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Covid19 Vaccine Induced Interstitial Lung Disease

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Covid19 Vaccine Induced Interstitial Lung Disease

Three years have elapse since Covid-19 virus spread through the United States. It is understood that Covid-19 is caused by SARS-CoV-2 virus that originated in Wuhan China in 2019. Vaccination brought hope to the world. Covid-19 vaccine was a critical tool in attempting to reduce the spread of a potentially deadly virus to some, and severe illness to others. Covid-19 vaccine was originally approved by the FDA for emergency use. This vaccine quickly became very effective at reducing the spread of the virus. Nevertheless, a rare adverse effect has been identified unbeknownst to Covid-19 vaccine clinical trials.

Multiple reports of vaccine induced interstitial lung disease (ILD) have surfaced. Interstitial lung disease (ILD) is a group of lung disorders that affect the interstitium; this is the lung tissue between the air sacs, medically known as alveoli and small blood vessels that surround the alveoli [1]. Interstitial lung disease has been linked to potential serious side effect of covid-19 vaccine [2-4]. Therefore, an overview of covid-19 vaccine induced ILD, including its clinical manifestation, diagnosis, and treatment is intended by this literature review.

Background

Covid-19 pandemic has affected millions of people worldwide. Vaccination has been essential in combating the virus. It is important to note that covid-19 vaccine has been proven safe and effective worldwide. Covid-19 vaccine was such an outstanding science accomplishment in a very challenging time to say the least. Scientists have developed covid-19 vaccines from viral vector to messenger ribonucleic acid (mRNA) technology which have been very effective at mitigating morbidity and disease severity [5].

Like any vaccine, covid-19 vaccine also has side effects from mild local reaction, such as sore arm, inflammation at the injection site to more systemic reaction such as headache, and fever, and serious reaction such as anaphylaxis [6]. One adverse effect that has been of particular interest is the reported vaccine-induced interstitial lung disease (ILD) which is rare but a serious side effect. The term "interstitial lung disease" refers to a broad and diverse range of parenchymal lung illnesses, including those of unknown etiology such as idiopathic pulmonary fibrosis (IPF), [1].

Interstitial Lung Disease

Interstitial lung disease is a condition where there is repeated alveolar epithelial injury [1]. This is typically a progressive disorder of lung scarring, best known as pulmonary fibrosis. As fibrotic tissue develops and progresses, impaired gas exchange develops within the alveoli. This leads to a decrease in lung function. Fibrosis is irreversible and often progressive in nature. There are many causes of ILD such as underlying connective tissue disorders, autoimmune disorders, environmental hazards such as exposure to mold, asbestos, and other harmful antigens [1]. Often, if ILD etiology is discovered, ILD can be managed and potentially stopped from causing further lung scarring. When the origin cannot be found it is called idiopathic pulmonary fibrosis with a poor prognosis once diagnosed. The literature now also suggests a correlation and potential Covid-19 vaccine induced ILD.

Vaccine Pathophysiology

The viral RNA is introduced into the host cell by the mRNA vaccines like Pfizer and Moderna, which then manufactures the viral spiked S protein of the Covid19 strain, inducing an immunological response [7,8]. Scientists took covid19 virus blueprint RNA to create mRNA, this viral RNA enters the cells and learns to replicate covid protein spikes resulting in the immune system producing antibodies. In traditional vaccines, the viral spike protein is delivered by a weakened virus in adenovirus vector vaccines such as like Johnson & Johnson and AstraZeneca. In those who are susceptible, an inflammatory cascade in the lungs brought on by the immunological reaction to the vaccine may result in ILD. Uncertainty surrounds the pathogenesis of vaccine induced ILD. It is believed to be cytotoxic injury and immune-mediated response to the vaccine [9]. This cellular insult could potentially lead to interstitial inflammation and fibrosis. The lipid nanoparticles (LNP) used to transport mRNA in covid19 vaccine formulary has been found to be highly inflammatory in mice during preclinical trials, and there's evidence that ionizable lipids within LNP can stimulate proinflammatory response [10].

Another possibility is molecular mimicry, in which the antibody against the spike protein of SARS-CoV-2 reacts unfavorably with structural related host proteins [11,2,12]. The S protein shedding antigen related peptide fragments into circulation may result in an inflammatory response [10]. Additionally, angiotensin-converting enzyme 2 (ACE2) receptors are manifested in

the respiratory tract where the interaction with the viral spiked protein can induce a hyperinflammatory response [11]. Rijkers et al describes that in rare cases side effects such as hypersensitivity reactions, thrombosis and thrombocytopenia can occur [7].

Clinical Characteristics of covid19 vaccine induced ILD

Individuals have reported symptoms in as little as two days to weeks after covid-19 vaccine. Adverse reactions appear to be more pronounced after the second dose. The symptoms included exertional dyspnea (shortness of breath with activity) dry cough, fatigue, fever, hypoxia, or low blood oxygen saturation in room air. The symptoms were similar to Covid-19 virus; however, these patients tested negative for Covid like Covid-19 virus; however, these patients test negative for Covid.

One case was reported on a 60-year-old male with a history of other chronic lung disease who developed dyspnea 4 days after second dose of covid-19 vaccine [4]. This gentleman ended up requiring mechanical ventilation as he worsened into acute respiratory failure. Chest x-ray and CT (Computed Tomography) scan revealed ground glass opacities. Fortunately, he recovered after being treated with corticosteroids. In this case, the patient had well-controlled asthma and COPD, and his medications were not changed before this reaction. This case was suspected of vaccine induced ILD [4].

Covid-19 Vaccine Clinical Trials

Diagnosing ILD can be challenging as this is a rare occurrence. Furthermore, ILD has not been reported in international clinical studies with Covid19 vaccines, including tozinameran and Spikevax [13]. A randomized controlled clinical trial phase 2 of Covid-19 vaccine consisted of 8,183 participants who reported that the most common local side effects were swelling and redness at the injection site, and the most common systemic side effects included fever, fatigue, myalgia, and headaches [14,6]. It is also mentioned that systemic events were more common after the second dose [14]. Also, it is worth mentioning Covid-19 mRNA vaccines are the first vaccines to be developed [5]. Note that inclusion criteria in clinical trials have largely enrolled younger, relatively healthy adults [3,6]. Park et al describes that there was a limited amount of elderly enrolled in covid-19 vaccine clinical trials [2]. Therefore, there is a lot of information to be discovered, making it difficult to diagnose covid-19 vaccine induced ILD, this is possibly due to lack of data.

Diagnosis

The diagnosis of vaccine induced ILD necessitates a high degree of suspicion, particularly in cases when patients experience symptoms just a few weeks after receiving the vaccine [11]. A chest x-ray or computed tomography (CT) scan are frequently part of the diagnostic process and can detect pulmonary fibrosis or interstitial infiltrates and determine ground glass opacities [11,13]. A restrictive pattern with decreased lung capacity and poor gas exchange may be seen in pulmonary function testing (PFT). A bronchoscopy is required to diagnose vaccine induced ILD, a bronchoalveolar lavage may be used to confirm pulmonary fibrosis such as interstitial pneumonitis [5]. To check for inflammatory or infectious causes of ILD, a lung biopsy might be necessary.

Covid-19 Vaccine Induced ILD Reports

The incidence of vaccine-induced ILD is not well established as it is a rare side effect of covid-19 vaccine, nonetheless there is a growing number of academic journals and studies that suggests a strong correlation between the vaccine and the development of ILD. There have been reports of vaccine-induced ILD following COVID-19 vaccination, particularly with the mRNA vaccines [8,12,13]. In a retrospective study published in January of 2023, 545 participants surveyed 0.7% reported acute exacerbation of ILD, and 3.1% a milder form of ILD exacerbation in patient already known to have ILD [5].

Although this literature review focuses on ILD, cases of myocarditis have also been continuously reported with BNT162b2-mRNA vaccine, and thrombotic thrombocytopenia with viral vector-based vaccines [2]. A prospective observational analysis was performed with 11 participants with the median age being 80 years old. All other potential diagnosis such as ILD were excluded. It was found that eight out of eleven participants developed organized pneumonia, and four out of those eight participants developed diffused alveolar damage after administration of BNT162b2-mRNA vaccine [2]. Additionally, CT scans revealed vaccine related hypersensitivity pneumonitis, a form of ILD, 15 days after receiving covid-19 vaccine.

The cureus journal of medical science published a report about a 61-year-old woman who developed acute transverse myelitis and ILD after receiving second dose of CoronaVac vaccine. CT scan showed ground glass opacities, and she responded well to methylprednisolone [11]. This person had a pre-existing condition of asthma and hypertension under control. Severe acute ILD was also reported on a 72-year-old male with a history of heavy smoking, hospitalized with dyspnea and fever after day 7 of second dose of BNT162b2 mRNA covid-19 vaccine [12]. Diagnostics indicated ground glass opacities on CT scan thought to have been triggered by overreactive response in combination with risk factors.

Interstitial pneumonitis, also known as hypersensitivity pneumonitis, has been reported in numerous studies. Shimizu et al describes three cases reported to have developed interstitial pneumonitis post covid-19 vaccination with (Pfizer) [3]. These three patients' ages were 62 years old, 66 years old, and 85 years old with pre-existing lung conditions that were well controlled. All three individuals developed dyspnea, fever, and fatigue 20-21 days after Pfizer vaccine, and all had ground-glass opacities in their CT scans with increased in white blood cell count in bronchoscopy lavage, particularly lymphocytes and mild eosinophils. They responded well to corticosteroid therapy.

Another case report published by respirology case reports revealed two males; 67 years old and 70 years old with pre-existing ILD with respiratory symptoms after receiving Covid-19 mRNA vaccine diagnosed with drug related interstitial pneumonitis [9]. Once again bronchoscopy lavage presented lymphocytes. CT scan showed ground-glass opacities, and both responded well to corticosteroids [9]. Another case reported a 71-year-old woman with no underlying conditions who developed exertional dyspnea after receiving mRNA covid vaccine that also revealed ground glass opacities eight days post vaccination. A bronchoscopy was performed that revealed 4.0% neutrophils, 1.1% macrophages, 37.5% macrophages, and 57.5% lymphocystis This led to a diagnosis of ILD hypersensitivity pneumonitis. This patient also responded well to corticosteroids [13].
A case reported a 60-year-old man with chronic lung condition

of asthma and chronic obstructive lung disease (COPD) who developed dyspnea four days after second dose of covid-19 vaccine [4]. CT also revealed ground-glass opacity and increased white blood cell count with bronchoscopy lavage. There was also another case presentation of a 76-year-old woman with stable rheumatoid arthritis (RA) that was well controlled on methotrexate. This woman also developed hypersensitivity pneumonitis following Covid-19 vaccine and required hospitalization 17 days post vaccination with increased dyspnea and persistent cough [5]. All diagnostics demonstrated same results previously discussed.

It is worth noting that in all reported cases, patients had tested negative for Covid19 virus. All underlying medical conditions were well controlled. Previous imaging did not have underlying ILD with exception of patient with underlying ILD who developed respiratory exacerbation post covid-19 vaccination. Patients did not experience any changes in environment or medication adjustment in the past 6 months prior to receiving covid-19 vaccine. The majority of covid vaccine induced ILD were classified as hypersensitivity pneumonitis, especially after receiving the mRNA BNT162b2 Pfizer vaccine.

Treatment

The severity and prognosis of vaccine induced ILD affects how the illness is managed. Evidence suggests that steroid administration and no longer receiving covid-19 vaccine results in improved prognosis [4]. Mild cases may resolve on their own, and with the assistance of temporary supplemental oxygen and bronchodilators. In cases of moderate-to-severe ILD, corticosteroids may be beneficial to reduce inflammation. In some instances, immunosuppressive medications in combination with corticosteroids will certainly maintain inflammation at bay. Caution should be practiced when prescribing steroids and immunosuppressive therapy as these therapies have their own set of side effects and can increase the risk for infection [3].

Conclusion

Although the prevalence of covid vaccine induced ILD is rare, clinicians need to be aware of the possibility of ILD adverse effects and understand the manifestations. If ILD is left untreated, fibrotic tissue can progress and increase poor prognosis. Ongoing research will provide further understanding and clarification. However, caution should be used if the suspected antigen is the vaccine on patients who develop hypersensitivity pneumonitis ILD after receiving covid-19 vaccine. In general, the common side effects of covid-19 vaccine are still better than developing serious complications from covid-19 virus itself. Overall covid-19 vaccine has been proven to be very effective and safe for the vast majority worldwide. Therefore, the benefit of receiving the vaccine far outweighs the risks. Most importantly, the implementation of covid-19 vaccination has demonstrated a reduction in the spread of covid, and mortality, finally putting an end to this pandemic.

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