling with the same parameters described at a rate of 80/120 drops/min. It was applied daily, for 5 days. Over the next 5 days the concentration was reduced to 3  $\mu\text{g}/\text{NmL}$  and administered daily. In total 10 treatments.

After, the patient was administered i.v. GSH 1.2 g + Vit. C 2 g. dissolved in 100 mL of physiological solution. Administer twice a week. Four treatments in total.

Additionally, the patient received: Enoxaparin 40 mg subcutaneously, once/day, 5 days. Oxionid® 600 IP Ozonized Oil dermal application twice a day.

Since the disease coincides with acute oxidative stress, Glutathione (GSH) was included due to its ability to donate electrons and stabilize the free radicals generated by the virus. GSH is a non-enzymatic antioxidant, and is one of the first lines of defense against oxidative damage. During aging, the GSH content decreases it and the immune system suffers from a deficiency in the induction of the Th1 response. The reduced Th1 cytokine secretion, which is associated with GSH depletion, could weaken the host's defenses against viral infections.<sup>17</sup>

### Evolution

**At 24h** the fever subsides **After 5 sessions**, the skin lesions begin to subside, and the intensity of the itching decreases. **By the 10th day** the lesions disappear. Fig. 4 Mild fatigue remains for 10 days, which gradually subsides.

The laboratories are completely normalized: Hb 14.7 g / dL, platelets  $250 \times 10^3 / \mu\text{L}$ , eosinophils  $0.29 \times 10^3 / \mu\text{L}$ , lymphocytes  $1.64 \times 10^3 / \mu\text{L}$ , leukocytes  $7.58 \times 10^3 / \mu\text{L}$ , PCR 1.5 mg / L. Rapid COVID-19 test, negative towards the 12th day.



**Figure 3.** Photos prior starting the treatment. They show cutaneous lesions rash erythematous rash, dermatitis type of more or less 20 days of evolution.



**Figure 4.** Photos taken 7 days after treatment. The resolution of the lesions is clearly observed. Patient without itching.

## Conclusion

Systemic ozone therapy may be potentially useful in SARS-CoV-2. The rationale and mechanism of action have already been clinically demonstrated with other viral infections and its effectiveness has been demonstrated with pre-clinical and clinical studies.

Its mechanism of action widely covers the pathophysiology of COVID-19:

- It produces the induction of adaptation to oxidative stress, therefore, it produces a rebalancing of the cellular redox state.<sup>11</sup>
- It restores the balance between the Nf-Kb and Nrf2 pathways, thus controlling inflammatory processes.<sup>11</sup>
- It produces an increase in blood flow (perfusion) and oxygenation of tissues to vital organs (i.e., renal, pulmonary and cardiac circulation).<sup>11</sup>
- The evolution of the two cases presented was rapid. These patients were stabilized and their treatment maintained under ambulatory conditions.
- The application of ozone therapy proved to be safe and effective, since no adverse events manifested during its application. Combined ozone therapy and supplements such as GSH and vitamin C may be helpful in managing SARS-CoV2 infection and larger studies are needed to verify these effects.

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