Original Article

Efficacy of Stromal Vascular Fraction and Platelet-Rich Plasma Therapy on Post-COVID-19 Nephrotic Syndrome in Diabetic Type 1 Patient: A Case Report

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Abstract

Extrapulmonary complications in currently infected or recovered COVID-19 patients is a concerning problem. One of these complications is post-COVID nephrotic syndrome which usually requires anti-inflammatory agent for treatment. Among the various anti-inflammatory agents available, the combination of autologous activated platelet-rich plasma (aaPRP) and stromal vascular fraction (SVF) is a potential breakthrough therapy. It not only exerts an anti-inflammatory effect, but also a regenerative effect. To our knowledge, this is the first report of aaPRP and SVF therapy in post-COVID nephrotic syndrome patient. A 27-year-old type 1 diabetic female patient was admitted to Hayandra Clinic with symptoms of nephrotic syndrome after being recovered from COVID-19. The use of SVF and aaPRP combination therapy showedimmediate significant improvement in patient's overall kidney function and clinical manifestations.

Keywords: coronavirus disease 2019, nephrotic syndrome, platelet-rich plasma, stromal vascular fraction

Introduction

Nephrotic syndrome, a clinical syndrome which is characterized by massive proteinuria, hypoalbuminemia and edema is a disease caused by the increase in permeability of glomerulus due to the podocyte injury.[1] The new coronavirus disease 2019 (COVID-19) infection is one of the causes associated with this syndrome, them. Post-COVID nephrotic syndrome is one of the extrapulmonary complications found in currently infected or recovered COVID-19 patients. The systemic inflammation caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a causative agent of COVID-19, may damage the kidneys and cause various health issues including nephrotic syndrome.[2,3]

Moreover, as angiotensin converting enzyme-2 (ACE-2) receptor is also being expressed in the kidney, SARS-CoV-2 may infect the kidneys through this receptor causing further damage. Binding of the virus with ACE-2 receptor facilitates the virus to enter the cell enabling it to complete its intracellular replication and inducing cytotoxicity.[4] This extrapulmonary complication is a huge concern as it leads to a more severe illness affecting the

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survival of the patients and the quality of life of recovered patients. In addition, the mortality rate is also increased because of these complications. [2,3] As inflammation is the main cause of this complication, hence, anti-inflammatory agent is required to treat it. However, high dose and long-term use of these anti-inflammatory agents such as corticosteroids may cause further injury in the process.[5] Thus, an alternative anti-inflammatory agent is required to cure the disease. the combination of stromal vascular fraction (SVF) and autologous activated platelet-rich plasma (aaPRP) is a potential cellular therapy which has both regeneration and anti-inflammatory effect. Therefore, this case report aims to report the efficacy of this combination therapy for the treatment of post-COVID nephrotic syndrome.

Case Presentation

A 27-year-old female patient was presented to Hayandra Clinic after she got recovered from COVID-19. Her chief complaints were generalized edema and declined renal function. The patient had a significant medical history of type I diabetes mellitus and valvular heart disease. In addition, the patient had also undergone surgeries for appendicitis and retinopathy. Moreover, the patient had received three injections of corticosteroid to treat the declining renal function. The laboratory evaluation also depicted abnormal findings i.e.massive proteinuria, hypoalbuminemia (3.04 g/dL) and hematuria. Blood urea nitrogen (BUN) and creatinine was also found elevated in the patient with a severely decreased renal function. Based on these clinical and laboratory findings, the patient was diagnosed with nephrotic syndrome. The patient was then recommended to undergo autologous SVF and aaPRP therapies. For this, SVF and aaPRP were administered four times in combination, followed by four solitary aaPRP administrations. Each administration was given at least one week apart through infusion. The patient was also given 3 doses of 500 mg methylprednisolone per day which was later discontinued shortly after SVF and aaPRP therapies were given.

The cell number and viability of patient's SVF from the first (SVF 1) to the fourth SVF administration (re-SVF 3) are shown in table 1. The patient was given SVF 1 as scheduled by the patient. The patient then returned 2 weeks after the first therapy for evaluation and for 2nd administration (re-SVF 1). On evaluation, the proteinuria was found improved from massive to mild proteinuria, no more erythrocytes were found in the urinalysis and no edema was observed. After a week, the patient returned for further evaluation and 3rd administration (re-SVF 2). The clinical evaluations showed that the patient was able to do more activities, was less fatigued with no edema reappearance. One week later, the patient again returned for final dose of SVF (re-SVF 3) Furthermore, the patient did not complain any symptoms on clinical evaluation. After the completion of combination therapy, the patient was continued with four single aaPRP administration therapies.[6]

Table 1: Patient's SVF cell number and viability.

	SVF 1	Re-SVF 1	Re-SVF 2	Re-SVF 3
Cell number	3.33×10^9	2.97×10^9	690×10^6	460×10^6
Viability (%)	99.90	99.66	98.59	99.81

The first aaPRP administration therapy started one week after the last combination therapy. Later, laboratory evaluation showed significant improvements in the patient with decreased creatinine level from 2.8 mg/dL to 2.5 mg/dL and increased blood albumin from 3.04 g/dL to 3.4 g/dL. The remaining three aaPRP administrations were given on weekly basis.

The patient was also assessed for physical activity before and after the therapy through the International Physical Activity Questionnaire (IPAQ). After the treatment, physical activity of the patient was increased from 2 hours/week to 3-4 hours/day. the patient's walking time also improved from 1 hour/day to 90 minutes/day. These improvements led to an increase in physical activity from moderate level of 2346 MET minute/week to high level of 5685 MET minute/week.

Discussion

Kidney complication is a common extrapulmonary complication after recovering from COVID-19. Nephrotic syndrome is one possible kidney complication caused by COVID-19 infection. In this case study, the patient had history of type 1 diabetes mellitus which predisposed her to the nephrotic syndrome. Although the etiology which associates type 1 diabetes mellitus and nephrotic syndrome remains unclear, some studies have associated both with immunological basis.[7] The patient was diagnosed with nephrotic syndrome based on the clinical findings which included generalized edema, massive proteinuria, hypoalbuminemia and microscopic haematuria. These results indicated that the patient had glomerulonephritis which ultimately caused nephrotic syndrome.[1] This damage to the kidney was actually a complication of SARS-CoV-2 infection that was brought about through direct or indirect mechanisms. Being the most active participants in urine filtration, reabsorption and excretion, podocytes and proximal straight tubular cells are the most likely candidates of SARS-CoV-2 host cells in direct mechanism. The virus gains entry into podocytes through the peptidase domain of ACE-2 receptor. As S1 protein has a receptor binding domain, hence this step is achieved by the interaction between S1 protein and receptor. When the

virus infects podocytes, it undergos morphological alterations including effacement of foot processes, vacuolation and even detachment from basement membrane of the glomerulus. Thus, this will cause proteinuria in the patient which leads to hypoalbuminemia. Thereafter, plasma oncotic pressure decreases which leads to the escape of fluid into tissues and fluid retention due to increased aldosterone secretion caused by the decrease of plasma volume. Ultimately, it led to the edema found in the patient. On the other hand, COVID-19 may also cause indirect damage to the kidney causing nephrotic syndrome through the systemic inflammation process. Systemic inflammation will induce release of cytokines, chemokines and infiltration of leukocytes. The podocytes' cytoskeleton is reorganised due to the cytokines such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), leading to change in the morphology and function of these cells.[8,9]

Anti-inflammatory agents such as corticosteroids have been proven useful to treat nephrotic syndrome. Besides regulating inflammation which prevents further injury of the podocytes, glucocorticoid effects of corticosteroids can give an anti-proteinuria effect by protecting podocyte integrity. Moreover, glucocorticoids also help prevent apoptosis of podocytes and increase their progenitors by activating various molecular signals. However, these effects are only achieved if the dose is right and if the patient is not resistant to these steroids.[10] Long-term use and high dose may also cause steroid-related toxicity which causes further harm.[5] Thus, to prevent such harms, the patient in this case study was given the combination of stromal vascular fraction (SVF) and autologous activated platelet-rich plasma (aaPRP) therapies.

The outcome of the patient was satisfactory with the addition of SVF and aaPRP therapies. The patient no longer had edema and became more active physically as measured by the International Physical Activity Questionnaire (IPAQ). Moreover, proteinuria was lessened which indicated the improvement in podocytes. A possible explanation to these improvements is the anti-inflammatory effect exerted by aaPRP. It reduces the inflammatory cytokines which may further induce changes in the morphology and function of podocytes.[11-13] Another possible explanation is the presence of mesenchymal stem cells in SVF which induces regeneration and differentiation of new podocytes. This is achieved through the paracrine actions exerted by SVF through various growth factors which had antiapoptotic, mitogenic and other actions that prevent the effacement, detachment and apoptosis of podocytes.[14] By the end of the therapy, the systemic anti-inflammatory effect exerted by aaPRP also ameliorated the hyperglycemia experienced by the patient from 176 mg/dL to 97 mg/dL. These results suggest that as the patient was suffering from autoimmune type 1 diabetes, the anti-inflammatory effect of aaPRP was able to abolish adverse autoimmunity against insulin-producing cells and was also able to stimulate β-cells proliferation.[15]

Conclusion

The use of stromal vascular fraction (SVF) and autologous activated platelet-rich plasma (aaPRP) therapy showed a promising outcome on adult patient with post-COVID nephrotic syndrome. However, as this is only a case report, further studies are required to confirm these findings.

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