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COVID, Obstructive Airway Diseases and Eosinophils

A complex interplay

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Introduction:

Eosinopenia is associated with a high risk of serious disease during infection with the severe acute respiratory syndrome coronavirus 2, the causative agent of COVID-19. Persistent eosinopenia correlates with low rates of recovery, while the resolution of eosinopenia predicts improvement.[1] Eosinophils have an important role in the pathogenesis of chronic respiratory diseases such as asthma and COPD. In COPD, eosinopenia is associated with poorer patient outcomes and short-term readmission after discharge.[2] Eosinophils also play a key role in allergic diseases, including asthma. Moreover, many patients with asthma can have intentionally induced eosinopenia by biological drugs. In addition, persistent peripheral eosinopenia indicates a poor survival in sepsis.[3] In this context, the role of eosinophils remains a puzzle in COVID-19 especially in those with severe disease or in those with an associated obstructive lung disease. It is unclear if they directly play a pathobiological role in sepsis and lung injury or whether they are just sentinel cells that are harbingers of danger.

The incidence of eosinopenia in COVID-19 patients varies from 50.8% to 94%.[3–5] A lower prevalence of 26.93% was noted in a study from Spain, possibly due to a large sample size and a

pollen season study period.[6] Eosinopenia on admission is associated with a higher risk of severe disease and intensive care unit admissions. Yan et al noted that eosinophil levels were significantly low in COVID-19 patients with critical disease and the eosinophil counts remained low or progressively declined in those with fatal outcomes.[7] Similarly in another study, maximum reduction in eosinophils was observed on the 4th day from onset and these patients with low counts were more likely to have fever, fatigue, dyspnea and worse lesions in CT scan than those with normal counts.[8] Peripheral eosinophil counts typically return to near normal levels as patients recover from moderate-to-severe infection suggesting that normalization of the blood eosinophil count indicates recovery.[9] Low eosinophil counts, on admission was found to improve continuously reaching significantly higher levels in survivors than non survivors with a greater increase indicating a better outcome.[10] Surprisingly, the prognostic utility of peripheral eosinophil counts varied with patient race and ethnicity.[11] In contrast, increased levels of eosinophils were noted among patients with severe COVID-19 in a large cohort. But, this observation cannot be generalized as they used a different technique and counted low density eosinophils.[12] Thus, the current evidence suggests a protective role for eosinophils on mortality and length of hospital stay in patients with COVID-19.

There is mixed evidence regarding the prevalence of asthma in patients with COVID-19 or the effect of asthma and its treatment on the progression of the disease.[13] Theoretically, patients with asthma could be at a higher risk considering their increased susceptibility to common respiratory virus-associated exacerbations. The prevalence of asthma was markedly lower among those diagnosed with COVID-19 compared to the population of Wuhan (China) at large.[14] In a group of 140 hospitalized patients from Wuhan, no cases of asthma and allergic rhinitis were reported while the prevalence of asthma and allergic rhinitis in the province was 4.2% and 9.7% respectively.[5] A low incidence of 2.1% was noted in severe asthma patients from Belgium and none of them had a severe course or death.[15] Similarly low incidence was reported from Italy, Russia and Australia.[16] However, contradictory data were reported from Germany and the United States, where higher asthma prevalence was noted among patients with COVID-19.[16] Though asthma was not a risk factor for poor prognosis, higher mortality was observed among those who had experienced an acute exacerbation in the previous year.[17] Since eosinopenia is a biomarker for the severity of COVID-19, the eosinophil reduction/depletion induced by anti-IL5 and anti-

IL5 receptor blocking monoclonal antibodies raises a real concern. However, reports on the safety of patients using the monoclonal antibodies for asthma or atopic dermatitis are reassuring.[14,15,18] A study from Spain on 545 patients receiving different biologics for severe asthma found no increased risk, no greater disease severity or higher mortality.[18] A large study on asthmatics with infection confirmed by PCR did not find anti-IL5 biologics to increase the risk of infection or worsen outcomes. In contrast, systemic corticosteroids were an independent risk factor for worst COVID-19 severity and all-cause mortality.[19] Nevertheless, there is clear evidence that asthma presents a lesser risk for developing severe COVID-19 and the current medications, including inhaled corticosteroids and biologics remain safe for use.[9,15,18]

Available data definitely suggests a higher risk for severe COVID-19 in COPD patients. An early case series on COVID-19 from China reported a higher prevalence of COPD in patients with severe presentation and worse outcomes.[20] A meta-analysis of studies in Chinese and English languages showed that the pre-existing COPD has a fourfold higher risk of developing severe COVID-19.[21] The prevalence of COPD on hospitalized COVID patients ranges from 0 to 10% in China, 2.4 to 14% in New York City and 5.6 to 9.2% in Italy.[22] In COPD, higher blood eosinophil counts predict a positive response to corticosteroid and eosinopenia is associated with worsening of symptoms and severity of exacerbations.[2]

Eosinophils remain in the blood only for about 8 to 12 hours before they migrate into tissues, where they are active for several days.[9] They have potent pro-inflammatory effects and participate in inflammation, immunoregulation and host defense against many diseases including viral infections.[4] Proliferation, development and activation of eosinophils are controlled by IL-5, IL-3 and GM-CSF.[23] The immune mechanism of eosinopenia in COVID-19 remains unclear. It is likely to be multifactorial, involving inhibition of the main steps in the eosinophil life cycle, apoptosis induced by type 1 IFN during acute infection, or association with eosinophil consumption by their antiviral actions.[1,24] It is also unclear if it is indeed eosinopenia that leads to poor outcomes or eosinopenia is a manifestation of impaired GM-CSF signaling or IL-33 secretion or the diminished expression of its receptor ST2 in the airway epithelium.[25] Thus, eosinopenia could be either the sign of host exhaustion trying to clear COVID-19 virus or a primary risk factor for a severe infection.[24,26] It is not clear whether SARS-COV-2 could involve

the bone marrow and cause the decrease of peripheral blood eosinophils. Nevertheless, increased production of neutrophils in bone marrow leading to a reduction in eosinophil production was also reported.[8,27] Again, it is not clear whether eosinopenia is the result of direct virus targeting or the result of generally impaired immunity.[14]

Considering the anti-viral effects of eosinophils, the reported eosinopenia in COVID-19 patients is of special interest.[28] Studies have indicated a potential role of eosinophils in promoting viral clearance and antiviral host defense. Respiratory virus infections are associated with asthma exacerbations in children and adults, among which Rhino virus is the most common agent.[14] Asthma was identified as the single most common comorbid condition among hospitalized individuals with H1N1 infection, with rates of asthma ranging from 10% to 32%.[29] Interestingly, there are no reports regarding asthma exacerbation due to COVID-19. There were only a few reports on asthma exacerbations during the SARS and MERS epidemics as well. Though biologic agents that induce eosinopenia reduce asthma exacerbations, these patients have not been reported to have increased viral infections.[1] In fact, a large population-based cohort study showed that patients with nonallergic asthma had a higher risk of severe COVID-19 when compared with allergic asthma.[30] Eosinophils in the respiratory tract might represent a ‘‘double-edged sword,’’ promoting antiviral responses on one side or results in an exaggerated host response leading to tissue damage.[9]

This lack of susceptibility to COVID-19 in patients with pre-existing asthma and allergic airway disease appears in contrast with the established link between these chronic respiratory conditions and susceptibility to common respiratory viruses, especially rhinoviruses.[6] However, rhinovirus uses the ICAM-1 molecule as an entrance into respiratory epithelial cells, which is overexpressed in allergic airways. In contrast, corona virus uses another host cell receptor, the angiotensin-converting enzyme2 (ACE2). Expression of ACE2 is increased in patients with COPD, diabetes mellitus and hypertensives on ACE inhibitors explaining their higher risk of developing COVID-19. On the other hand, lower expression of ACE has been noted in the airways of asthmatic patients which obviously reduce the chances of a COVID infection. Moreover, inhaled steroids can down regulate ACE2 receptors, suppress cytokine production and coronavirus replication.[31] The use of inhaled corticosteroids was found to be associated with a decreased level of ACE2

and transmembrane protease serine 2 gene expression from sputum in asthmatic patients.[32] An inhaled steroid, Ciclesonide, reduced the SARS-CoV-2 RNA replication as well as host inflammation in the lungs in in-vitro studies.[33]

In summary, eosinopenia that might also represent a low T2 immune status is associated with poor outcomes in asthma and possibly in non-asthmatic COPD. However, it is unclear if the eosinophils are directly contributing or not to the pathobiology of SARS-CoV2 lung injury. There is even less clarity around the role of lung eosinophils as this has not been extensively investigated. Eosinophils are unlikely to be directly involved in lung injury as the use of anti-eosinophil biologics has not been associated with poor outcomes in asthma patients with COVID-19. Eosinophil numbers in peripheral blood are therefore likely to be just a biomarker of the biological activity of Th2 cytokines. There is very little information on their numbers or activity in the airways in patients with COVID-19. The general consensus is to continue to manage airway diseases, both asthma and COPD, as per current guidelines with appropriate use of corticosteroids and bronchodilators, and judicious use of biologics as indicated.

Authors' Contributions

JB conceptualized and wrote the initial manuscript draft. JB and PN contributed to the literature review. PN did the critical review and both the authors approved the final version of the manuscript.

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