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COVID-19, severe asthma, and biologics

Coronavirus disease 2019 (COVID-19) is an acute respiratory syndrome that emerged in the city of Wuhan and rapidly spread throughout the world causing a global pandemic.[1] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as its causal agent.[1] Factors such as older age or presence of comorbidities are frequently identified as variables with a negative effect on patients' prognosis.[2] If we focus on the preexistent respiratory conditions, a higher risk of developing a severe infection has been reported in patients with chronic obstructive pulmonary disease.[3] However, there is controversial evidence regarding the prevalence of asthma in patients diagnosed as having COVID-19 (eTable 1) or the effect of asthma and its treatment on the clinical evolution of COVID-19.

We report 2 patients with severe asthma on treatment with benralizumab, an antieosinophil monoclonal antibody, who have been affected by COVID-19.

A 56-year-old woman who has been followed at our severe asthma unit for late-onset, severe, eosinophilic asthma with bronchiectasis without criteria for asthma–chronic obstructive lung disease overlap syndrome. Her asthma was controlled with high-dose ICS, long-acting β2-agonist, montelukast, ipratropium, and benralizumab. On March 8, 2020, she went to the emergency department owing to a 24-hour episode of fever, arthralgia, myalgia, dyspnea, and brownish expectoration. On physical examination, no wheezing was found. Complementary tests revealed a unilobar opacity in the right lung, a slightly increased C-reactive Protein and lactate dehydrogenase (Table 1), and a positive polymerase chain reaction result for SARS-CoV-2. A dose of levofloxacin 500 mg for 14 days and systemic corticosteroids (1 mg/kg) were administered owing to the brownish expectoration and history of bronchiectasis (lopinavir/ritonavir and hydroxychloroquine were not started according to the hospital's protocol, at that moment, because the patient did not have hypoxemia). The patient was discharged on the fourth day of admission owing to clinical stability, which was maintained without oral corticosteroids. After 1 week, the patient was asymptomatic. Notably, 4 of her relatives also received a diagnosis of COVID-19.

The other case is a 62-year-old man with severe eosinophilic asthma on treatment with benralizumab since July 2018. Previously, he had received treatment with omalizumab and mepolizumab, which were both discontinued because of poor response. As comorbidities, he had moderate obstructive sleep apnoea, chronic rhinosinusitis with nasal polyps, bronchiectasis, and obesity (body mass index of 33 kg/m^2). He did not fulfill the criteria of asthma–COPD overlap syndrome. On March 25, 2020, he experienced cough, fever, and darker and thicker expectoration than his usual, therefore he self-medicated with a dose of levofloxacin 500 mg for 3 days. Owing to a lack of improvement in symptoms, he was evaluated at a primary care where a chest X-ray examination was performed, which revealed peripheral and bilateral opacities, more evident in mid/lower lung areas, compatible with COVID-19 pneumonia (Fig 1); thus, he was referred to the emergency department. One of his relatives, who lived with him, had the same symptoms. Complementary test results revealed lymphopenia with increased levels of lactate dehydrogenase, C-reactive protein, D-dimers, and fibrinogen (Table 1) and a baseline partial pressure of oxygen of 59 mm Hg. The diagnosis of SARS-CoV-2 pneumonia was assumed considering the epidemic context, symptoms, radiologic and laboratory findings, and following the recommendations of the Spanish authorities at that moment. The patient requested his voluntary discharge. He was placed at home isolation and was monitored by his primary care physician. He was treated with a dose of azithromycin 500 mg (3 days), hydroxychloroquine 200 mg twice a day (5 days), and amoxicillin-clavulanic acid 875/125 mg (7 days). After 1 week, he had no symptoms, and he completed 14 days more of isolation.

Owing to the respiratory nature of COVID-19, it could have been reasonable to expect that patients with asthma, especially severe ones, could have a worse prognosis. However, both patients had a good response to the infection, which could provide some support to the recommendations made concerning COVID-19 and asthma that encourage the continuation of maintenance therapies in patients with asthma. For example, the recent 2020 Global Initiative for Asthma report recommends advising

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Disclosures: Dr. García-Moguel is a consultant, speaker, and researcher promoted by GlaxoSmithKline, AstraZeneca, Teva Pharmaceuticals, Mundipharma, Chiesi Farmaceutici S.p.A, Novartis, and Leti. Dr. Díaz Campos is a consultant, speaker, and researcher promoted by GlaxoSmithKline, AstraZeneca, Teva Pharmaceuticals, and Chiesi. Dr. Fernández Rodríguez is a consultant, speaker, and researcher promoted by Novartis and AstraZeneca. The remaining authors have no conflicts of interest to report.

Funding: The authors have no funding sources to report.

Table 1
Laboratory Data Reported at the Emergency Department

Laboratory data	Patient 1	Patient 2
Neutrophils	N (1.9 × 1000 cell/μL)	N (3.3 × 1000 cell/μL)
Lymphocytes	N (1.3 × 1000 cell/μL)	↓ (1.1 × 1000 cell/μL)
Eosinophils	N (0.0 × 1000 cell/μL)	N (0.0 × 1000 cell/μL)
Platelets	N (245 × 1000 cell/μL)	N (226 × 1000 cell/μL)
Hemoglobin	N (14.4 g/dL)	N (14.8 g/dL)
CRP	↑ (2.83 mg/dL)	↑ (26.19 mg/dL)
ALT	N (25 U/L)	N (28 U/L)
AST	↑ (30 U/L)	N (33 U/L)
CK	N (90 U/L)	NA
LDH	↑ (242 U/L)	↑ (266 U/L)
D-dimer	NA	N (367 ng/mL)
Ferritin	N (216 ng/mL)	NA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatinine kinase; CRP, C-reactive protein; N, normal; NA, not available; LDH, lactate dehydrogenase.

patients with asthma to continue taking their prescribed asthma medications.[4]

In our opinion, the treatment with benralizumab and the rest of the maintenance asthma medications may have had a protective effect on our patients. A recent consensus paper highlights the importance of maintaining asthma control in the context of this pandemic.[5] The same publication states that there is no evidence of an impaired immune response to this infection in patients with asthma on treatment with monoclonal antibodies.[5]

In contrast, a positive effect of ICS in the defense and against SARS-CoV-2 infection cannot be ruled out. Possible mechanisms have already been listed, such as the in vitro inhibition of the replication of SARS-CoV-2 by inhaled ciclesonide[6] and budesonide[7] and the reduction of expression of angiotensin-converting enzyme 2 receptor in atopic subjects utilized by protein S of the virus.[8] In addition, some reports describe the important role of macrophage infiltration in the deterioration of patients with COVID-19.[9] ICS, such as budesonide, suppress the synthesis of the granulocyte macrophage-colony stimulating factor.[10] The potential advantages of ICS do not apply to systemic corticosteroids; data reveal potential harm with increased time for viral clearance and no evidence of clinical benefit.[11]

Recent data have revealed that an important proportion of patients with COVID-19 developed eosinopenia during the infection, and it has been suggested that an increase in eosinophils might indicate a clinical improvement in this disease.[12] Because benralizumab has a cytotoxic effect on eosinophils mediated by the NK cells, it seems unlikely that an increase in eosinophils could have taken place in our patients, although we do not have the analytical data to confirm this fact. This suggests that the rise in eosinophil levels may not be necessary for a successful COVID-19 recovery.

To the best of our knowledge, this is the first report of patients with severe asthma and biologic treatment who have been affected by COVID-19. It would be necessary to have a higher number of cases and a deeper understanding of this viral infection to the potential relevance of asthma and its treatment with corticosteroids and biologics in the evolution of the infection. Despite these limitations, we believe that our data encourage the continuation of maintenance therapy and biologic treatment of patients with asthma in the context of this pandemic.

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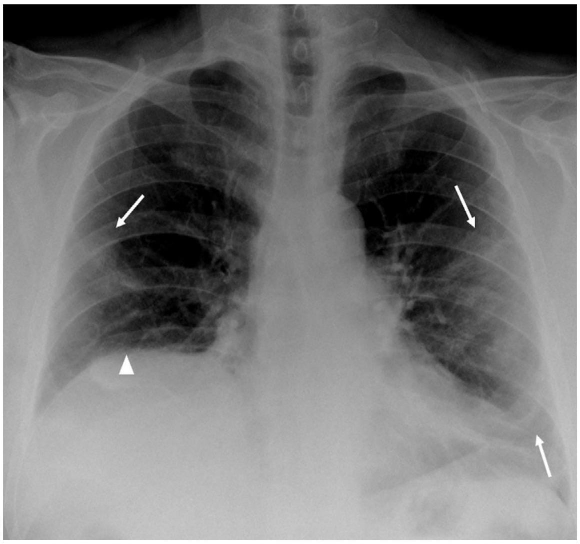

Figure 1. Peripheral parenchymal opacities in the middle and lower areas in both lungs, which is more extensive in the left lung (arrows). Elevation of the right hemidiaphragm (arrowhead).

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2020.06.012.

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Coronavirus disease 2019−associated urticaria with angioedema in a morbidly obese man successfully treated with glucocorticoids

The onset of severe urticaria has been linked to viral infections in both children and adults.[1] Here, we describe a patient who is a morbidly obese man, smoker, with severe refractory urticaria, angioedema, and systemic symptoms requiring oral glucocorticoids, and who was subsequently diagnosed as having coronavirus disease 2019 (COVID-19) and had a successful outcome. The patient was a 36-year-old obese man who presented with a complaint of acute urticaria (Fig 1). He woke up (day 0) with generalized erythema and pruritus with gradual onset of generalized urticaria (palms and soles included). He was seen in an emergency department (ED) and was prescribed methylprednisolone dose pack and an oral dose of diphenhydramine 50 mg twice daily. On day 6, he returned to the ED for a relapse of his symptoms and was continued on a dose of both oral prednisone 20 mg twice daily and oral diphenhydramine 50 mg twice daily; he was also started on a dose of oral cefdinir 500 mg 4 times daily. On day 9, he woke up with generalized erythema, pruritus, urticaria, and angioedema of his lips. When he arrived at the ED (within 20 minutes), he was experiencing dyspnea, cough, and wheezing. He was treated with nebulized albuterol, diphenhydramine, epinephrine, and famotidine, and was administered methylprednisolone intramuscularly and saline intravenously. He responded and was asymptomatic when discharged from the ED. He continued both oral prednisone 20 mg and oral diphenhydramine 50 mg, each twice daily, and stopped cefdinir.

He was seen in our clinic on day 11 and could not relate his urticaria to time, place, or action, but had experienced anosmia and ageusia the day before the visit. He had no other symptoms. His past medical, social, and family histories and review of systems were unremarkable except for a 15 pack-year smoking history (currently 2.5 packs/day). He had no history of asthma and worked as a door host at a bar.

Physical examination revealed an obese man (body mass index of 44) with normal vital signs and unremarkable examination findings other than slight erythema of the nasal mucosal membranes and scattered urticaria lesions on his torso. Complete blood cell count, serum tryptase, and COVID-19 tests were ordered. He was prescribed a dose of oral prednisone 20 mg twice daily and high dose of oral cetirizine. However, he continued oral diphenhydramine 50 mg twice daily instead. On day 13, his COVID-19 test result was reported to be positive. Complete blood cell count was within normal limits except for a white blood cell count of 13,100 cells/μL (reference range, 3.8-10.8 cells/μL) and absolute neutrophil count of 9419 cells/μL (reference range, 1500-7800 cells/μL), which was attributed to glucocorticoids. Serum tryptase level was 5.9 μg/L (reference range, $<$11 μg/L).

On day 16, his urticaria was controlled, and he had no other COVID-19 symptoms except for continued anosmia and ageusia. On day 18, he attempted to taper his dose of oral prednisone 20 mg to a single daily dose, and his urticaria had exacerbated. His smell and taste had returned. Both prednisone 20 mg and diphenhydramine 50 mg twice daily were continued. On day 22, he was asymptomatic, thus he began to taper his prednisone, started a dose of oral cetirizine 10 mg twice daily, and stopped diphenhydramine. His repeat COVID-19 test result was negative (day 20). He stopped all medications on day 27 and remained asymptomatic.

This patient had persistent refractory urticaria necessitating oral glucocorticoids for several weeks. He had no other clinical symptoms except for a mild systemic allergic reaction 9 days after the onset of urticaria. Such systemic symptoms have been reported in cases of severe urticaria.[2] He was morbidly obese and a heavy smoker, placing him at higher risk for severe COVID-19.[3] He was immediately and continually treated with oral glucocorticoids. We speculate that a cause-and-effect relationship may have existed, such that COVID-19 caused his severe urticaria and a systemic allergic reaction, including acute bronchospasm, which was the only time he ever experienced wheezing symptoms. Cutaneous manifestations of COVID-19 have been described in a cohort of 88 Italian patients, 20% of whom had cutaneous symptoms (3.4% had urticaria) but none as a presenting sign or symptom.[4] There was also a report of urticaria with facial angioedema on day 11 of a mild case of COVID-19, which resolved within 24 hours with high-dose antihistamine treatment. Glucocorticoids were not required, and the urticaria was not accompanied by any systemic signs or symptoms.[5]

Could systemic glucocorticoids be beneficial if started early at the onset of COVID-19? The very few retrospective studies evaluating glucocorticoid use in COVID-19 found mixed results and was only reported in severe cases.[6] The only prospective study, entitled Randomized Evaluation of COVID-19 Therapy, found that a dose of dexamethasone 6 mg daily used in patients hospitalized with COVID-19 was associated with decreased mortality among those on invasive mechanical ventilation or oxygen.[7] There was no benefit in mild to moderate cases not requiring supplemental oxygen. There are no reports of glucocorticoids being used from the beginning of COVID-19 for outpatients. Specifically, only dexamethasone and intravenous methylprednisolone have been used and only in hospitalized patients.[6]

Other than this case report, what could be the rationale for performing a controlled study evaluating the value of oral corticosteroids initiated as soon as COVID-19 was diagnosed? Triggers for asthma exacerbations include viral respiratory tract infections, and rhinovirus and respiratory syncytial virus are the most frequent viral triggers.[8] The treatment of choice for these asthma exacerbations include prednisone or its equivalent. This patient

Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.

eTable 1
Prevalence of Asthma Among Patients With Coronavirus Disease 2019

	Country	Total patients n	Asthma n (%)	COPD n (%)	Patient characteristics
Arentz et al[1]	US	21	2 (9.1)	7 (33.3)	Patients admitted to ICU
Bhatraju et al[2]	US	24	3 (14)	1 (4)	Patients admitted to ICU
Borobia et al[3]	Spain	2226 (460 deaths and 1766 live discharges)	115 (5.2) - 3.7% of deaths and 5.5% of live discharges	153 (6.9) -14.1% of deaths and 5.0% of live discharges	Admitted to hospital[b]
Garg et al[4]	US	160[a]	28 (17.5)	17 (10.6)	Hospitalized patients
Goyal et al[5]	US	393-130 requiring IMV	49 (12.5) - 13.1% of those requiring IMV	20 (5.1) - 5.4% of those requiring IMV	Admitted to hospital
Guan et al[6]	China	1590	0 (0)	24 (1.5)	Hospitalized patients with laboratory-confirmed COVID-19
Richardson et al[7]	US	5700	479 (9)	287 (5.4)	Admitted to hospital and with confirmed SARS-CoV-2 infection by PCR
Zhang et al[8]	China	140 (58 were severe)	0(0)	2 (1.4) (both were severe)	Hospitalized patients with laboratory-confirmed COVID-19

Abbreviations: COPD, chronic obstructive lung disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IMV, invasive mechanical ventilation; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]The full report refers to a higher number of patients, but comorbidities are only reported on these.
[b]Of the total number of patients, 75 were admitted to the ICU, and of those, 4 (5.3%) had asthma.

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