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Classification of Interstitial Lung Diseases and Interstitial Lung Diseases with Etiology of Covid-19

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Abstract: Interstitial lung diseases are a group of diffuse parenchymal lung disorders associated with substantial morbidity and mortality. Knowledge achieved in recent years has resulted in the publication of the new classification of idiopathic interstitial cases of pneumonia, according to which there are three groups: major, rare, and unclassified. The novelty of the new classification comes from the fact that difficult-to-classify entities can be treated according to the disease behaviour classification. Idiopathic pulmonary fibrosis is the most lethal of the interstitial lung diseases and presents high heterogeneity in clinical behavior. The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced coronavirus disease (COVID-19) dominated the year 2020. Initial reports of the long-term sequelae of COVID-19 include manifestations and exacerbations of interstitial lung disease (ILD), underscoring a pressing need for a better understanding of this group of diseases. The year 2020 brought significant scientific advances in our understanding of the pathogenesis, diagnosis, and treatment of ILD in idiopathic pulmonary fibrosis (IPF) ILD as well as non-IPF ILD.

Keywords: immunopathology; COVID-19; cytokine storms; IFN-η; TNF-α.

INTRODUCTION

The interstitial lung diseases (ILDs), also referred to as diffuse parenchymal lung diseases, are a diverse group of pulmonary disorders that are classified together because of similar clinical, radiographic, physiologic, or pathologic manifestations. The terms used in this group of disorders can be confusing: idiopathic indicates an unknown cause and interstitial pneumonia refers to involvement of the lung parenchyma by varying combinations of fibrosis and inflammation, in contrast to air space disease typically seen in bacterial pneumonia. In general, the major abnormality in interstitial lung disorders is disruption of the distal lung parenchyma. The lung has two interstitial connective tissue compartments: the parenchymal interstitium (alveolar wall or the alveolar septa) and the loose-binding connective tissue (peribronchovascular sheaths, interlobular septa, and visceral pleura). The parenchymal interstitium represents an

anatomic space that is lined by alveolar epithelial cells and capillary endothelial cells. The epithelium and endothelium share a common basement membrane. The interstitium contains the lung's connective tissue elements (collagen, elastin, and reticulin fibrils), extracellular matrix-ground substance, or matrix, of glycosaminoglycans including a complex mixture of polysaccharide molecules (eg, proteoglycans, glycoproteins), and noncollagenous proteins (fibronectin and laminin). 2-3 Small numbers of interstitial cells reside in the connective tissue spaces of the lung-macrophages, mast cells, plasma cells, fibroblasts, and myofi broblasts. When the lung is injured, epithelial cell basement membranes lose their integrity, heralding the appearance, depending on the injury, of a variety of inflammatory cells, regenerating type II epithelial cells and fibroblasts, resulting in the accumulation of extracellular matrix components. Continuation of this process can be fueled by persistent injury (bloodborne or inhaled) or by profibrotic cytokines released from the regenerating alveolar epithelium, inflammatory cells, and the proliferating fibroblasts themselves. This is reflected pathologically as either inflammation and/or fibrosis. In some ILDs, malignant cells, amyloid fibrils, or granulomas infiltrate the interstitial space and interfere with lung function. Several of the ILDs are bronchiolocentric (hypersensitivity pneumonitis, pulmonary Langerhans' histiocytosis X, sarcoidosis) implying inflammation or fibrosis of respiratory and terminal bronchioles and the adjacent alveolar structures. In addition, several of the ILDs, such as desquamative interstitial pneumonia, alter the lung interstitium but are more accurately classified as an alveolar filling process with prominent accumulation of macrophages. In other instances, the alveolar lumens are defaced by the following: proliferating fibroblasts (organizing pneumonia), red blood cells (diffuse alveolar hemorrhage), proteinaceous material (alveolar proteinosis); obliterated by coalescing granulomas (sarcoidosis), calcium microliths (alveolar microlithiasis), or a hamartomatous proliferation. Today, one of the main etiological factors of interstitial pneumonia is coronavirus infection[70]. Today, one of the main etiological factors of interstitial pneumonia is coronavirus infection. The immunological features of COVID-19 and the classification of interstitial lung disease are outlined in this review, along with possible mechanisms of SARS-CoV-2-induced immune alterations, their impact on illness outcomes, and their implications for future COVID-19 therapy.

1-1 Clinical Classification of Interstitial Lung Disease: Collagen Vascular Disease Associated

Scleroderma

Polymyositis/dermatomyositis

Systemic lupus erythematosus

Rheumatoid arthritis

Ankylosing spondylitis

Mixed connective tissue disease

Primary Sjögren's syndrome

Behçet's syndrome

1-2 Clinical Classification of Interstitial Lung Disease: Drug- and Treatment-Induced Partial Listing

Antibiotics

Nitrofurantoin

Sulfasalazine

Cephalosporins

Minocycline

Ethambutol

Antiarrhythmic

Amiodarone

Angiotensin-converting enzyme inhibitors

Tocainide

Beta-blocking agents

Anti-inflammatory

Gold

Penicillamine

Nonsteroidal anti-inflammatory agents

Lefluonomide

TNF-alpha inhibitors

Neurotropic and psychotropic

Dilantin

Fluoxetine

Carbamazepine

Antidepressants

Chemotherapeutic agents

Antibiotics

Mitomycin C

Bleomycin

Alkylating agents

Busulfan

Cyclophosphamide

Chlorambucil

Melphalan

Antimetabolites

Methotrexate

Azathioprine

Cytosine arabinoside

Nitrosoureas

Carmustine (BCNU)

Lomustine (CCNU)

Others

Procarbazine

Nilutemide

Alpha-interferon

Paclitaxel

Interleukin-2

L-Tryptophan

Dopaminergic drugs

Bromocryptine

Radiation

Oxygen

Paraquat

Bacille Calmette-Guérin

Cocaine

1-3 Clinical Classification of Interstitial Lung Disease: Primary or Unclassified Disease Related

Sarcoidosis

Pulmonary Langerhans' histiocytosis X

Amyloidosis

Lymphangioleiomyomatosis

Tuberous sclerosis

Neurofibromatosis

Lymphangitic carcinomatosis

Gaucher's disease

Niemann-Pick disease

Hermansky-Pudlak syndrome

Adult respiratory distress syndrome

Bone marrow transplantation

Acquired immunodeficiency syndrome (AIDS)

Post-infection

Pulmonary vasculitis

Respiratory bronchiolitis

Interstitial cardiogenic pulmonary edema

Pulmonary veno-occlusive disease

Agnogenic myeloid metaplasia

Familial hemophagocytic lymphohistiocytosis

Diabetes mellitus

Lysinuric protein deficiency

Alveolar filling diseases

Alveolar proteinosis

Diffuse alveolar hemorrhage syndromes

Lipoid pneumonia

Bronchioloalveolar carcinoma

Pulmonary lymphoma

Chronic aspiration

Eosinophilic pneumonia

Alveolar microlithiasis

Alveolar sarcoidosis

Bronchiolitis obliterans organizing pneumonia

Metastatic pulmonary calcification or ossification

1-4 Clinical Classification of ILD: Occupational and Environmental Exposure Related

Inorganic

Silicosis

Asbestosis

Talc pneumoconiosis

Kaolin pneumoconiosis

Diatomaceous earth pneumoconiosis

Aluminum oxide fibrosis

Berylliosis

Indium compounds

Hard metal fibrosis

Coal workers' pneumoconiosis

Baritosis (barium)

Antimony pneumoconiosis

Siderosilicosis (iron oxide)

Polyvinylchloride pneumoconiosis

Shale pneumoconiosis

Siderosis (arc welder's lung)

Stannosis (tin)

Silicone pneumonitis

Wood burning interstitial fibrosis

Textile worker's pneumonitis

Flock lung (nylon)

Organic (hypersensitivity pneumonitis)

Bagassosis (sugar cane)

Bird breeder's lung (pigeons, parakeets, etc)

Chicken handler's lung

Duck fever

Dove handler's disease

Farmer's lung

Coffee worker's lung

Tobacco grower's lung

Coptic disease (mummy wrappings)

Cheese worker's lung

Fishmeal workr's lung

Furrier's lung

Meat worker's lung

Mushroom worker's lung

Paprika splitter's lung

Miller's lung (wheat flour)

Wood worker's disease

Sequoiosis

Maple bark stripper's lung

Malt worker's lung

Tea grower's lung

Suberosis (cork)

Lycoperdonosis (Lycoperdon puffballs)

Compost lung

Humidifier lung

Sauna taker's lung

Woodman's disease (oak and maple)

Pauli's hypersensitivity pneumonitis (reagent)

Pituitary snuff disease

Detergent worker's lung (isocyanates)

Japanese summer-type hypersensitivity

Thatched roof lung

Familial hypersensitivity pneumonitis (wood dust)

Vineyard sprayer's lung

Laboratory worker's lung (rat urine)

Mollusk shell hypersensitivity pneumonitis

Goose down hypersensitivity pneumonitis

Ceramic tile worker's pneumoconiosis

Toluene diisocyanate hypersensitivity pneumonitis

Machine operator's lung

Popcorn worker's lung

1-5 Clinical Classification of ILD: Idiopathic Interstitial Pneumonias and Autoimmune Diseases

Acute interstitial pneumonia (Hamman-Rich syndrome)

Idiopathic pulmonary fibrosis

Familial pulmonary fibrosis

Lymphocytic interstitial pneumonitis

Cryptogenic organizing pneumonia

Nonspecific interstitial pneumonitis

Desquamative interstitial pneumonitis

Autoimmune hemolytic anemia

Idiopathic thrombocytopenic purpura

Cryoglobulinemia

Inflammatory bowel disease

Celiac disease

Whipple's disease

Primary biliary cirrhosis

Chronic active hepatitis

Cryptogenic cirrhosis

1-6 Histologic Classification and Response to Therapy: Treatment Responsive

Chronic eosinophilic pneumonia

Acute eosinophilic pneumonia

Idiopathic

Drug-induced

Nonspecific interstitial pneumonia

Collagen vascular disease

Idiopathic

Drug induced

Hypersensitivity pneumonitis

Bronchiolitis obliterans organizing pneumonia

Idiopathic (cryptogenic organizing pneumonia)

Collagen vascular disease

Drug-induced

Radiation

Graft-versus-host disease

Infection

Desquamative interstitial pneumonia

Lymphocytic interstitial pneumonitis

Idiopathic

Primary Sjögren's syndrome

Collagen vascular disease

Other autoimmune disease

Hypogammaglobulinemia

Acquired immunodeficiency syndrome

Pulmonary capillaritis

Wegener's granulomatosis

Microscopic polyangiitis

Other small vessel vasculitis

Collagen vascular disease

Goodpasture's syndrome

Isolated pulmonary capillaritis

Granulomatous interstitial pneumonitis

Sarcoidosis

Hypersensitivity pneumonitis

Drug-induced

Mycobacterial and fungal infections

Berylliosis

Alveolar proteinosis

Idiopathic variety

Vasculitis

Wegener's granulomatosis

Churg-Strauss syndrome

1-7 Histologic Classification and Response to Therapy: Sometimes Treatment Responsive

Diffuse alveolar damage

Acute respiratory distress syndrome (ARDS) (all causes)

Cytotoxic drugs

Idiopathic pneumonia syndrome (bone marrow transplantation)

Collagen vascular disease

Acute interstitial pneumonitis (Hamman-Rich syndrome)

Toxic gas inhalation

Diffuse alveolar hemorrhage (bland)

Goodpasture's syndrome

Idiopathic pulmonary hemosiderosis

Systemic lupus erythematosus

Pulmonary veno-occlusive disease

Granulomatous interstitial lung disease

Pulmonary Langerhans' histiocytosis X

Berylliosis

Common variable immunodeficiency

1-9 Acute Noninfectious Interstitial Lung

Disease and Their Underlying Histology

Acute idiopathic interstitial pneumonia (Hamman-Rich syndrome)

Organizing diffuse alveolar damage (acute)

Fibrotic nonspecific interstitial pneumonia (progressive)

Acute eosinophilic pneumonia

Eosinophilic pneumonia

Diffuse alveolar damage

Organizing pneumonia

Hypersensitivity pneumonitis

Granulomatous interstitial pneumonitis

Nonspecific interstitial pneumonitis (cellular)

Organizing pneumonia

Usual interstitial pneumonitis (chronic)

Nonspecific interstitial pneumonitis (fibrotic)

Drug-induced ILD

Diffuse alveolar damage (cytotoxic drugs)

Organizing pneumonia (amiodarone, gold)

Eosinophilic pneumonia (NSAIDs, minocycline)

Nonspecific interstitial pneumonia (nitrofurantoin, amiodarone)

Usual interstitial pneumonitis (progressive)

Bronchiolitis obliterans organizing pneumonia (idiopathic)

Organizing pneumonia

Nonspecific interstitial pneumonia (cellular)

Nonspecific interstitial pneumonia (fibrotic)

Acute immunologic pneumonia (collagen vascular disease)

Pulmonary capillaritis (SLE, PM-DM, MCTD, Scl, RA)

Organizing pneumonia (PM-DM, RA)

Cellular/fibrotic nonspecific interstitial pneumonia (PM-DM, RA, SLE, Scl)

Diffuse alveolar damage (SLE, PM-DM, MCTD, Scl)

Usual interstitial pneumonitis (SLE, PM-DM, RA, Scl)

Diffuse alveolar hemorrhage syndromes

Pulmonary capillaritis (CVD, Vas, Drugs, GPS)

Bland pulmonary hemorrhage (IPH, GPS, Coag, MS)

Diffuse alveolar damage (Drugs, ARDS, Hamman-Rich syndrome)

1. Pathogenesis of COVID-19

The immunopathology of covid-19

It has been demonstrated that in severe and critical COVID-19 patients, SARS-CoV-2 interferes with normal immunological responses, impairing the immune system and triggering uncontrollably high inflammatory responses. These individuals have increased levels of immunoglobulin G (IgG) and total antibodies, granulocyte and monocyte abnormalities, lymphopenia, lymphocyte activation and dysfunction, and elevated cytokine levels. The ensuing sections provide a detailed description of COVID-19's immunological patterns.

Lymphopenia

One important characteristic of COVID-19 patients, particularly in severe cases, is lymphopenia. A significant predictor for severe patients is lymphopenia, which is more common in patients with severe COVID-19 at the time of admission [9, 10]. Patients also exhibit a significant decrease in the quantity of NK, B, CD4+ T, and CD8+ T cells [2, 11, 13]. In extreme cases, lymphocyte percentages were reported to be less than 20%. 14 Subsequent examination revealed that severe cases had significantly fewer T cells overall, particularly CD8+ T cells, than moderate instances [15]. According to Qin et al. (12), there is a reduction in the proportion of memory helper T cells (CD3+CD4+CD45RO+) in severe cases as compared to non-severe cases. According to these findings, lymphopenia may serve as a predictor of the prognosis and degree of the COVID-19 virus. Even so, some non-severe and pregnant cases have lymphopenia; nevertheless, compared to severe patients, the proportion of non-severe patients with lymphopenia is much smaller [25, 26]. It's interesting to note that the number of B cells is within the normal range [12], which is consistent with the results of our study [7], suggesting that NK or T cell impairment is more significant than B cell impairment.

Lymphocyte activation and dysfunction

Investigations were done on T cell activation in certain COVID-19 instances [28]. The CD8+ T cell response was more common than the CD4+ T cell response in research involving 128 convalescent samples. In addition, compared to the mild group, virus-specific T cells from the severe cases displayed a central memory phenotype and high levels of interferon (IFN)-γ, tumour necrosis factor (TNF)-α, and interleukin IL)-2 [29]. Comparing COVID-19 patients' CD4+ and CD8+ T cells to those of healthy controls, Zhou et al. [30] found that patients' CD4+ and CD8+ T cells had higher expression of CD69, CD38, and CD44. Furthermore, particularly in severe cases, there is a marked increase in the expression of OX40 and 4-1BB, important molecules that support clonal expansion and prime immunological responses [32], suggesting that COVID-19 patients are likely to have activated T cells. Additionally, a different study showed that blood levels of activated CD4+ and CD8+ T cells exist prior to symptom alleviation [33].

Furthermore, patients with COVID-19 exhibit fatigue characteristics in their T cells. When comparing the prodromal stage to the outwardly symptomatic stage, the levels of programmed cell death protein-1, T cell immunoglobulin domain, and mucin domain-3 on CD8+ T cells are elevated; maximal levels are observed under severe circumstances [26]. Furthermore, cytotoxic lymphocytes, such as CD8+ T cells and NK cells, have higher expression of the killer cell lectin-like receptor subfamily C member 1 receptor [34, 35]. Accordingly, in COVID-19 patients, higher levels of fatigue and a lower functional variety of T cells may indicate a more severe course [36].

Abnormalities of granulocytes and monocytes

In COVID-19 patients, there is also an aberrant number of monocytes and granulocytes. Severe patients had much higher neutrophil counts and neutrophil-to-lymphocyte ratios than non-severe

patients, which are typically critical markers for severe cases and poor clinical outcomes [37, 9, 10, 12, 15]. In another investigation, higher neutrophil counts were discovered in 38% of the 99 Wuhan patients [22]. In the meantime, patients with severe conditions showed lower percentages of monocytes, basophils, and eosinophils [12, 37].

Increased production of cytokines

Severe COVID-19 is also characterized by increased cytokine production. A "cytokine storm" of inflammatory cytokines, such as IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interferon-inducible protein-10 (IP10), monocyte chemotactic protein 1 (MCP1), macrophage inflammatory protein-1α, IFN-γ, and TNF-α, is present in the majority of severe COVID-19 cases [2,3,12,15]. Specifically, in severe situations, the most increased cytokines are IL-1β, IL-6, and IL-10 [25, 26]. Additionally, our investigation revealed that cytokine levels—specifically, those of IL-6 and IL-10, which showed a sharp rise in levels—as well as TNF-α and IFN-γ are higher in severe and critical COVID-19 cases [27].

The blood of non-severe patients has elevated levels of cytokines such as IL-1β, IL-1RA, IL-2R, IL-6, IL-7, IL-8, IL-9, IL-10, IFN-η, TNF-α, G-CSF, GM-CSF, IP10, and MCP1, but they are notably lower than those of severe patients [2, 12, 22].

Increased antibodies

The foundation for diagnosing COVID-19 is the identification of SARS-CoV-2-specific antibodies (IgM and IgG) in conjunction with nucleic acid tests. Zhang et al. [37] discovered an intriguing correlation between the severity of the disease and an elevated IgG response, suggesting a straightforward supplementary marker for differentiating between instances that are severe and those that are not. According to another study, less than 40% of patients had antibodies during the first seven days of their sickness, and by day 15, that number had quickly increased to 100%. Compared to IgM and IgG, total antibody titers were significantly faster and were independently linked to a worse clinical outcome in COVID-19 patients [38].

In a different study, all patients tested positive for antiviral IgG within 19 days of the onset of symptoms [39]. According to Nicol et al. [40], the specificity of IgG was likewise very good, with a sensitivity of 100% for detection occurring more than 14 days after the onset of symptoms; in contrast, the specificity of IgA (78.9%) and IgM (95.8%) was significantly different. These discoveries, which are consistent with our study's findings that patients with relatively high B cell levels had poor survival, suggest that B cell activation and proliferation in COVID-19 patients, particularly in severe cases, are associated with a bad outcome [26, 27].

Comparison with SARS-CoV-induced immunopathology

The innate immune system, which detects pathogens and releases pro-inflammatory cytokines to initiate the immune response, sets the stage for the adaptive immune system's responses, which include T cells that can directly destroy virus-infected cells and B cells that generate antibodies specific to the pathogen. The immune response results in the production of cytokines, which draw pro-inflammatory cells, such as neutrophils and macrophages, to the infection site in order to trigger an inflammatory response. These reactions can harm healthy host tissues, even though they are essential for the removal of the virus [41]. However, there isn't any conclusive proof that the alterations found in SARS, including lymphopenia, lymphocyte malfunction, and abnormalities in granulocytes and monocytes, are unique immunological responses to COVID-19.

Potential mechanisms of sars-cov-2-inducedimmunopathology

It is crucial to clarify the processes driving immunological alterations in COVID-19 patients in order to direct treatment approaches. The next section discusses the possible pathways of immunological alterations caused by SARS-CoV-2.

Depletion and exhaustion of lymphocytes

Multiple possible pathways could be at play for both lymphocyte depletion and dysfunction. (1) It has been shown that interactions between the virus's S proteins (spike glycoprotein) and angiotensin-converting enzyme 2 (ACE2) receptors allow SARS-CoV-2 to infect human respiratory epithelial cells [33]. Furthermore, a crucial aspect of SARS-CoV-mediated pathogenesis is the ability of SARS-CoV-2 to directly infect T cells and macrophages [41]. We therefore propose that SARS-CoV-2 entrance into lymphocytes is facilitated by ACE2 receptor expression on lymphocytes, particularly on T cells. An additional investigation revealed an inverse relationship between TNFα, IL-6, and IL-10 levels and a drop in T cell count. This suggests that elevated levels of inflammatory cytokines may contribute to the depletion and fatigue of T cell populations that occur concurrently with the advancement of disease [42]. Furthermore, as spleen atrophy and lymph node necrosis have been reported, the SARS-CoV-2 virus may directly damage lymphatic organs, including the spleen and lymph node, further causing lymphopenia [14, 43, 44]. (4) Lastly, blood samples from patients with severe COVID-19 showed elevated lactic acid levels, which may prevent lymphocyte proliferation [14].

Increased neutrophils

In patients with COVID-19, there may be a close correlation between neutrophil upregulation and lymphopenia. It is well known that microbial infection can cause neutrophils to be directly recruited to tissue locations [45, 46]. As a result, COVID-19 patients' compromised lymphocytes may quickly result in a microbial infection, which will encourage the activation and recruitment of neutrophils in the patient's blood.

Cytokine storm

A cytokine storm is a sudden, sharp rise in cytokine levels that has been observed frequently in tumors treated with chimeric antigen receptor T (CAR-T) cells [47, 48]. Patients with severe COVID-19 produce a large amount of cytokines, which can lead to a cytokine storm and other negative effects in the body. Therefore, it's essential to comprehend the mechanisms underlying cytokine storms. After contracting SARS-CoV-2, CD4+ T cells can be quickly transformed into pathogenic T helper (Th) 1 cells, which release GM-CSF. This in turn triggers the production of CD14+CD16+ monocytes with elevated IL-6 levels, hence quickening the inflammatory process [30]. According to single-cell research, patients with COVID-19 have a rise in a subpopulation of CD14+IL-1β+ monocytes, which may facilitate enhanced IL-1β production. This finding highlights the characteristics of immune cell interaction [49]. There is mounting evidence that Th17 cells that produce the inflammatory cytokine IL-17 also attract neutrophils and monocytes/macrophages to the infection site and initiate cascades of other cytokines, including IL-1β and IL-6 [50]. Furthermore, patients with COVID-19 showed evidence of and confirmation of the Th17 response [11]. Prior research has demonstrated that when mice are infected with strain 3 of the hepatitis virus, monocytes and macrophages can release inflammatory cytokines [51, 52]. More thorough research is needed to determine whether SARS-CoV-2 causes a cytokine storm through monocytes or macrophages [26]. Moreover, eosinophils can release a significant number of cytokines and directly contribute to the fight against RNA viruses. IL-6 is a crucial mediator of the cytokine storm in COVID-19 patients, among these cytokines [53].

Antibody-dependent enhancement

Preexisting sub-neutralising antibodies can boost the entry and reproduction of a virus, a phenomenon known as antibody-dependent enhancement (ADE) of virus infection. This effect has been reported for a number of viruses, including the dengue and ebola viruses [54, 55]. It has been demonstrated that the Middle East respiratory syndrome (MERS) virus can more easily enter cells through the Fc component of a neutralising monoclonal antibody that binds to the Fc receptor (FcR) on those cells. The antibody targets the receptor-binding region of the S protein of the virus [43]. This corroborates the link between high antibody levels and unfavourable

outcomes for COVID-19 patients. However, more research is needed to fully understand the ADE-mediated inflammatory response and the correlation between pre-existing antibodies and the severity and course of the COVID-19 virus.

Clinical implications of sars-cov-2-induced immunopathology

Patients with COVID-19 in the clinic may have different outcomes depending on the SARS-CoV-2-mediated immunological markers. We describe the relationship between immunological alterations and COVID-19 clinical outcomes in the sections that follow.

The effect of lymphopenia on microbial infection

Patients with COVID-19 frequently exhibit lymphopenia, which may be a crucial component linked to the severity and mortality of the illness [21]. In many disorders, there is a mutual influence between microbes and immunological homeostasis [56]. A well-known polysaccharide (1,3)-β-D-glucan is an essential structural element of the fungal cell wall. In our earlier investigation, we discovered that (1,3)-β-D-glucan levels are much greater in patients with severe COVID-19 and low lymphocyte numbers than in patients with high lymphocyte levels [27]. Furthermore, the majority of microbe-infected individuals had low lymphocyte counts, suggesting that patients who are lymphopenic are at a higher risk of contracting microbes [27]. Similar to what we found in our investigation, Chen et al. [3] showed that several microorganisms could be cultivated from a single patient. Overall, the findings indicate that microbial infection in patients with COVID-19 promotes disease progression and severity.

The effect of elevated cytokine production on clinical manifestations

There is mounting evidence that severe shock and organ failure syndromes can be brought on by viral infection [8, 57]]. This this phenomena was also studied in relation to COVID-19. According to Chen et al. (2003), out of 99 patients, 43 (43%) had abnormal myocardial zymograms with elevated creatine kinase and lactate dehydrogenase levels; some had renal function damage with elevated urea nitrogen or creatinine levels; and most had abnormal liver function with alanine aminotransferase and/or aspartate aminotransferase levels above the normal range. Additional research revealed that a subset of patients experienced various organ failures, which could be attributed to immunological responses mediated by SARS-CoV-2 [9, 11, 18, and 58]. Viral sepsis and inflammatory-induced lung damage can be triggered by a cytokine storm, which can result in ARDS, respiratory failure, shock, organ failure, and possibly even death [59]. Furthermore, elevated levels of pro-inflammatory cytokines in severe COVID-19 instances can result in multiple organ failure, tissue damage, and shock [42]. Prolonged elevated cytokine levels (CXCL10, CCL7, and IL-1RA) are linked to lung damage and dysfunction as well as lethal consequences [60]. Pro-inflammatory cytokine blood levels are also elevated in SARS-CoV and MERS-CoV infections, indicating a possible similarity in cytokine storm-mediated illness severity [61, 62]. Our research revealed a strong correlation between IL-6 levels and indicators of heart, kidney, and liver dysfunction [27]. Additionally, we discovered that indicators for γ-glutamine transferase levels are elevated in response to an increase in IL-10. When combined, the aforementioned studies point to a strong correlation between high cytokine levels and severe syndromes of multiple organ dysfunction, which may offer a promising target for prevention or treatment for patients with COVID-19 and severe syndromes.

3. Summary

The immunopathology of COVID-19 is characterized by the interference with normal immune responses, leading to high inflammatory responses. Severe and critical cases of COVID-19 exhibit increased levels of immunoglobulin G (IgG) and total antibodies, granulocyte and monocyte abnormalities, lymphopenia, lymphocyte activation and dysfunction, and elevated cytokine levels.

Lymphocyte activation and dysfunction are also observed in severe cases, with the CD8+ T cell response being more common than the CD4+ T cell response. Patients with COVID-19 exhibit

fatigue characteristics in their T cells, with higher levels of programmed cell death protein-1, T cell immunoglobulin domain, and mucin domain-3 on CD8+ T cells. Additionally, cytokines are increased in severe cases, with the most increased cytokines being IL-1β, IL-6, and IL-10. Increased antibodies are the foundation for diagnosing COVID-19, with an elevated IgG response suggesting a straightforward supplementary marker for differentiating between severe and non-severe cases. To direct treatment approaches, it is crucial to clarify the processes driving immunological alterations in COVID-19 patients and explore potential pathways of immunological alterations caused by SARS-CoV-2.

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