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REVIEW

Eosinophils and COVID-19: diagnosis, prognosis, and vaccination strategies

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Abstract

The unprecedented impact of the coronavirus disease 2019 (COVID-19) pandemic has resulted in global challenges to our health-care systems and our economic security. As such, there has been significant research into all aspects of the disease, including diagnostic biomarkers, associated risk factors, and strategies that might be used for its treatment and prevention. Toward this end, eosinopenia has been identified as one of many factors that might facilitate the diagnosis and prognosis of severe COVID-19. However, this finding is neither definitive nor pathognomonic for COVID-19. While eosinophil-associated conditions have been misdiagnosed as COVID-19 and others are among its reported complications, patients with pre-existing eosinophil-associated disorders (e.g., asthma, eosinophilic gastrointestinal disorders) do not appear to be at increased risk for severe disease; interestingly, several recent studies suggest that a diagnosis of asthma may be associated with some degree of protection. Finally, although vaccine-associated aberrant inflammatory responses, including eosinophil accumulation in the respiratory tract, were observed in preclinical immunization studies targeting the related SARS-CoV and MERS-CoV pathogens, no similar complications have been reported clinically in response to the widespread dissemination of either of the two encapsulated mRNA-based vaccines for COVID-19.

Keywords Respiratory tract; Granulocytes; SARS-CoV-2; Inflammation; Vaccination; Asthma; Interferon (IFN)γ

Introduction

First identified in 1879 by Paul Ehrlich [1], eosinophils are a small subset of granulocytes that represent a relatively small fraction of the pool of the circulating leukocytes under homeostatic conditions. Eosinophils develop from pluripotent progenitor cells in the bone marrow that differentiate under the control of various cytokines, including interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor, and undergo development from committed progenitors in response to transcriptional signals from PU.1 as well as the c/EBP and GATA families of transcription factors [2]. Once released into circulation, eosinophils ultimately migrate to tissues, both at homeostasis and in association with numerous disease processes, most notably parasitic infestation and allergy [3–6]. While the Th2 cytokine, IL-5, is best known for its role in promoting eosinophil differentiation and activation, eosinophils can be generated and maintained at low levels in circulation and tissues in the absence of this mediator [7].

The properties and essential functions of eosinophils remain poorly understood. The profound degree of eosinophilia observed in response to Th2 cytokine–mediated diseases, notably that associated with allergies and parasitic infection, prompted an initial focus on the roles and properties of eosinophils in these settings. Based on the results from these earliest studies, eosinophils were perceived as end-stage effectors capable of delivering largely cytotoxic mediators to promote host defense, often associated with collateral damage and tissue dysfunction. In recent years, a more nuanced view of eosinophils has emerged, largely due to the results of studies focused on resident homeostatic populations [5, 8, 9], cell type–specific heterogeneity [10–12], and eosinophil functions that are not directly linked to classical Th2 responses [9,

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13–15]. These findings build directly on principles initially outlined by Lee et al. [16] in the "LIAR" hypothesis, in which local immunity and tissue remodeling were presented as unifying features of eosinophil function.

To this end, several groups have explored the role of eosinophils in the setting of acute virus infection [17, 18]. Studies in mouse models revealed that eosinophils can promote host defense in experiments involving *Sendai virus*, human immunodeficiency virus, influenza virus, respiratory syncytial virus (RSV), and the RSV-related pathogen, pneumonia virus of mice [19–27]. Among these findings, Adamko et al. [25] reported eosinophil-mediated antiviral activities in guinea pigs sensitized to ovalbumin prior to infection with parainfluenza virus. Drake et al. [21] identified nitric oxide production as a critical mechanism underlying eosinophil-mediated reductions in viral burden. Likewise, Phipps et al. [19] reported an eosinophil-mediated clearance of RSV from the airways of hypereosinophilic mice mediated by the TLR7-MyD88 signaling axis, and Sabogal Pineros et al. [26] found that eosinophils could internalize and inactivate both RSV and influenza via a mechanism that was defective in cells isolated from patients with asthma. Likewise, Percopo et al. [20] reported that cytokine-activated eosinophils provided profound protection against the lethal sequelae of infection with PVM. Most recently, Samarasinghe et al. [27] found that adoptive transfer of eosinophils from allergen sensitized and challenged mice resulted in diminished virus replication and morbidity in recipient mice infected with influenza. However, the critical underlying mechanism, i.e., whether eosinophils promote direct broad-spectrum antiviral activity or (as per the LIAR hypothesis) serve to activate and regulate local immunity at sites of viral infection, remains undetermined.

In the sections to follow, we will review the current literature that links the circulating and tissue eosinophils with the diagnosis, pathogenesis, and vaccine strategies used to combat coronavirus disease 2019 (COVID-19), the multi-system disease that results from acute infection with the coronavirus pathogen, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; Table 1). The reader is referred to the many excellent reviews of this pathogen and the pandemic at large for additional insight into coronavirus biology and disease pathogenesis [28–32]. Likewise, several related reviews provide an in-depth focus on the topics covered in this review [33–38].

Eosinopenia and the role of eosinophils in COVID-19

Diagnosing eosinopenia

Mature human eosinophils are released from the bone marrow and circulate in the peripheral blood for a period of 1–2 days before they migrate into the tissues. Eosinophil counts are determined via a standard Wright–Giemsa-stained leukocyte differential either visually or by automated instruments that detect their unique staining properties, including a bilobed nucleus and large red-staining granules within the cytoplasm. At homeostasis, eosinophils represent a minor population of the circulating leukocytes. The US National Institutes of Health Clinical Center Laboratory normal range for blood eosinophils is 40–360 cells per microliter or 0.7–5.8% of the total circulating leukocyte population. Clinical eosinophilia, the term used to describe elevated eosinophil counts in peripheral circulation, has been defined as > 500 eosinophils per microliter of blood. By contrast, eosinopenia may be somewhat more difficult to recognize. Although the formal definition of eosinopenia is < 10 eosinophils per microliter of blood [39], some clinical laboratories score eosinophil counts of "0" as within normal limits.

Of critical note, eosinopenia is not pathognomonic for any disorder or clinical state. Many clinical conditions (including severe infection with the pandemic SARS-CoV-2 pathogen, as discussed in the section to follow) have been associated with clinical eosinopenia, including a wide variety of acute bacterial and virus infections, chronic obstructive pulmonary disease, burn injuries, and alcoholism [40–43].

Eosinopenia and the diagnosis and prognosis of SARS-CoV-2 infection

There are now numerous reports that document eosinopenia in patients that present with moderate-to-severe COVID-19 [44–52]. Eosinopenia is not an isolated finding in any of these cases and is typically accompanied by reductions in peripheral lymphocyte, platelet, and monocyte counts, as well as elevated levels of C-reactive protein and IL-6. While not all of these reports document eosinopenia that falls within the formal definition of this condition (as above, < 10 per microliter of blood), eosinophil counts have been included in several algorithms used to predict disease severity. Collectively, the results from these studies document eosinopenia as a presenting sign of SARS-CoV-2 and report an association between eosinopenia and disease severity. Ma et al. [53] introduced a risk stratification score (COVID-19-REAL) based on both clinical and hematologic factors and included eosinophils at < 5 per microliter among the criteria used to identify patients who are likely to be presenting with COVID-19. Similarly, Tordjman et al. [54] introduced the PARIS score, in which presenting eosinophil counts < 60 per microliter were among several hematologic parameters included in an algorithm used to predict the likelihood of a SARS-CoV-2 diagnosis.

Peripheral eosinophil counts typically return to near-normal levels as patients recover from moderate-to-severe infection [46–48, 51, 52, 55]. For example, Chen et al. [55] found that eosinophil counts, while low at admission, ultimately rebounded in a cohort of patients who ultimately

Table 1 Key points

Eosinopenia and COVID-19	Eosinopenia • Has been reported at diagnosis and during the course of severe COVID-19 • Typically persists in patients with fatal outcomes
Molecular mechanisms underlying eosinophil responses to COVID-19	Severe disease has been associated with • Aberrant Th2 responses • Emergence of $CD62L^{+}$ eosinophils in response to IFNγ • Upregulated expression of PD-L1 on circulating eosinophils
COVID-19 in patients with eosinophil-associated diseases	COVID-19 presents • No specific increased risk to patients diagnosed with asthma or EGIDs noted at this time • No specific contraindications to therapy
Eosinophil-associated complications and misdiagnoses associated with COVID-19	Complications reported include • Pulmonary eosinophilic vasculitis • Eosinophilic pneumonia • Eosinophilic myocarditis Conditions that have been misdiagnosed as COVID-19 include • Eosinophilic granulomatosis with polyangiitis
Vaccines	Eosinophil-mediated enhanced disease • Was observed in animal models of vaccines designed to prevent SARS-CoV-1 and MERS-CoV • Has not been reported in response to either of the FDA-approved lipid encapsulated mRNA vaccines currently in use to prevent SARS-CoV-2 infection and COVID-19

recovered from severe COVID-19. By contrast, eosinophil counts remained low throughout the course of infections with fatal outcomes. Of interest, Glickman et al. [56] found that the prognostic utility of peripheral eosinophil counts and percentages varied based on patient race and ethnicity.

Several groups have explored the value of peripheral blood eosinophil counts at patient presentation for distinguishing between COVID-19 and influenza virus infection. As both respiratory virus infections present with fever, malaise, headache, and cough, it would be helpful to identify factors that might predict a specific diagnosis. Among these reports, Shen et al. [57] found that patients diagnosed with COVID-19 presented with small but significantly lower eosinophil counts than those ultimately diagnosed with influenza. While the definitive differential diagnosis will of course rely on virus-specific diagnostic strategies, several algorithms that include peripheral eosinophil counts have already been developed to assist clinicians to discriminate between these two respiratory virus infections [58, 59].

Mechanisms underlying eosinopenia and eosinophil responses to COVID-19

Mechanistically, eosinopenia may result from one or a combination of factors, including decreased production and/or release of eosinophils from the bone marrow, increased sequestration within the vasculature (i.e., margination), increased migration to somatic tissues, and/or decreased survival in peripheral circulation. The precise mechanism or mechanisms underlying eosinopenia associated with COVID-19 remain unclear at this time. Among these potential mechanisms that may result in eosinophil depletion, self-perpetuating pathologic hyper-inflammation (i.e., the cytokine storm) has been identified as a central feature of severe COVID-19 [60–63]. Under these conditions, cytokines may act individually or via additive or synergistic mechanisms to modulate responses (e.g., margination, apoptosis) of circulating, recruited, and/or tissue-resident eosinophils. Interestingly, stress-based cortisol responses which in other circumstances might lead to eosinopenia [64] are impaired in moderate-to-severe COVID-19 [65–68].

Several intriguing insights have emerged from unbiased systematic evaluations of leukocyte populations and plasma cytokines in patients diagnosed with COVID-19. Lucas et al. [69] presented the results of longitudinal profiling of both plasma cytokines and peripheral blood leukocytes from 113 patients who required hospitalization due to COVID-19. Among their findings, they report that progressive severity was associated with an aberrant Th2 and eosinophil response, including elevated levels of IL-5, IL-13, IgE, and eotaxin-2

accompanied by increasing numbers of eosinophils in peripheral blood. Rodriguez et al. [70] performed longitudinal profiling of circulating immune cells from 39 patients during recovery from severe COVID-19. Among their findings, they identified a unique subset of interferon (IFN)-induced CD62L(L-selectin)-positive eosinophils that emerged just before clinical deterioration. These results are somewhat unexpected, as proinflammatory activation typically results in CD62L downregulation in eosinophils [71]; as such, the clinical consequences of this immunomodulatory response have not yet been defined. Similarly, Vitte et al. [72] performed an unbiased mapping study focused on critical surface markers of circulating leukocytes in patients diagnosed with COVID-19. In these cases, eosinophil-mediated expression of the programmed death receptor ligand 1 (PD-L1) correlated positively with disease severity. We note that Arnold et al. [73] previously identified a role for IFNγ in promoting PD-L1 expression in eosinophils. IFNγ has been identified in numerous studies as a critical component of the COVID-19-associated cytokine storm [67–77]. As such, further exploration of the dynamics and kinetics of the production and signaling mediated by IFNγ might provide a critical insight into the role of eosinophils and their responses to COVID-19.

Interestingly, and despite the modulation of blood eosinophil counts during the course of this disease, few to no eosinophils have been detected in bronchoscopy specimens and only occasionally in lung tissue at autopsy [78, 79].

COVID-19 in patients with eosinophil-associated diseases and complications

Asthma

Individuals with inflammation-associated predisposing comorbidities (e.g., obesity, diabetes, hypertension) are at significantly increased risk for severe COVID-19 [80–82]. These observations led to concern regarding the relative risk posed to those diagnosed with asthma, a condition associated with both chronic inflammation and respiratory dysfunction [83, 84]. Given the previous findings suggesting a role for eosinophils in host defense against respiratory virus infection [17, 18, 24], Carli et al. [85] considered the possibility that Th2-predominant eosinophilic asthma might be protective against severe COVID-19. This hypothesis was supported by the findings of Camiolo et al. [86], who found that peripheral blood eosinophil counts in stratified cohorts of asthma patients correlated inversely with the expression of the SARS-CoV-2 receptor, ACE2, in the bronchial epithelium. Consistent with these findings, Ferastroanu et al. [87] reported that patients carrying a diagnosis of asthma who presented with a high eosinophil count (≥ 150/μl) were less likely to be hospitalized with COVID-19 and, if hospitalized, were less likely to succumb to severe disease. Similarly, in their evaluation of outcomes in one of the earliest patient cohorts, Li et al. [88] reported that the prevalence of asthma was markedly lower among those diagnosed with COVID-19 compared to the population of Wuhan at large.

Interestingly, a similar analysis of the potential role of allergic airways inflammation and the pathogenesis of respiratory virus infection was presented earlier by Varner [89]. These concepts were recently considered and expanded in a systematic review published by Veerapandian et al. [90].

There are numerous case reports, clinical studies, and several meta-analyses published to date that indicate that a diagnosis of asthma presents no increased risk for developing severe COVID-19 and that current medication regimens, including inhaled corticosteroids (ICS) and biologics, remain safe for use at this time [91–96]. Interestingly, a meta-analysis of 131 studies presented by Liu et al. [97] that included more than 400,000 cases revealed that patients with asthma may have a lower risk of death due to COVID-19. Similarly, results from a recent systematic review and meta-analysis published by Sunjaya et al. [98] indicated that individuals diagnosed with asthma are at a lower risk for developing COVID-19 and are less likely to require hospitalization.

By contrast, Lee et al. [99] found that, although asthma was not a risk factor for poor prognosis, higher mortality was observed among those who had experienced an acute exacerbation during the previous year. Similarly, Choi et al. [100] reported that a pre-existing diagnosis of asthma was associated with poor outcomes among those with COVID-19, although asthma severity and the use of asthma medications were not independent risk factors. However, a study published by Izquierdo et al. [101] revealed that asthma patients with COVID-19 were significantly older and suffered from more relevant comorbidities (hypertension, diabetes, dyslipidemia, and obesity) than were reported among asthma patients who remained uninfected and that the use of medications (including ICS and biologics) was associated with an overall protective effect among those diagnosed with COVID-19.

Eosinophilic gastrointestinal diseases (EGIDs)

Similar concerns emerged for patients diagnosed with and undergoing treatment for EGID. Chiang et al. [102] reported a diminished expression of ACE2 in esophageal tissue from adults with eosinophilic esophagitis (EoE) compared to healthy controls. While the number of patients that have been evaluated remains limited, Savarino et al. [103, 104] reported that a diagnosis of EGID presents no specific increased (or decreased) risk with respect to prognosis and outcomes of SARS-CoV-2 infection.

Eosinophil-associated complications of COVID-19

Several isolated incidents of eosinophil-associated complications of COVID-19 have been reported in the literature. Among these cases, Luecke et al. [105] documented a case of isolated pulmonary eosinophilic vasculitis in an older male patient undergoing mechanical ventilation for severe COVID-19. Similarly, Murao et al. [106] reported a case of acute eosinophilic pneumonia triggered by COVID-19 that responded to treatment with prednisolone. Likewise, Craver et al. [107] documented the case of a previously healthy 17-year-old male who presented in cardiac arrest and was diagnosed post-mortem with fatal eosinophilic myocarditis associated with a positive nucleic acid test for SARS-CoV-2. Finally, two case reports documented clinical findings of three patients who presented with eosinophilic granulomatosis, with polyangiitis, and with signs and symptoms that largely mimicked those of acute SARS-CoV-2 infection [108, 109]. Collectively, the findings presented in these case studies suggest that clinicians should be on high alert for eosinophil-associated findings and complications associated with COVID-19.

Eosinophils and vaccines to prevent SARS-CoV-2 infection

Vaccines and strategies promoting mass vaccination have most certainly changed the course of human history [110]. Unfortunately, several previous trials of vaccines designed to target respiratory viruses have resulted in untoward consequences. Among the most egregious of these results emerged from a 1960s trial in which a formalin-fixed RSV vaccine formulation was administered to infants and toddlers; in response to a subsequent encounter with the natural RSV pathogen, many vaccines experienced an aberrant Th2 response accompanied by profound and in some cases lethal eosinophilic inflammation in the lower respiratory tract [111–113]. As such, any new vaccine formulation designed to target respiratory virus pathogens needs to consider and to rule out the possibility of similar aberrant immune-mediated inflammatory responses. Animal model studies focused on vaccine strategies designed to combat SARS-CoV and MERS-CoV were notable for significant Th2-mediated eosinophilic lung immunopathology [114–118]. At the same time, several vaccination strategies were identified that might be effective at combating this complication. Among these, Iwata-Yoshikawa et al. [119] reported that co-vaccination with toll-like receptor agonists, including lipopolysaccharide, poly U, or poly I:C, limited the Th2-mediated eosinophilic response to a UV-inactivated vaccine preparation of SARS-CoV. Similarly, Hoda-Okubo et al. [120] found that co-inoculation with delta inulin, an oligosaccharide and TLR4 agonist [121], enhanced Th1 (i.e., IFNγ-mediated) responses to both recombinant subunit and inactivated SARS-CoV vaccines and protected against Th2-mediated lung pathology.

These findings provide important insight into strategies that might be used to develop vaccines against pandemic SARS-CoV-2. While there are several vaccine formulations in current use worldwide, at this time, only two have been granted emergency use authorization by the US Food and Drug Administration (FDA). Both vaccines include mRNA encoding the SARS-CoV-2 Spike (S) protein encapsulated in a lipid coat that facilitates transfection of target host cells [122–124]. There are no published reports of any Th2-mediated pulmonary immunopathology associated with any of the vaccines currently in use, although concern might be heightened once one or more of these vaccines become available to young children [125]. Of note, while the specific formulations used in these mRNA-based vaccines remain a proprietary information at this time, it would not be surprising to find that one or more of the vaccine components (i.e., the specific lipid carrier molecules and/or the virus nucleic acid itself) serve to direct appropriate immune responses via the activation of cognate pattern recognition receptors. However, this conjecture remains speculative at this time.

Conclusions

Eosinophils are circulating and tissue-dwelling leukocytes that have been implicated in allergic respiratory pathology and antiviral host defense. While eosinopenia has been identified as a factor that may facilitate disease diagnosis and determine prognosis, this finding is neither definitive nor pathognomonic for COVID-19. While recent case reports document misdiagnosis and eosinophil-associated complications of COVID-19, current evidence suggests that patients with longstanding eosinophil-associated disorders are at no increased risk for severe disease at this time. Finally, although vaccine-associated aberrant inflammatory responses were observed in animal model studies of vaccines under development to combat SARS-CoV and MERS-CoV, no similar complications have been reported to date in response to the now widespread distribution of the two FDA-approved mRNA-based COVID-19 vaccines.

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