ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Case Report

Onset of Asthma After COVID-19 Pneumonia

Giovanna Ferrandu[1], Filippo Maria Di Flamminio[2], Antonio De Palma[2], Marta Mercati[2], Silvio Di Carlo[2], Antonella Spacone[3]* and Giustino Parruti[1]

[1]*Infectious Diseases Unit, Pescara General Hospital, Pescara, Italy*

[2]*Covid-Unit, Pescara General Hospital, Pescara, Italy*

[3]*Respiratory Medicine Unit, Pescara General Hospital, Pescara, Italy*

***Corresponding Author:** Antonella Spacone, Respiratory Medicine Unit, Pescara General Hospital, Pescara, Italy.

Received: November 30, 2020; **Published:** December 11, 2020

Abstract

Background: The current global Coronavirus disease (COVID-19) pandemic is characterized by an acute respiratory and systemic syndrome, related to infection by SARS-CoV2, the largest known positive-sense RNA virus, now considered a "superantigen" that may cause an abnormal adaptive immune response and "cytokine storm". So far, specific pathological pathways have been proposed, enabling such a massive immune activation to elicit latent diseases in genetically predisposed patients.

The susceptibility of asthmatic patients to common respiratory viruses has been well characterized in the recent medical literature. Respiratory virus infections account for up to 80% of acute exacerbations of asthma in children and half of such episodes are reported in adults. In contrast, the possible relationship between COVID19 pneumonia and asthma onset in genetically predisposed patients is yet unknown.

This case report describes a young patient who developed asthma after COVID-19 interstitial bilateral pneumonia. A 39-years-old female, non-smoker, without any underlying pneumological or autoimmune disorder, was diagnosed with COVID-19 pneumonia at our Center. She had no history of asthmatic episodes until hospital entry. She has, however, a homozygote twin sister suffering from atopic asthma.

Three months after resolution of acute COVID-19 pneumonia, persistent cough accompanied by dyspnea and wheezing were reported by the patient at her first follow-up visit. Her pulmonary function testing (PFT) showed mild obstruction, with a positive bronchodilator response, RAST test being positive for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae.*

This clinical case describes the asthmatic onset after Covid-19 infection and pinpoints the hypothesis that pathological immune anomalies induced by SarsCov-2 infection may elicit bronchial hyperreactivity in a genetically predisposed patient.

Keywords: *Covid-19; Asthma; SARS-CoV-2*

Introduction

The first cases of the coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), were reported in China in December 2019 [1], rapidly spreading all over the world in a global pandemic [2]. Coronaviruses (CoVs) are the largest known positive-sense RNA viruses and seriously impact human and animal health. The CoVs that infect

humans include low-pathogenicity CoVs (CoV-229E, CoV- NL63, CoV-OC43, and CoV-HKU1) usually causing mild to moderate illness and high-pathogenicity CoVs that can lead to severe, potentially lethal outcomes, as in the case of COVID-19 disease [3].

SARS-CoV-2 is the third epidemic that has been caused by a coronavirus, after those of severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS), started in 2012. COVID-19 rapidly spread throughout China and is currently outraging all over the world. Susceptibility to SARS-CoV2 infection is equally distributed over all age classes, but COVID-19 related disease primarily affects patients over 40 years of age, its mortality rate increasing in the presence of comorbidities, such as diabetes, metabolic syndrome and hypertensive cardiac disease [4], children being mostly asymptomatic carriers [5,6]. Symptoms of COVID-19 indeed vary among individuals, ranging from asymptomatic infection, which is anyhow frequent across all age classes, to acute, mild to severe and even critical respiratory failure, rarely accompanied by multiple organ failure at presentation [3]. Hyperactivated adaptive immunity and the consequent "cytokine storm" is at present the main potential pathological mechanism acknowledged for the rapid progression COVID-19 pneumonia and respiratory failure [7].

The median incubation period is estimated to be 5.1 days, with 97.5% of symptomatic infections becoming evident within 11.5 days after infection [8]. The most common symptoms include fever, cough, fatigue, slight dyspnea, sore throat, headache and conjunctivitis [9,10]. Gastrointestinal involvement has been reported in a significant proportion of cases, with diarrhea, nausea and vomiting lasting up to 1 week. The majority of individuals with symptoms and severe clinical patterns has one or more coexisting medical conditions, such as diabetes, metabolic syndrome, hypertension and cardiovascular disorders, more fatalities being reported among elderly and frail patients [11].

Asthma is a chronic inflammatory airway disease that is susceptible to triggering factors, such as aeroallergens, air pollutants, and viral infections, and a considerable global healthcare burden despite major advances in its prevention and management [12,13]. Theoretically, asthmatic patients should have increased susceptibility to and experience greater severity of SARS-CoV-2 infection due to a deficient antiviral immune responses and the tendency for exacerbation, elicited by common respiratory viruses. However, current evidence is against the expected prevalence of asthmatic individuals among COVID-19 patients. The prevalence of chronic respiratory disease (asthma and chronic obstructive pulmonary disease) among patients with SARS and COVID-19 pneumonia at disease onset appears to be lower than in the general population [12], suggesting that lung disease, patients' behavior or, more likely, their treatments may have some yet undocumented protective effect [13]. In particular, some aspects of the type 2 immune response, including type 2 cytokines (such as IL- 4 and IL-13) and the accumulation of eosinophils, might have protective effects against COVID-19 in asthmatic patients [12].

A major body of evidence accrued in recent weeks, indicating that, like in previous human coronavirus outbreaks, the main lifelong chronic lung damage after COVID-19 pneumonia may manifest as pulmonary fibrosis [14]. Virus-induced lung injury, immune responses as well as tissue healing mechanisms are central to fibrogenesis [15].

At variance with such mainstream findings, our experience suggests, for the first time to our best knowledge, that SARS-CoV2 infection and COVID-19 pneumonia may trigger asthmatic onset in genetically predisposed individuals.

Case Report

P.S. is a 39-years-old female, non-smoker, without any underlying pneumological or autoimmune disorder, reporting no history of asthmatic crisis or symptoms. She reported, however, many relatives with an asthmatic history in pediatric age: in particular, her homozygote twin sister suffers with an atopic form of allergic asthma.

In April, 2020, she was diagnosed with SARS-CoV2 infection. She was shortly after admitted to the Covid Unit of Pescara General Hospital due to cough, mild dyspnea and middle-grade fever, all lasting for some 5 days. On clinical examination, high fever and tachyarrhythmia

(cardiac frequency 110 b/min), without murmurs, rubs or gallops were evidenced. Pulse oximetry revealed a saturation of 91% breathing in room air, with mild tachypnea (25 breaths per minute); dullness to percussion over the right basal lung with decreased breath sounds over the same area, with crackles, completed the presenting picture. Laboratory tests demonstrated 3600/μL (4000 - 10000) leukocytes, C-reactive protein at 47 mg/L (0 - 5), D-dimer 5,0 mg/L (0,50) and IL-6 12 pg/ml (5.3-7.5); procalcitonin was in the normal range (<0.1 ng/mL). Serum electrolytes, renal and liver function tests were normal. Arterial blood gas analysis showed: PaO_2 55 mmHg, $PaCO_2$ 35 mmHg, pH 7.48 and SatO2 93%. High-resolution computed axial tomography (HRCT) detected a basal consolidation, with small ground-glass opacities bilaterally (Figure 1). The patient was treated with azithromycin 500 mg e.v, oxygen therapy and steroids (prednisone 40 mg bid). Her clinical condition improved, and after 20 days, her nasopharyngeal/oropharyngeal swabs were repeatedly negative. She was discharged in room air (PaO_2 102 mmHg $PaCO_2$ 43 mmHg pH 7.43) and instructed to continue steroid treatment for additional 10 days.

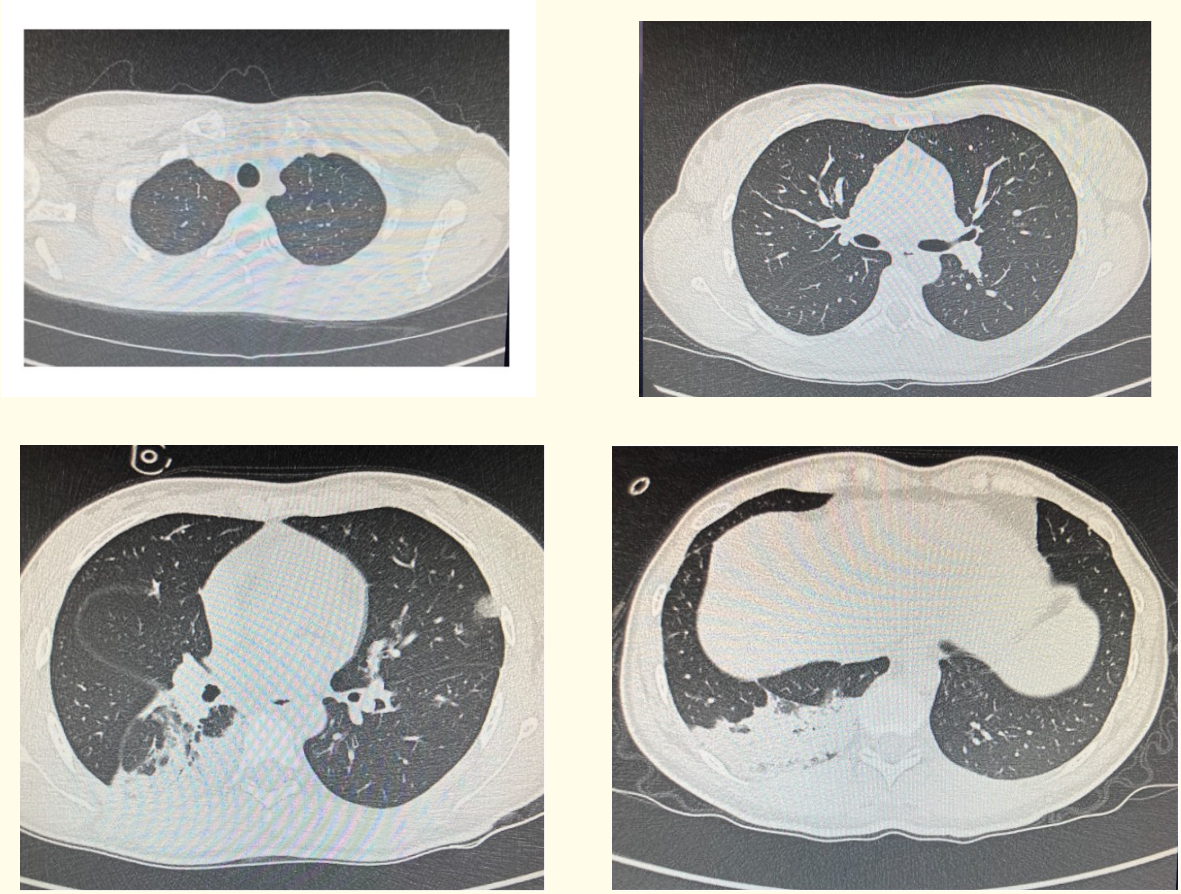


Figure 1: *Images of HRTC in acute SARS2*

At her first follow-up visit, 3-months after discharge, the patient reported a "sense of heaviness of the breath", cough, and occasional wheezing at night. Control HRCT (Figure 2) and echocardiography were normal.

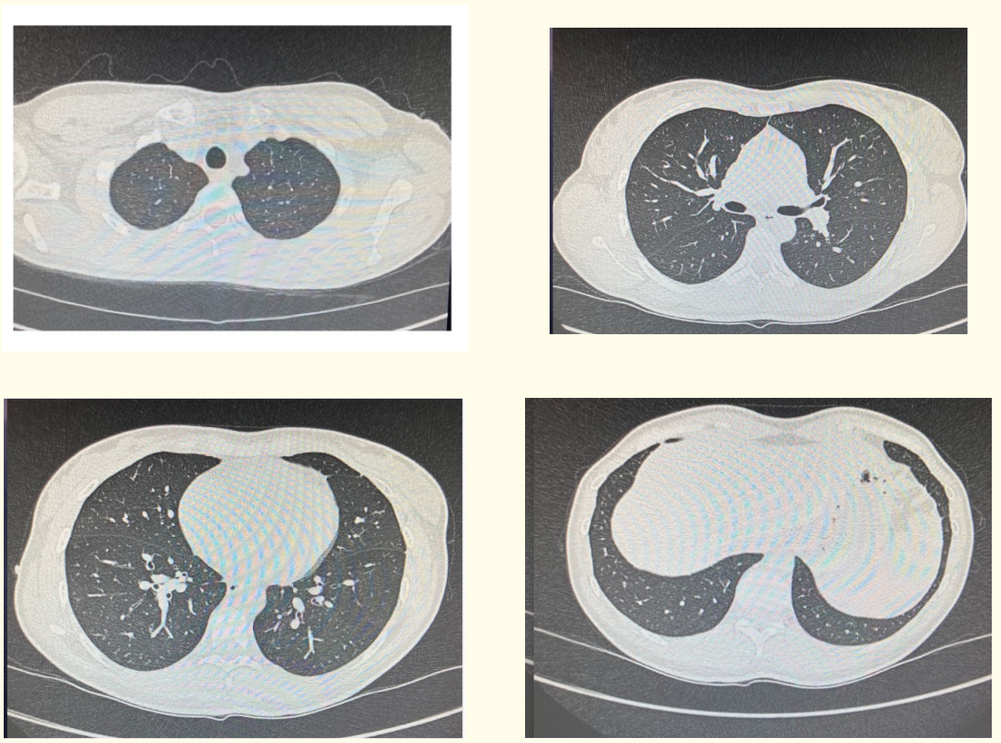
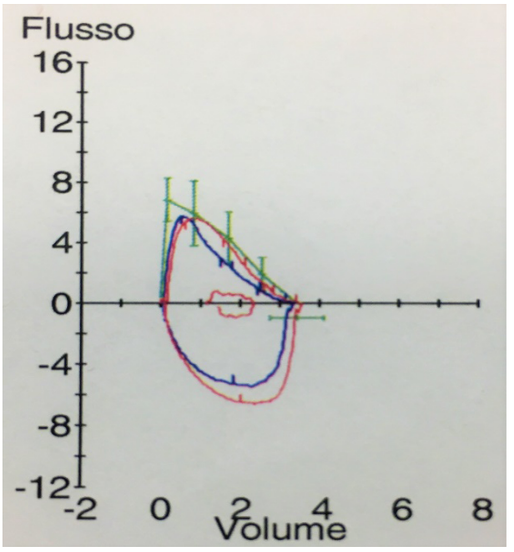
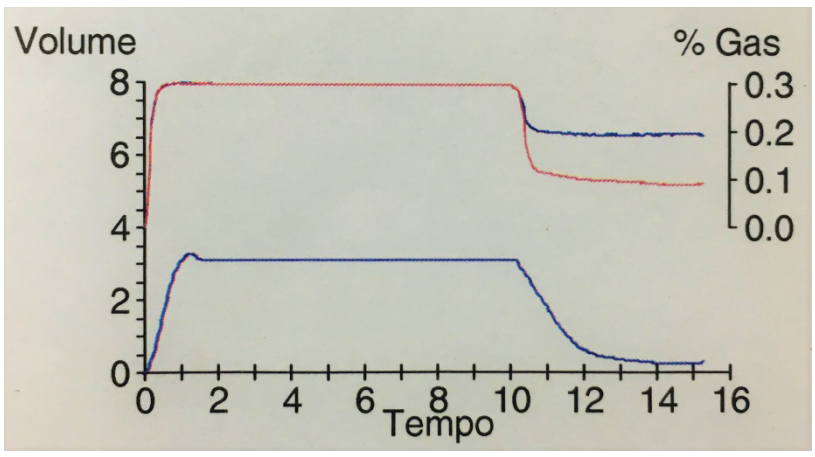


Figure 2: *Images of HRTC at follow up*

Her PFT results are reported in table 1, showing a forced vital capacity (FVC) of 3.62 lt - 97% predicted, a forced expiratory volume 1s (FEV1) of 2.51lt - 87% predicted, with positive bronchodilator response and normal carbon monoxide diffusing capacity. The patient was subjected to RAST (serum-specific IgE), with evidence of reactivity for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* Table 1.

Pulmonary Function Test			**Spirometry + Diffusion Lung Co**				
							
SPYROMETRY							
Volumes			Pre Administration Of Salbutamole 400 Mcg		Post Administration Of Salbutamole 400 Mcg		Post (%) Change
	UoM	*Ref.*	*Meas.*	*% Ref.*	*Meas.*	*% Ref*	*%*
FVC	Lt	3,45	3,62	97	3,54	103	3
FEV1	Lt	2,98	2,51	86	2,90	97	+15
FEV1/FVC	%	82	69	93	82	100	13

FEF25-75%	Lt/sec	3,67	2,13	58	2,87	78	35
FEF 50%	Lt/sec	4,25	2,77	65	4,11	97	48
FEF 75%	Lt/sec	1,88	0,95	50	1,33	71	40
PEF	Lt/sec	6,85	5,78	84	7,15	104	24



	UoM	*Ref.*	*Pre Meas.*	*Pre % Ref.*
DLco	mmol/ kPa*- min	8,9	7,3	82

Lymphocyte subsets, gamma globulines, inflammation indexes upon admission and follow up are reported in table 2. Total IgE were 47 U/ml (cutoff 100 U/l). She started regular home treatment with bronchodilators and inhaled corticosteroid medications, reporting rapid benefit at her next follow-up visit.

	SARS-Cov2 INFECTION			**FOLLOW UP**			***RANGE***
Immune System	A*	B*	C*	1° CHECK	2° CHECK	3° CHECK	*According to our laboratory std.*
Neutrophils (%)	70,7	87,7	37,1	55,7	55,9	87,3	40-60%
Neutrophils (10^3 /Lt)	3,9	8,3	1,6	2,9	3,4	12,7	1,4 – 6,5
Lymphocytes (%)	28,7	5,1	43,4	31,0	31,2	6,8	22-44%
Lymphocytes (10^3 /Lt)	1,0	0,5	1,9	1,6	1,9	1,0	1,2 – 3,4
Monocytes (%)	8,8	14,2	13,5	12,1	8,8	5,2	3-9%
Monocytes (10^3 /Lt)	0,48	0,5	0,6	0,5	0,5	0,8	0,18 – 1,35
Eosinophils (%)	0,5	6,3	4,7	4,1	3,7	0,4	<5%
Eosinophils (10^3 /Lt)	0,03	0,2	0,2	0,1	0,2	0,1	0,0 – 0,7
Basophils (%)	0,01	0,00	0,10	0,00	0,00	0,00	<2%
Basophils (10^3 /Lt)	0,05	0,00	0,10	0,10	0,00	0,00	0,0 – 0,1
Inflammation indexes							
CRP (mg/Lt)	0,1	126,96	0,52	0,53	1,05	1,22	0 - 5
PCT (ng/mLt)	0,45	<0,02	<0,02	<0,02	<0,02	<0,02	<0,02
IL-6 (pg/mLt)	19,89			0,92			5,3 - 7,5
Lymphocyte subsets							
#CD3 (%) CD	844 (79,05)			1015 (80,11)			55 - 80
#CD4 (%) CD8(%)	531 (49,63)			567 (44,67)			35 - 55
#CD8 (%)	272 (25,38)			397 (31,26)			20 - 30
#CD16 (%)CD	141 (13,23)			128 (10,12)			1 - 20
#CD19 (%)	44 (4,17)			81 (6,39)			5 - 15
#CD4/CD8 [ratio]	1,96			1,43			1,4 - 2,0
*A= “pre-admission”; B=”at the admission”; C=”at discharge”							

Table 2: *Main immune parameters, inflammation indexes and lymphocyte subsets upon admission and follow up.*

Discussion

Respiratory virus infections account for up to 80% of acute exacerbations of asthma in children, half of such episodes being reported in adults [15,16]. Despite increased evidence that viral infections are involved in asthma exacerbations, it is less clear which viruses (adenovirus, common coronaviruses, bocaviruses, influenza, rhinoviruses) are involved and the extent to which they individually contribute to asthma exacerbations [17].

Message., *et al.* showed that, in response to RV infection, asthmatic individuals display increased clinical severity, impaired lung function, bronchial hyperreactivity, and eosinophilic inflammation, which all affect virologic and clinical outcomes, possibly related to augmented Th2 or impaired Th1 and/or IL-10 responses [18].

CoVs are detected at a mean prevalence of 8.4% in asthma exacerbations [19]. Notably, there are no reports on asthma exacerbations due to COVID-19, whereas a few reports on asthma exacerbations during the SARS and MERS epidemics appeared [18]. Many studies have shown a low prevalence of asthma in SARS-Cov patients; Morais-Almeida., *et al.* found that angiotensin-converting enzyme (ACE2) and transmembrane protease serine 2 (TMPRSS2) are SARS-Cov2 receptors. A recent report from the USA and the UK, however, noted that asthma may be common in children and in adults with mild to severe COVID-19 [19].

The low prevalence of COVID-19 in allergic patients with asthma could be due to reduction in ACE2 gene expression. Moreover, patients infected by SARS-CoV-2 frequently show reduced blood eosinophil counts at presentation [20]. Blood eosinophil levels are a well-known predictor of airway T2 inflammation [21], and measurements of blood eosinophil levels can be used as an accessible proxy to examine the association between airway T2 inflammation and COVID-19 outcomes. These findings may partly explain the low rates of asthma exacerbations or onset [21].

In such a scenario, we describe a patient without any underlying pneumological or autoimmune disorder, with familiarity for asthma and no history of past asthmatic crisis. Three months after suffering COVID-19 pneumonia, she developed a clinical picture compatible with asthma. This diagnosis was confirmed by PFT. Allergic tests showed a condition of allergic asthma, with normal levels of IgE; during Sars-Cov pneumonia, IgE levels were 47 U/mL, once more in the normal range [n.v 0-402 U/ml].

Usually the onset of asthma occurs after inflammatory postviral inflammation. After SARS-CoV-2 enters the host cell, activation of the innate immune system may lead to the early release of proinflammatory cytokines (IL-6, TNF-α). In patients with predisposing risk factors, the adaptive immune response may be heavily triggered, so that antigen-presenting cells (APCs), including dendritic cells present CoV antigen to T cells, eliciting the differentiation of Th0 cells into the Th1, Th2, and Th17 subsets, are activated [21]. If adaptive immune responses are insufficient to eliminate the virus, innate immune responses are likely to be retriggered, which can lead to dysregulated release of proinflammatory cytokines, a potential pathological mechanism for rapid progression of this disease. This pathological mechanism is inhibited by T-reg cells and type 2 cytokines (IL-4, IL-5, IL-13). T reg cells also inhibit Th2 cells and decrease the levels of type 2 cytokines too. In COVID-19, the level of T reg cells in pneumonia is decreased. In our case Treg cells levels also fell, based on CD4 level (44% of lymphocytes subsets). The temporary low inhibition of Th2 and the increase in type 2 cytokines could explain the onset of asthma after environmental allergens are taken up by dendritic cells and presented to Th0 cells. In asthma, Th0 cells differentiate into Th2 subsets and produce Type 2 cytokines (IL-4, IL-5, IL-13). Epithelium-derived IL-33, IL-25, and TSLP (thymic stromal lymphopoietin) also contribute to the accumulation of type 2 cytokines by stimulating ILC2, and possibly acting on DCs. These processes lead to type 2 immune responses, causing pathophysiological changes of asthma, including IgE production, local eosinophilia, mucus production, and activation of effector cells, such as eosinophils, basophils, and mast cells.

Conclusion

This case raises the possibility that, as in other viral infections, the asthmatic inflammatory state may worsen after exposure to SARS-COV2. In genetically predisposed subjects, prolonged CD4+ lymphopenia, frequent in SARS-CoV2 infection, might activate the same pathological pathways in cell-mediated immunity as in asthma. However, these phenomena and their causative mechanisms require further studies in new-onset asthma in predisposed persons who contracted SARS-COV2.

Acknowledgments

None.

Conflict of Interests

All authors declare that they have no competing interests.

Bibliography

1. Li Q., *et al.* "Early transmission dynamics in Wuhan, China, of novel Coronavirus-infected pneumonia". *New England Journal of Medicine* 382.12 (2020): 1199-1207.
2. Morens DM., *et al.* "Pandemic COVID-19 joins history's pandemic legion". *mBIO* 11.3 (2020): e00812-20.
3. Liu S., *et al.* "COVID-19 and asthma: reflection during the pandemic". *Clinical Reviews in Allergy and Immunology* 59 (2020): 78-88.
4. Wang T., *et al.* "Comorbidities and multi-organ injuries in the treatment of COVID-19". *Lancet* 21.395 (2020): e52.
5. Davenne E., *et al.* "Coronavirus and COVID-19: focus on a galloping pandemic". *Revue Medicale Liege* 75.4 (2020): 218-225.
6. Yang Y., *et al.* "The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China". *Review Journal of Autoimmunology* 109.3 (2020): 1-16.
7. Qing Y., *et al.* "The pathogenesis and treatment of the `Cytokine Storm' in COVID-19". *Journal of Infectious* 80. 6 (2020): 607-613.
8. He F., *et al.* "Coronavirus disease 2019 (COVID-19): What we know?" *Journal Medical Virology* 92.7 (2020):719-725.
9. Chen N., *et al.* "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". *The Lancet* 395 (2020): 507-513.
10. Yang X., *et al.* "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study". *Lancet Respiratory Medicine* 8 (2020): 475-481.
11. Yang J., *et al.* "Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis". *International Journal of Infectious Diseases* 94.5 (2020): 91-95.
12. Halpin DMG., *et al.* "Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective". *The European Respiratory Journal* 55.4 (2020): 2001009.
13. Rajan S., *et al.* "The global initiative for asthma guidelines: change in the recommendation for the management of mild asthma based on the SYGMA-2 trial - A critical appraisal". *Lung India* 37.2 (2019): 169-173.

14. Gu J., *et al.* "Pathology and pathogenesis of severe acute respiratory syndrome". *American Journal of Pathology* 170.4 (2007): 1136-1147.

15. Tse G., *et al.* "Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS)". *Journal of Clinical Pathology* 57.3 (2004): 260-265.

16. Johnston SL., *et al.* "Community study of role of viral infections in exacerbations of asthma in 9-11 year old children". *British Medical Journal* 310.6989 (1995): 1225-1229.

17. Nicholson KG., *et al.* "Respiratory viruses and exacerbations of asthma in adults". *British Medical Journal* 307.6910 (1993): 982-986.

18. Message SD., *et al.* "Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production". *Proceedings of the National Academy of Sciences* 105.36 (2008):13562-13567.

19. Zheng X-y., *et al.* "Regional, age and respiratory-secretion-specific prevalence of respiratory viruses as- sociated with asthma exacerbation: a literature review". *Achieves of Virology* 163.4 (2018): 845-853.

20. Van Bever HP., *et al.* "Childhood severe acute respiratory syndrome, coronavirus infections and asthma". *Pediatric Allergy and Immunology* 15.3 (2004): 206-209.

21. Morais-Almeida M., *et al.* "Asthma and the coronavirus disease 2019 pandemic: a literature review". *International of Archives of allergy and Immunology* 181 (2020): 680-688.

Volume 10 Issue 1 January 2021