

Exosome Therapy for Livedoid Vasculitis Following COVID-19 Vaccination: A Case Report

Tsung-Kun Lin^{1,2,*}, Chih-Feng Chang^{3,*}, Gwo-Ping Jong^{4,5} 

¹Department of Pharmacy, Tri-Service General Hospital, Taipei, Taiwan, Republic of China; ²School of Pharmacy, National Defense Medical University, Taipei, Taiwan, Republic of China; ³Division of Cardiology, Department of Internal Medicine, Taichung Armed Force General Hospital, Taichung, Taiwan, Republic of China; ⁴Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan, Republic of China; ⁵School of Medicine, Chung Shan Medical University, Taichung, Taiwan, Republic of China

*These authors contributed equally to this work

Correspondence: Gwo-Ping Jong, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan, Republic of China, Email cgp8009@yahoo.com.tw

Abstract: Livedoid vasculitis is a vascular autoimmune disorder affecting the skin. It most commonly occurs in young women. The occurrence of this condition after the coronavirus 2019 (COVID-19) vaccination is rare. The available literature suggests limited use of exosomes in the treatment of livedoid vasculitis. We present the case of a 65-year-old Chinese man who developed livedoid vasculitis after COVID-19 vaccination. We posit that the etiology in this case may be either COVID-19 vaccine-induced immune stimulation or activation of the condition by a rare vaccine component. This case is unique, with no previously reported precedents. The patient was treated intravenously for 1 month with stem cell-derived exosome therapy, using stem cells derived from exfoliated human deciduous teeth. This resulted in improvement in the livedoid vasculitis, with no reemergence of symptoms. This case highlights the therapeutic benefits of exosome treatment for livedoid vasculitis after COVID-19 vaccination. However, large-scale studies are needed before this outcome can be generalized.

Keywords: livedoid vasculitis, COVID-19 vaccination, exosomes, elderly, exfoliated human deciduous teeth

Introduction

Livedoid vasculitis is a chronic autoimmune disease with periodic and recurrent exacerbations.¹ Clinically, it is characterized by three main typical features: livedo racemosa, skin ulcerations, and atrophie blanche. It usually affects both lower limbs bilaterally. Clinical features of Livedoid vasculitis include purpuric macules and papules, followed by the development of acute-onset, small, painful, crusted ulcers. Livedoid vasculitis as a direct consequence of COVID-19 vaccination is not commonly reported, although livedoid skin reactions and other vascular conditions have been observed.^{2,3}

Exosomes are nanosized vesicles that can be released by stem cells as well as other cell types. Given their ability to transport proteins, lipids, and nucleic acids between cells, they have been explored for therapeutic potential in various conditions.^{4,5} They have shown some promise in regenerative medicine and immune modulation. Investigations into the effectiveness of exosome therapy in inflammatory and autoimmune conditions are ongoing.⁵ However, there have been no studies or clinical trials on their use in the treatment of livedoid vasculitis. Livedoid vasculitis is typically treated with anticoagulants, immunosuppressants, and therapies aimed at symptom management and ulcer prevention.⁶ To date, there are no reports on the treatment of Livedoid vasculitis with exosomes. Herein, we report the use of stem cells from human exfoliated deciduous teeth (SHED)-derived exosome therapy in a patient who developed livedoid vasculitis following administration of the third dose of a COVID-19 vaccine (Moderna mRNA-1273).

Case Report

A 65-year-old Chinese man was diagnosed with livedoid vasculitis 5 days after the third dose of a COVID-19 vaccine by a rheumatologist and dermatologist. He presented to our cardiovascular clinic two years later, following referral from a rheumatologist. At presentation, the patient reported a 24-month history of progressively worsening painful skin tightening



and erythematous papules on both thighs (Figure 1). Throughout this period, he had been treated with antiplatelet agents, oral steroids, danazol, and antihistamines; however, his symptoms had progressed (Figure 1). The patient had no relevant medical history and had never smoked cigarettes or abused any substances. He also had no family history of autoimmune diseases. Upon physical examination, we found symmetrical erythematous papules on both thighs (Figure 2). Transcutaneous oximetry revealed

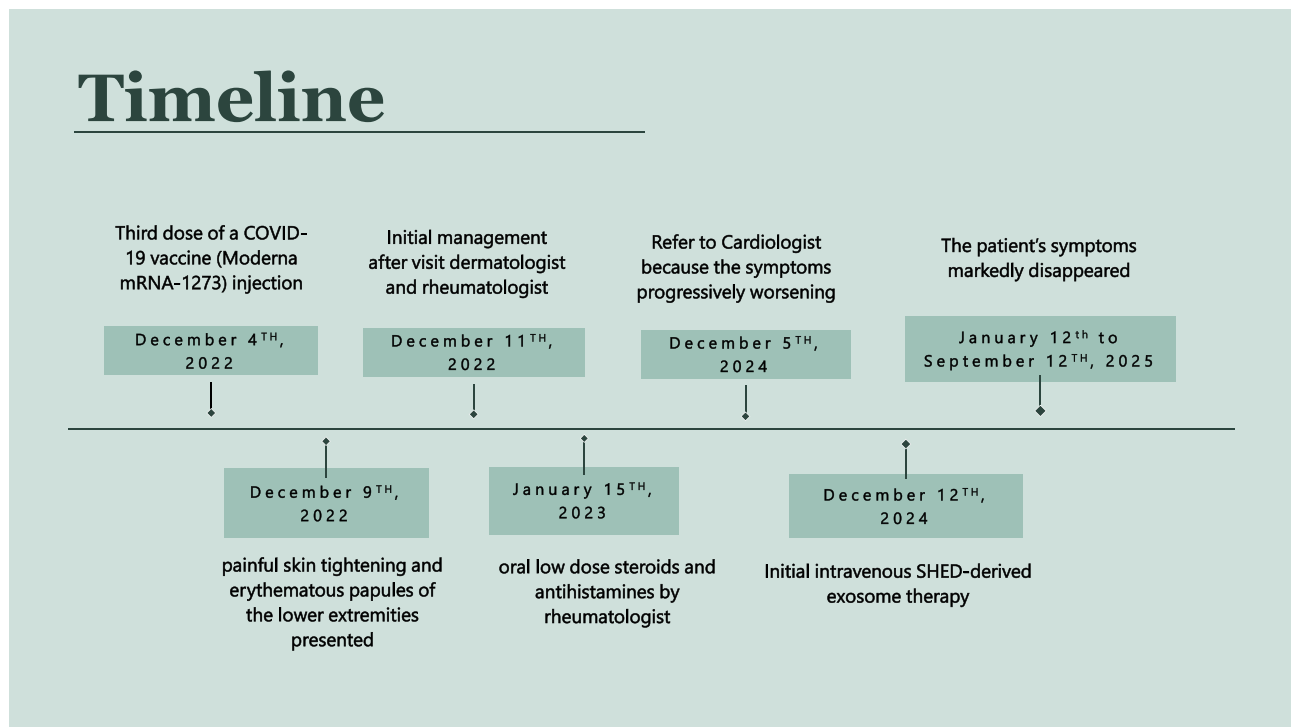


Figure 1 Timeline of this patient.



Figure 2 Erythematous papules appeared on both thighs following the COVID-19 vaccine.



Figure 3 The erythematous papules had disappeared on both thighs following exosome therapy.

stable tissue oxygenation. Laboratory studies showed normal homocysteine levels, protein C activity, and antinuclear antibody levels. Moreover, he was found to be negative for factor V mutation (Leiden heterozygotes), prothrombin gene mutation, lupus anticoagulants, and anticardiolipin antibodies. Histologic analysis of a blood vessel biopsy specimen confirmed livedoid vasculitis. Despite treatment with low-dose steroids and antihistamines for 2 years, the patient's symptoms had persisted and progressively worsened. Therefore, we decided to begin intravenous SHED-derived exosome therapy. SHED-derived exosome was administered as 2-weekly infusions at a recommended dose of 5 mL for 3 cycles. At one-month follow-up, the patient's symptoms had disappeared (Figure 3). No reemergence of symptoms was noted at a 12-month follow-up until now.

Discussion

The prevalence of livedoid vasculitis in general and its association with COVID-19 vaccines is estimated at 5% and 2%, respectively.^{7,8} Livedoid vasculitis is characterized by chronic-recurrent thromboembolic disease with occlusions of dermal vessels, typically in the lower extremities. The lesions frequently leave hyperpigmented areas and atrophic scars. Histological findings include microthrombosis, subendothelial hyalinization of dermal blood vessels, and vasculitis. The etiology of livedoid vasculitis is unclear. It may be an autoimmune disease, the obstruction of capillaries by cryoglobulins, or a form of antiphospholipid syndrome.^{9,10} Furthermore, vascular and capillary lesions characteristic of livedoid vasculitis have been reported to occur in response to certain medications and vaccinations.^{11,12}

Exosomes are membrane vesicles released by various type of cells, including erythrocytes, platelets, monocytes, neutrophils, endothelial cells, mesenchymal stem cells, and malignant cells, during cell activation or several types of programmed cell death.^{13–15} Exosomes derived from SHED are tissue-specific, mesenchymal stem cell-derived exosomes. SHED-derived exosomes were isolated from biofluids of human exfoliated deciduous teeth. Similarly, previous studies have demonstrated the inhibition of cell apoptosis and the anti-inflammatory effects of SHED-derived exosomes.^{16,17} Thus, SHED-derived exosomes are ideal candidates for treating autoimmune diseases and for use in regenerative medicine and immune modulation.

Our patient's condition differed from that of a previously described patient who developed livedoid vasculitis following a COVID-19 vaccination.¹² The vasculitis was observed only at the injection site on her left upper arm and its surrounding area. However, our patient presented with livedoid vasculitis on both thighs. We posit that either the vaccine stimulated the immune system or a rare component of the vaccine triggered the skin disorder. Compared with recent advances in the therapeutic landscape for Livedoid vasculitis, exosome therapy may offer an alternative.¹⁸ To the best of our knowledge, successful treatment of following COVID-19 vaccination with exosome therapy has not been reported in any previous English-language studies.

This case report has some limitations. These include measurements taken without a functional rating scale (For example, the patient-completed Short Form 36 (SF-36) health survey questionnaires have been used to evaluate health-related quality of life, which was collected before and after treatment), the lack of a pathological diagnosis, and the possibility of natural recovery over time. However, we believe that the remarkable clinical results and the absence of side effects provide valuable evidence supporting exosomes as an effective alternative to standard treatment for livedoid vasculitis caused by the COVID-19 vaccine.

In summary, this report describes the successful treatment of livedoid vasculitis following COVID-19 vaccination with intravenous exosomes. Our case illustrated the apparent therapeutic benefits of this treatment. However, further research and clinical trials are needed to explore the potential role of exosome therapy in managing livedoid vasculitis following COVID-19 vaccination.

Ethics Statement

This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. It was approved by the Institutional Review Board of Chung Shan Medical University Hospital (CS2-25008). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Disclosure

The authors declare no conflicts of interest in this work.

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