Review

Capillary Leak Syndrome after SARS-CoV-2 Infection and COVID-19 Vaccines: A Comparative Review

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Abstract: Systemic capillary leak syndrome (SCLS) is an uncommon, potentially life-threatening disorder defined as recurrent attacks of pseudo-shock. This syndrome occurs due to the disruption of endothelial cells, which leads to increased vascular permeability, causing intravascular fluid to leak into the extravascular space and albumin to be retained in the interstitial space. SCLS can lead to hypovolemia, peripheral hypoperfusion, and acute renal insufficiency. The syndrome is presented with fever, generalized edema, pleural effusions, dyspnea, hypovolemia, hemoconcentration, prerenal azotemia, shock, and syncope. After ruling out other causes of hypovolemic shock, the diagnosis of SCLS can be considered on the presence of the classical triad of hypotension, hemoconcentration, and hypoalbuminemia. Eliminating the precipitating factors is the cornerstone of SCLS management. It is advisable to be very cautious and weigh the risks and benefits of vaccination of people with a history of this condition. This review will discuss and compare different aspects of SLCS after SARS-CoV-2 infection and COVID-19 vaccination.

Keywords: COVID-19; COVID-19 vaccines; capillary leak syndrome

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic showed us that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is not merely a respiratory disease but it can lead to several disastrous extrapulmonary complications as a result of immune response dysregulation [1]. Systemic capillary leak syndrome (SCLS) is among the essential immune diseases triggered by the SARS-CoV-2. This condition had been observed with a high frequency in COVID-19 infected patients, so authorities believe that this life-threatening condition might be a variant of the COVID-19 related multisystemic inflammatory syndromes (MIS) [2]. Reviewing the COVID-19 related literature has revealed three SARS-CoV-2 related SCLS: 1) new-onset SCLS, 2) flare-up of the preexisting SCLS, and 3) vaccine-induced SCLS [3]. With the introduction of COVID-19 vaccines, rare similar cases have been reported following SARS-CoV-2 vaccination, some with fatal outcomes [4], and it is anticipated to be increasingly identified with the increase in the

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vaccinated population. Here, we have reviewed the literature and compared the capillary leak syndrome in the settings of SARS-CoV-2 infection and vaccination.

2. Definition and etiology

Systemic capillary leak syndrome is an uncommon, potentially life-threatening disorder defined as recurrent attacks of pseudo-shock, whose frequency, severity, and duration are variable, with each bout lasting 24-48 hours [5]. On the other hand, SCLSs are classified into acute or chronic and primary or secondary, based on the relapses of attacks, the severity of manifestations, and the presence of precipitating factors [6]. The primary, spontaneous, or idiopathic SCLS is Clarkson's disease, while secondary cases occur due to certain precipitating factors, including hematologic malignancies, immune disorders, trauma, toxins or chemicals, medication, surgery, transplantation, and infections [7]. Among the aforementioned precipitating factors, we can name immune disorders such as Sjögren's syndrome, systemic sclerosis, and juvenile dermatomyositis [8-10], malignancies, such as monoclonal gammopathies, lymphoma and myeloproliferative disorder [11,12], and medications such as G-CSF, interferons, rituximab and chemotherapeutic agents such as checkpoint inhibitors [13-17] as the most commonly reported triggers of SCLS in the literature.

Among infections responsible for SCLS, we can name influenza as the most common, and respiratory syncytial virus (RSV), West Nile virus (WNV), hantavirus, rotavirus, brucellosis, meningococcemia, malaria, Zika, Ebola, and dengue fever as the less prevalent ones [18-25]. It is demonstrated that viruses, like the influenza virus, causing upper respiratory tract infections are predominantly responsible for SCLS; coronaviruses are also believed to lead to this complication. Since the pandemic's beginning, there have been great case reports of SCLS following SARS-CoV-2 infection is anticipated [26].

Vaccination is another crucial trigger for SCLS [27]. Previously, SCLS had been reported following influenza vaccination [28]. However, the introduction of SARS-CoV-2 vaccines has brought about several new or exacerbated cases of SCLS [29,30]. Most cases of SARS-CoV-2 vaccination-induced SCLS have been reported with adenoviral vector and mRNA vaccines [31].

3. Pathophysiology

Systemic capillary leak syndrome occurs due to the disruption of endothelial cells, which leads to increased vascular permeability, causing intravascular fluid to leak into the extravascular space and albumin to be retained in the interstitial space [32]. This phenomenon can lead to hypovolemia, peripheral hypoperfusion, and acute renal insufficiency [33]. In viral infections, this condition can be triggered by direct viral toxicity on the endothelial barrier of massive inflammatory mediators secretion [5,34]. This inflammatory response in the lungs leads to pulmonary capillary leak syndrome, which manifests as progressive hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS) [35,36]. The elevation of proinflammatory cytokines and chemokines, like CCL2, IL-1, IL-6, IL8, IL-12, and TNF-α during the SARS-CoV-2 infection has a critical role in damaging the respiratory system and other organs [37]. The most significant injury occurs in angiotensin-converting enzyme 2 (ACE2) rich areas, which are entry gates of the virus [38]. On the other hand, the occurrence of SCLS in the settings of COVID-19 vaccines can be attributed to the SARS-CoV-2 spike glycoprotein encoded by the RNA or the viral vector [39].

4. Manifestations

A great majority of acute SCLSs are preceded by a nonspecific prodrome of the flu-like syndrome [40]. Nonetheless, some acute cases follow an episode of sepsis, anaphylaxis, or even an intense physical exertion [41]. This syndrome is presented with fever, generalized edema, pleural effusions, dyspnea, hypovolaemia, hemoconcentration, prerenal azotemia, shock, and syncope. Peripheral, periorbital, or facial edema may only be

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detected [6]. It is a form of vascular leak syndrome defined as the presence of at least two of the following: hypotension, edema, and hypoalbuminemia [42]. However, the chronic form is characterized by fluctuating episodes of diffuse edema, weight gain, and hypoalbuminemia rather than hypotension [43]. Interestingly, consciousness is preserved during the bouts of a chronic SCLS, even in severe attacks [40].

5. Laboratory findings

It is observed that polycythemia, hypoalbuminemia, and neutrophilic leukocytosis are the most common laboratory findings in SCLS cases. Other abnormalities are thrombocytosis, rhabdomyolysis, lactic acidosis, coagulopathy, paraproteinemia, and increased VEGF levels [44]. However, it should be considered that thrombocytosis was not observed in some previous studies. In a study, it was seen that a significant number of patients showed monoclonal plasma cell (PC) proliferation [6], and monoclonal protein was detected via electrophoresis in a group of patients [45]. Acute renal failure (known as a total elevation in creatinine of 0.3 mg/dL or a reduction in urine volume to less than 0.5 mL/kg/h for a period longer than 6 hours, observed within 48 hours of the beginning of symptoms) is another critical, noted an abnormality in SCLS patients [6].

6. Diagnosis

In any patient presenting with generalized edema, hypotension, hemoconcentration, or hypoalbuminemia shortly after being infected with SARS-CoV-2 or after receiving a SARS-CoV-2 vaccine, SCLS should be considered [46]. There are no specific diagnostic criteria and tests for SCLS. Therefore, the diagnosis of capillary leak syndrome is that of exclusion. After ruling out other causes of hypovolemic shock, the diagnosis of SCLS can be considered on the presence of the classical triad of hypotension, hemoconcentration, and hypoalbuminemia. For example, the pulmonary capillary leak syndrome diagnosis is based upon clinical and radiologic findings and exclusion of heart failure [5,35]. However, in deceased patients, postmortem electron microscopy examinations of lung tissues, showing loosening of interendothelial junctional complex and increase in protein concentrations and cytokine levels of the bronchoalveolar fluid (BALF), retrospectively confirms the diagnosis [47].

7. Differential diagnosis

The similarities between SCLS and Kawasaki disease (KD) in the context of COVID-19 is to the extent that it is sometimes known as SARS-CoV-2–induced Kawasaki-like hyperinflammatory syndrome (SCiKH syndrome) [48]. Moreover, COVID-19-related multisystem inflammatory syndrome (MIS) is another similar condition that predominantly occurs in the pediatric population. It usually occurs in the late phase of SARS-CoV-2 infection, is manifested by elevated inflammatory biomarkers, and is managed with anti-inflammatory agents such as corticosteroids and IV immunoglobulins (IVIg) [11,49]. Sepsis is another condition commonly mistaken for SCLS. However, procalcitonin levels, blood cultures, and evidence of active infection on the chest or abdominal imaging can help in differentiating it from other differential diagnoses [7]. Other conditions that can present with hemoconcentration, hypoalbuminemia, and hypotension include nephrotic syndrome, malnutrition, cirrhosis, angioedema, and anaphylaxis, which should be excluded on clinical and paraclinical findings [29].

8. Treatment

In general, eliminating the precipitating factor is the cornerstone of SCLS management. SCLS is predominantly managed conservatively in the early stages with osmotic drugs, diuretics, colchicine, renal replacement therapy, hemofiltration, and albumin transfusion [50,51]. However, in later phases, surgical drainage might be needed to extract the accumulated fluids from body cavities to restore vital organs function [52]. In order to better manage SCLS, some authorities classify this condition into 4 grades: grade 1

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(hypotension responsive to oral fluid therapy), grade 2 (intravenous hydration without hospital admission), grade 3 (life-threatening and requiring ICU admission), and grade 4 (fatal) [7].

Pulmonary capillary leak syndrome can be managed with oxygen therapy non-invasive or invasive mechanical ventilation [53]. Steroids help suppress the hyperinflammatory response [54,55], whereas theophylline, beta 2 agonists, aminophylline, lisinopril, montelukast, imatinib, and chronic treatment with IVIg may prevent relapses [50,56,57].

9. Prognosis

Complications of SCLS, triggered by any condition, include thromboembolism caused by the hemoconcentration and hyperviscosity, renal failure, pericardial effusions, tamponade, and cardiac arrest [6]. Moreover, compartment syndrome and the resultant amputations, in addition to sensorimotor neuropathy, can occur as a result of severe peripheral anasarca [58]. Mortality could be due to hypovolemic shock, rhabdomyolysis, arrhythmia, pulmonary edema, renal failure, refractory shock, and thromboembolism [39].

10. Prevention

As a preexisting SCLS can be exacerbated following any precipitating factors, such as infection or vaccination [59], it is better to be vigilant and weigh the risks and benefits of vaccinating individuals with a history of this disorder. Some authorities even prohibit adenoviral vector vaccines in individuals with a history of SCLS. If vaccinated, close monitoring with regular blood pressure measurement, weight, urine output, and hemoglobin and albumin levels is reasonable. Furthermore, in patients with a history of severe episodes of SCLS, who are decided to be vaccinated, administering IVIg before vaccination or monthly IVIg infusions during the COVID-19 pandemic may prevent further attacks [60,61].

11. Conclusion

As previously mentioned, Systemic capillary leak syndrome (SCLS) is an uncommon disease defined by the presence of extreme hypotension, hemoconcentration, and hypoalbuminemia due to leakage of plasma fluid and proteins into the interstitial space. SCLS is among the most important immune diseases triggered by the SARS-CoV-2. According to existing evidence, SARS-CoV-2 infection and COVID-19 vaccination could cause this life-threatening condition. SCLS could lead to severe complications like thromboembolism (caused by hemoconcentration and hyperviscosity), renal failure, pericardial effusions, tamponade, and cardiac arrest. Since there are no specific diagnostic criteria and tests for determining SCLS, the diagnosis is excluded. After excluding other causes of hypovolemic shock, the diagnosis of SCLS can be considered on the presence of the classical triad of hypotension, hemoconcentration, and hypoalbuminemia. A wide range of conditions can be listed as the differential diagnosis for cases of suspected SCLS. The most important ones are septic shock, nephrotic syndrome, anaphylaxis, hereditary angioedema, drug reactions, exudative enteropathy, and ovarian hyperstimulation. Early stages of SCLS should primarily be managed conservatively with osmotic drugs, diuretics, colchicine, renal replacement therapy, hemofiltration, and albumin transfusion. While, in later phases, surgical drainage might be needed to extract the accumulated fluids from body cavities to restore vital organs' function. Since SLCS has been observed in association with SARS-CoV-2 infection and COVID-19 vaccination, it should be considered a possible diagnosis in COVID-19 patients, and it is advisable to be very cautious and weigh the risks and benefits of vaccination of people with a history of this syndrome.

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Conflicts of Interest: Terence T. Sio reports that he provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure, Inc. and also as a member of the Advisory Board to Galera Therapeutics, which are not in any way associated with the content or disease site as presented in this manuscript. All other authors have no conflict of interests to be declared.

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