Exacerbation of Chronic Spontaneous Urticaria Symptoms in COVID-19 Patients, Case Report

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Abstract

Chronic spontaneous urticaria (CSU) is characterized by wheals lasting more than 6 weeks and can be accompanied by angioedema. Treatment of the disease varies depending on the severity and includes first-line therapeutics such as non-sedative antihistamines. Second- and third-line treatments are used in severe and uncontrolled form of CSU. Environmental exposure and infections could trigger worsening symptoms. The goal of this study is to assess the effect of SARS-CoV-2 infection on CSU symptoms and the efficacy of the second- and third-line therapeutics for CSU management in COVID-19 patients. Our findings show that SARS-CoV-2 infection exacerbates CSU symptoms. Worsening of disease was indicated by decreased Urticaria Control Test (UCT) and increased Urticaria Activity Score (UAS). Treatment management was modified by switching to second- and third-line therapeutics; however, therapeutic control was achieved only in one patient. Our data demonstrates that SARS-CoV-2 infection contributes to the severity of CSU. Symptoms of CSU are more challenging to manage and require changes in treatment protocol, including second- and third-line therapeutics. We believe that severe inflammation triggered by SARS-CoV-2 infection contributes to the worsening of CSU symptoms.

Keywords URTICARIA · COVID-19 · Chronic spontaneous urticaria

1 Introduction

Chronic spontaneous urticaria (CSU) is a major category of chronic urticaria where the wheals appear randomly [1]. Also, angioedema could be diagnosed in some patients [2, 3]. Wheals are characterized by red, raised, and itchy skin rash, which could last for months [2]. These symptoms could be controlled only by specific treatment such as on-sedative antihistamines, glucocorticosteroids, cytostatics, and omalizumab. The pathogenesis of CSU remains largely unknown. It is believed that the mechanism of CSU pathogenesis includes an altered function of the mast cells [3, 4], excessive IgE production [5–7], and circulation of autoreactive autoantibodies [8, 9]. Upon stimulation with IgE, mast cells could release cytokines and chemokines amplifying and sustaining skin inflammatory milieu in CSU [10–12]. Increased levels of pro-inflammatory cytokines, such as IL-6 and IL-18, in serum of CSU, support this assumption, which also correlates with severity of the disease [13, 14]. Therefore, it is suggested that the immune-mediated inflammation has substantial contribution to CSU pathogenesis [15].

Severe acute respiratory syndrome 2 (SARS-CoV-2) virus infection clinically identified as coronavirus infection disease 2019 (COVID-19) presents with symptoms of the upper and lower respiratory tract inflammation [16]. Patients could also have skin eruptions such as maculopapular and vesicular rashes, petechia, purpura, and livedo racemose [17, 18]. It is believed that dermal inflammatory reaction induced by SARS-CoV-2 contributes to the pathogenesis of cutaneous manifestations in COVID-19 [19]. This inflammation could also play role in the mechanisms of skin symptom exacerbation in CSU [20].

We present two cases with worsened CSU symptoms after SARS-CoV-2 infection. Exacerbation of CSU symptoms did not affect the severity of COVID-19. Additionally, CSU and COVID-19 comorbidity had limited effect on development of humoral immune response to SARS-CoV-2. In contrast, exacerbation of CSU was demonstrated in both patients and

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symptoms remained months after COVID-19 convalescence. The CSU treatment protocol was modified and included second- (high doses of cetirizine and desloratadine) and third (omalizumab)-line CSU therapeutics. We believe that severe inflammation induced by SARS-CoV-2 infection could contribute to pathogenesis of CSU symptom exacerbation.

2 Case 1

Patient 1, female 29 years old, was diagnosed with moderate form of CSU in February 2020. Data on clinical laboratory analysis at the time of diagnosis is summarized in Table 1.

The diagnosis was based on anamnesis, symptoms, laboratory results (Table 1), and allergy test data. At the same time, the patient had an additional comorbid diagnosis: persistent allergic rhinitis with a moderate form in remission. Sensitization to tree and weed pollen was established. The patient was recommended to exclude products that cause cross-reaction with pollen of trees and weeds and products rich in histamine, salicylates, and tartrazine. Also, the patient was suggested to refrain from using non-steroid anti-inflammatory drugs. The patient was requested to maintain diary UAS7 to register clinical symptoms of the disease. Treatment of CSU included cetirizine (10 mg/day), a standard dose for the first-line second generation anti-histamines (sgAHs), which was successful. Patient entered the remission phase in May 2020 when therapy was stopped.

At the end of June 2020, the patient was diagnosed with SARS-CoV-2 infection, which was confirmed by detection of virus-specific antibodies. The patient had a mild form of COVID-19, with the following symptoms: body temperature 38 °C for 3 days, headache, malaise, anosmia, and cough. Computer tomography (CT) analysis revealed 15% lung damage. COVID-19 treatment included paracetamol, intranasal interferon-alpha, and azithromycin (500 mg/day; 7 days). The patient complained that from the onset of the COVID-19, CSU symptoms returned (Fig. 1). The UAS7 score was elevated (23–28 points) indicating severe form CSU. That score remained high even when therapy with cetirizine standard dose was initiated. Therefore, the treatment protocol was modified where the sgAHs dose was increased 2-times (20 mg of cetirizine), indicating the switch to the second-line therapeutics.

Fig. 1 Skin lesions in CSU after COVID-19. Multiple wheals up to 10 mm in diameter

Table 1 Clinical laboratory results, case 1

test	Normal range	Case 1
Blood test results		
Hemoglobin (Hb) (g/L)	111 - 143	124
Erythrocytes (cells/L)	4.1 - 4.5 x10^{12}	4.38 x10^{12}
Hematocrit (Ht)	34 – 43%	35.5
Thrombocytes (cells/L)	217 - 343 x10^9	294 x10^9
Leukocytes (cells/L)	4.5 - 13.5 x10^9	6.09 x10^9
Neutrophils banded (%)	0-5	1.8
Neutrophils segmented (%)	43 – 59	45
Eosinophils (%)	1 – 5	1.5
Basophils (%)	0 – 1	0.7
Monocytes (%)	4 – 8	6
Lymphocytes (%)	30 – 46	45
ESR	2-15 mm/h	7 mm/h
Feces analysis	Protozoan and Helminth eggs are not detected	Protozoan and Helminth eggs are not detected
CRP	<6 mg/ml	<6 mg/ml
IgA (mg/ml)	0.7-4.0	1.3
IgM (mg/ml)	0.3-2.5	0.6
IgG (mg/ml)	6.65-16.45	7.7
IgE (IU/ml)	< 100	127.31

ESR, erythrocyte sedimentation rate; red color – changes outside the normal value range

In November 2020, the patient was consulted by allergy and immunology specialists. The UAS7 and ACT scores were 14 and 9 points, respectively, confirming the diagnosis of a severe uncontrolled form of CSU. Allergic rhinitis moderate form in remission was identified as a comorbidity. CSU management included the second-line sgAHs, cetirizine 40 mg, which is 4 times the therapeutic dose commonly used for treatment. However, even with this increased dose of cetirizine, only partial control of clinical symptoms was achieved. The UAS7 score was 11–14 points, indicating the mild controlled form of the disease.

In April 2021, despite hives still present, the patient decided to complete vaccination against SARS-CoV-2 with Sputnik V. Vaccination did not exacerbate CSU symptoms, so the patient treatment plan remained unchanged.

Post-vaccination, anti-SARS-CoV-2 spike protein antibodies were detected using the SARS-CoV-2-CoronaPass ELISA kit (Genetico, Moscow, Russia) suggesting its efficacy. Fifteen months after the COVID-19 diagnosis, remission was still not achieved, and the patient continued second-line sgAHs therapy, including 4 times higher dose of cetirizine.

3 Case 2

Patient, female, 33 years old, was diagnosed with severe form CSU on September 3, 2020. Clinical laboratory analysis at the time of diagnosis is presented in Table 2.

Serum analysis demonstrated IgG antibodies to roundworms ascaris; however, adult helminths and eggs were

Table 2 SClinical laboratory results, case 2

test	Normal range	Case 1
Blood test results		
Hemoglobin (Hb) (g/L)	111 - 143	**134 г/л**
Erythrocytes (cells/L)	4.1 - 4.5 x10^{12}	**5.01 x10*12/л**
Hematocrit (Ht)	34 – 43%	**39.8 %**
Thrombocytes (cells/L)	217 - 343 x10^9	**282 x10*9/л**
Leukocytes (cells/L)	4.5 - 13.5 x10^9	**7.99 x10*9/л**
Neutrophils banded (%)	0-5	**0%**
Neutrophils segmented (%)	43 – 59	**63.6%**
Eosinophils (%)	1 – 5	**0.8%**
Basophils (%)	0 – 1	**0.1%**
Monocytes (%)	4 – 8	**7.1%**
Lymphocytes (%)	30 – 46	**28.4%**
ESR	2-15 mm/h	**4 mm/h**
ELISA analysis of anti-helminth and anti-protozoan antibodies		
Ab to opisthorchis (CP)	**<=0.85**	0.14
Ab to echinococcus	**<=0.85**	0.08
Ab to toxocara	**<1**	0.04
Ab to trichinella	**<=0.85**	0.1
Ab to Giardia Lamblia	**<0.85**	0.33
Ab to ascaris	**<0.85**	**1.47**
Feces analysis	Protozoan and Helminth eggs are not detected	Protozoan and Helminth eggs are not detected
CRP	**<6 mg/ml**	**<6 mg/ml**
C1 inhibitor, level	**23.41 mg/dl**	**34.8 mg/dl**
C1 inhibitor, functional activity	**70-130%**	**136%**
C4	**0.1-0.4 g/l**	**0.203 g/l**
IgE	**< 100 IU/ml**	**37 IU/ml**

ESR, erythrocyte sedimentation rate; *Ab*, antibody; *CP*, coefficient of positivity. Red color – changes outside the normal value range

not found in feces samples (Table 2). Serum level of IgE was within the normal range. Autological serum skin test and dermographism Fric тest were negative. Allergic reaction to any known allergens using ImmunoCAP ISAC test was not detected.

The diagnosis of severe CSU was based on the anamnesis, symptoms, laboratory results, and negative allergy test data. Patient was recommended restricted diet of histamine-liberating products. She was prescribed treatment with sgAHs regular dose (desloratadine; 5 mg/day), the first-line therapeutic. Patient was requested to maintain UAS7 diary.

During a follow-up visit, the UAS7 score was 23 points. Patient was prescribed sgAHs regular dose regiment. It was recommended to increase the doze of desloratadine (4×; 20 mg/day), indicating the switch to the second-line CSU therapeutic. Still, even with this high-dose treatment, the UAS7 score remained 14, which is elevated. Patient also presented with angioedema, which was treated with prednisolone (15 mg/day/7 days).

In November 2020, the patient was diagnosed with SARS-CoV-2 infection, which was confirmed by a positive PCR test. Mild form of COVID-19 was characterized by fever (38.5 °C; 5 days), cough, and anosmia. CT analysis revealed 15% lung damage. Anti-SARS-CoV-2 IgM and IgG antibodies were detected by ELISA. Patient was treated with ibuprofen, paracetamol, and ceftriaxone (500 mg × 2/day × 7 days) as well as vitamins C and D.

Following the COVID-19 diagnosis, the patient had exacerbation of CSU symptoms with UAS7 score 32–38 points, indicating severe form (Fig. 2). CSU symptoms were also accompanied with angioedema (Fig. 3) which was treated with 4 × dose of desloratadine (20 mg/day) and prednisolone (60 mg; 5 days). However, symptoms of CSU remained uncontrolled even after COVID-19 convalescence. Therefore, the patient was hospitalized and received omalizumab (300 mg/once every 28 days), the third-line treatment medicine for CSU. Five days later, symptoms were reduced. By the end of the month, the dose of desloratadine was reduced to 5 mg/day, while omalizumab was continued (300 mg subcutaneously every 4 weeks) for an additional 6 months. The patient was considering vaccination with Sputnik V; however, decision was made against vaccination because of the detectable level of SARS-CoV-2 IgM antibodies 7 months after COVID-19.

Overall, the patient received six injections of omalizumab (300 mg/subcutaneously every 4 weeks). However, symptoms reoccurred 2 months later after omalizumab therapy was stopped. Currently, omalizumab therapy (150 mg/once every 28 days) is continued and patient is in therapeutic remission.

Fig. 2 CSU skin lesions in patient 2. Wheals on the skin of leg

Fig. 3 Angioedema in patient 2. Regions of angioedema

Table 3 Characteristics of CSU and treatment before, during, and after COVID-19

Patient	Before COVID-19		SARS-CoV-2 results		During COVID-19		After COVID-19	
	UAS7/angioedema	Treatment	PCR	IgG	UAS7/angioedema	Treatment	UAS7/angioedema	Treatment
1	0/−	Cetirizine (10 mg)	−	+	23–28/−	Cetirizine (20 mg)	14/−	Cetirizine (40 mg)
2	18/+ or −	Desloratadine (20 mg)	+	+	32–38/+	Desloratadine (20 mg); prednisolone (40 mg); omalizumab (300 mg/week)	32–38/+	Desloratadine (5 mg); omalizumab (150 mg/week)

4 Discussion and Conclusions

SARS-CoV-2 infection was shown to be more severe in patients with comorbidities [21]. Therefore, it was suggested that allergic conditions could be one of those comorbidities exacerbating COVID-19 symptoms and leading to a severe form of the disease [22]. To understand the role of allergy in COVID-19 severity, the frequency of severe forms of the disease was analyzed in patients with asthma comorbidity [23]. Data collected show that the prevalence of asthma patients is similar between COVID-19 patients and the general population, suggesting that allergic condition is not a predisposition for SARS-CoV-2 infection [22, 24]. Severity of COVID-19 was not affected in patients diagnosed with atopic dermatitis (AD) [25], an inflammatory disease, in which pathogenesis is characterized by type I hypersensitivity reaction [26]. However, it appears that SARS-CoV-2 infection could exacerbate asthma symptoms, as it was shown by Ono et al. [27]. Also, similar to asthma, AD symptoms worsened during COVID-19 [28, 29]. Therefore, it could be suggested that although the allergic reaction may not be a predisposing factor for severe COVID-19, SARS-CoV-2 infection could exacerbate symptoms of an allergic reaction.

Our observation demonstrates that SARS-CoV-2 infection could abrupt the remission and worsen clinical symptoms in two CSU patients (Table 3). Both patients had controlled CSU symptoms before COVID-19. One patient was in remission. However, SARS-CoV-2 infection caused the relapse of symptoms that could not be controlled using a high dose of sgAHs, the second-line therapy. In one patient, only the use of omalizumab, the third-line CSU therapeutic, led to therapeutically controlled remission. Even these extraordinary measures still did not restore remission in one patient after the relapse. Our data corroborate previous findings where urticaria-like skin rash was also described in COVID-19 patients [30, 31]. Our case study further brings awareness of the worsening of CSU after SARS-CoV-2 infection and provides therapeutic measure options to control the disease symptoms.

The pathogenesis of CSU symptom exacerbation remains largely unknown. Histopathology study had found vacuolar interface dermatitis in the skin samples from SARS-CoV-2-infected CSU [32]. Also, superficial perivascular lymphocytic infiltrate was shown in urticarial eruption [33]. It was suggested that the "cytokine storm" could target the skin initiating local inflammation [34]. The local inflammation could attract and degranulate mast cells, playing a central role in the pathogenesis of CSU wheals [35]. The hypothesis of hyperactivation of mast cells in SARS-CoV-2-infected CSU patients is supported by reduction of symptoms after use of sgAHs and omalizumab in these patients. The therapeutic efficacy of omalizumab in CSU could be explained by the drug's ability to reduce IgE autoantibodies' activity and decrease coagulation abnormalities triggered by SARS-CoV-2 infection [36]. Also, the hypothesis of the "cytokine storm" role could explain the efficacy of corticosteroids in the management of inflammation symptoms in presented cases. Therefore, we believe that the use and the efficacy of the corticosteroids and omalizumab, the second- and third-line therapeutics, respectively, in SARS-CoV-2-infected CSU, could be based on control "cytokine storm" and mast cell activation.

We conclude that:

1. SARS-CoV-2 infection is generally mild form in CSU patients.
2. In contrast, SARS-CoV-2 infection exacerbates CSU symptoms. This could require modification of the disease management by switching to the second- and third-line CSU therapy.
3. The therapeutic efficacy of corticosteroids suggests the role of "cytokine storm" in pathogenesis of exacerbation of CSU symptoms in COVID-19.
4. It appears that SARS-CoV-2 vaccination with Sputnik V did not exacerbate CSU symptoms.

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