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Urticaria and coronavirus infection: a lesson from SARS-CoV-2 pandemic

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Introduction

Urticaria is a condition involving both skin and mucosal tissues characterized by the presence of wheals, angioedema, or both. Histologically, the wheal is characterized by edema of the external derma with a minor dilatation of the vessels, in the absence of wall injury, with a peri-vessel granulocytic infiltrate of neutrophils and eosinophils and a little number of lymphocytes and macrophages. Angioedema is defined as the quick onset of a non-inflammatory edema of the deep derma, accompanied by ache or itch, resolving within 72 h (1, 2).

Urticaria is defined as acute (AU) if it lasts less than 6 weeks while chronic urticaria (CU) lasts \geq 6 weeks. It is estimated that 12-22% of the overall population has experienced at least one type of urticaria throughout life (3, 4). Although a precise origin is often not recognized, AU has been correlated with allergic reactions to drugs or foods, interaction with chemicals, mechanical stimulation, psychic stress, or infections. Different studies reported

Summary

Urticaria is a condition involving both skin and mucosal tissues characterized by the presence of wheals and/or angioedema. The acute form has been related to allergic reactions to drugs or foods, interaction with chemicals, or infections. We reviewed the association of urticaria with coronavirus infections. This review was carried out by the use of two search engines for published original articles, employing two key terms correlated to urticaria and viruses: "urticaria" and one term linked to each virus. The research of the relationships between SARS-CoV-2 and urticaria produced 18 papers (including a total of 114 cases). Surprisingly, the search for cases of urticaria in patients with SARS-CoV or MERS produced no results. We tried to interpret this discrepancy and attempted to analyze the possible pathogenesis of urticaria lesions in SARS-CoV-2.

a prevalence ranging between 37 and 58% of infections among subjects with AU (4, 5). Upper respiratory signs and symptoms are frequent in AU associated with infections (6, 7). Viral diseases have been also associated with the onset of atopic signs and an increase of IgE levels (8). Respiratory viruses include many different families of viruses comprising *coronaviridae* (9). Recently coronaviruses have focused international attention due to the current SARS-CoV-2 pandemic. Coronaviruses were not considered to be highly pathogenic to immunocompetent humans until the epidemics of severe acute respiratory syndrome (SARS) in 2002 and 2003 in China (10) characterized by inter-human transmission of SARS-CoV and associated with elevated death rates (11). Ten years after SARS, a different, extremely pathogenic coronavirus, the Middle East respiratory syndrome coronavirus (MERS-CoV) appeared in Middle Eastern nations (12-14). Finally, in December 2019, a novel coronavirus outbreak commenced in the city of Wuhan, China, caused by a betacoronavi-

rus, SARS-CoV-2 (15, 16). Although it is well recognized that coronavirus disease 2019 (COVID-19) is essentially a pulmonary infection, numerous data suggest that it should be regarded as a disease involving different organs and systems, including the skin (17, 18). In the present study we reviewed the association between urticaria and coronavirus infections.

Methods

This review was carried out by using both PubMed, and Google search engines for published original and review articles. We selected articles on these Web sites, by the use of the following key terms:

- “COVID-19”, “2019-nCoV”, and “SARS-CoV-2” in combination with “urticaria” or “rash” for SARS-CoV-2 infection.
- “SARS-CoV” in combination with “urticaria” or “rash” for SARS-CoV infection.
- “MERS” or “MERS-CoV” in combination with “urticaria” or “rash” for MERS-CoV-2 infection.

We evaluated all the studies written in English language and published in peer-reviewed journals. A main target of interest were the case reports of patients with either AU or CA correlated to coronavirus infection. We recorded the following data: author, publication year, region, number of subjects with skin manifestations, age, sex, type of infection, suspected or confirmed status for infection, cutaneous signs and their site, timeline and recovery duration, correlated symptoms, relationship between infection severity with skin lesions.

Results

After eliminating the overlaps between the two search engines, we were left with 23 works investigating the relationships between SARS-CoV-2 infection and urticaria. Of these, 18 reported cases of urticaria in 114 patients with SARS-CoV-2 infection (19-36). Unfortunately, not all studies reported the characteristics of the patients studied (gender, age, timing, *etc.*) and therefore it was not possible to perform a full analysis of the data. **Table I** summarizes some features of the patients. Among the selected papers, three larger patient series were present. Recalcati *et al.* (19) examined 88 Italian subjects: 18 (15.84 %) showed skin involvement, in 8 cases at onset before hospitalization and in 10 patients during hospital stay. Cutaneous symptoms included erythematous rashes (14 subjects), widespread urticaria (3 subjects) and chickenpox-like vesicles (1 patient). The trunk was the predominantly implicated region. Itching was weak or lacking and generally manifestations vanished in few days. There was no connection with disease severity (19). In a Spanish study, the incidence of urticarial rash was 19% in a group of 375 SARS-CoV-2 subjects with skin manifestations and correlated to a more serious course of the infection (30). Urticaria generally developed together with other symptoms and was frequently associated with itching (92%) (30). Finally, in a large retrospective analysis of skin manifestations during SARS-CoV-2 pandemics carried out in France all 14 urticaria subjects report-

ed had had SARS-CoV-2 infection. In these subjects, skin lesions appeared few days after the first SARS-CoV-2 systemic manifestations (33). The other works selected reported up to two cases of urticaria. Generally, the lesions vanished rapidly following the application of local corticosteroids and the use of oral antihistamines (21) or within 10 days after the onset (22).

However, urticaria must be differentiated from other conditions in which rashes or similar skin alterations can represent symptoms of underlying diseases. These include anaphylaxis, vasculitic or pigmentary urticaria, recurrent angioedema with eosinophilia, hereditary C1-inhibitor deficiency, some cutaneous expressions of ectoparasites, or granulomatous dermatitis with eosinophilia (2). In the large analysis reported above (33), the authors reported also skin lesions other than urticaria such as chicken pox like vesicles in 2 patients, while vascular manifestations such as violaceous macules with “porcelain-like” appearance, chilblain, livedo, nonnecrotic purpura, necrotic purpura, chilblain appearance with Raynaud’s phenomenon, and eruptive cherry angioma were described in 7 subjects. Forty other subjects with chilblain manifestations were described but their diagnostic PCR for SARS-CoV-2 scored negative or was not performed (33).

Surprisingly, we did not find cases of urticaria reported in patients with SARS-CoV and MERS.

Discussion

Viral infections are a potential cause of AU and COVID-19 does not represent an exception in this sense. In a recent study performed on 140 patients, urticaria was self-reported in about 1.4% of cases (37). The reason why limited data about urticaria and other respiratory viral infections are available in the literature is probably that skin lesions are short lived in most cases, which leads to a large underestimation of these phenomena. The potential severity and the worldwide spread of COVID-19, along with the availability of a precise diagnostic workout (which is missing during most other respiratory virus infections) have eventually led to accumulate an impressive amount of clinical data recording even minimal clinical signs of the disease. In most cases cutaneous lesions appear at the onset of the infection (25, 26, 31), thus skin signs may act as markers of infection in the many patients with an asymptomatic presentation of SARS-CoV-2 infection.

One reason why some patients develop urticarial skin reactions during the viral infection might be that the expression of the SARS-CoV-2 cell receptor gene angiotensin-converting enzyme 2 (ACE-2) has been reported in several human tissues including the skin (38). Moreover, viral infections may cause urticaria stimulating mast cell degranulation via complement activation (39). Furthermore, patients with AU show elevated levels of IL-6 and D-dimer, two inflammatory markers that are markedly increased during SARS-CoV-2 (40, 41). IL-6 represents the potential link between AU and infection. Urticarial rash combined with fever

Table I - Characteristics of the patients examined.

Authors	N. patients	Skin lesion	Timing with respect infection	Ref.
SARS-CoV-2 virus				
Recalcati <i>et al.</i>	17	Erythematous rash Urticaria	Before	19
Joob <i>et al.</i>	1	Rash	Before	20
De Medeiros <i>et al.</i>	1	Erythematous-edematous plaques	Before	21
Sachdeva <i>et al.</i>	3	Macular-papular rash Macular- papular exanthem Papular-vesicular lesions	After	22
Aktas <i>et al.</i>	1	Urticarial reaction	After	23
Fernandez-Nieto <i>et al.</i>	1	Urticarial eruption	After	24
Young <i>et al.</i>	1	Urticarial rash	Before	25
Henry <i>et al.</i>	1	Urticarial rash	Before	26
Genawan <i>et al.</i>	1	Urticaria	After	27
Rodriguez-Jimenez <i>et al.</i>	1	Urticarial eruption	After	28
Estebanez <i>et al.</i>	1	Urticarial rash	After	29
Galvan-Casas <i>et al.</i>	71	Urticarial rash	?	30
Van Damme <i>et al.</i>	2	Cutaneous rash	Before	31
Naziroglu <i>et al.</i>	1	Edematous plaques	Before	32
Bouaziz <i>et al.</i>	7	Exanthema Cold urticaria Chickenpox like vesicles	After	33
Adelino <i>et al.</i>	1	Wheels Facial angioedema	After	34
Najafzadeh <i>et al.</i>	1	Urticaria and angioedema	Before	35
Guarneri <i>et al.</i>	2	Urticaria	?	36

might be suggestive of SARS-CoV-2 infection (42). The possibility that drugs administered to SARS-CoV-2-infected patients may be involved in the appearance of urticaria should be also carefully considered. A severe drug-induced skin reaction similar to an acute systemic exanthematous pustulosis subsequent to hydroxychloroquine treatment has been reported. It can be distinguished by its longer incubation time, and more heterogeneous morphology firstly frankly urticarial in nature and subsequently characterized by targetoid and arcuate plaques, and by its resistance to treatment (22). Moreover, most patients with COVID-19 take acetaminophen, nonsteroidal antiinflammatory drugs and antibiotics during the first phases of the disease. It is certainly conceivable that the administration of these drugs may also play a role in the onset of urticarial manifestations, at least in some patients.

Conclusions

In conclusion, clinicians must be aware that urticaria may present during COVID-19 possibly in patients with a severe clinical course of the disease. The identification of this condition might lead to an

improvement in the diagnosis and therapy of COVID-19 as well as in a more rapid application of quarantine practices.

Conflict of interests

The authors declare that they have no conflict of interests.

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