Case Report

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Treating Erythromelalgia with an IV Infusion of an Extracellular Vesicle Isolate Product

Maxwell Dordevic* **and John Bender**

Department of Medicine, University of Texas, Austin Texas, USA

***Corresponding author:** Maxwell Dordevic, Department of Medicine, University of Texas, Austin Texas, USA, E-mail: mdordevic@utexas.edu

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Abstract

Erythromelalgia is classified as either primary or secondary. Primary Erythromelalgia (PE) is caused by a specific genetic mutation and results in affected patients developing an autoimmune disorder. Secondary erythromelalgia is often associated with myeloproliferative disorders. In some cases, secondary erythromelalgia occurs in neoplastic diseases and autoimmune neuropathies. Erythromelalgia is characterized by the combination of recurrent burning pain, warmth, and redness of the extremities. Burning severe pain is the most predominant symptom, and it can be disabling. The pain is usually caused and precipitated by warmth and physical activities. Bouts of pain typically start with an itch-like feeling and then progresses to a severe burning sensation with the duration ranging from several minutes to hours or even days. Pain symptoms are worse in summer and at night and are usually provoked and exacerbated by heat, ambulation, physical exercise, sitting, leg dependence, and coverage of extremities. Cooling and elevation are the most effective ways to relieve pain symptoms. Patients often immerse affected limbs in ice water, uncover their feet during sleep or walk barefoot in winter. Affected extremities can develop ulceration and gangrene which are not directly attributable to PE but are results of excessive exposure to low temperature in an attempt to relieve pain.

Keywords: Erythromelalgia; Autoimmune neuropathies; Raynaud phenomenon; Propranolol; Antecubital fossa

Introduction

Erythromelalgia is classified as either primary or secondary. Primary Erythromelalgia (PE) is caused by a specific genetic mutation and results in affected patients developing an autoimmune disorder. Secondary erythromelalgia is often associated with myeloproliferative disorders [1]. In some cases, secondary erythromelalgia occurs in neoplastic diseases and autoimmune neuropathies [2]. Erythromelalgia is characterized by the combination of recurrent burning pain, warmth, and redness of the extremities. Burning severe pain is the most predominant symptom, and it can be disabling. The pain is usually caused and precipitated by warmth and physical activities [3]. Bouts of pain typically start with an itch-like feeling and then progresses to a severe burning sensation with the duration ranging from several minutes to hours or even days. Pain symptoms are worse in summer and at night and are usually provoked and exacerbated by heat, ambulation, physical exercise, sitting, leg dependence, and coverage of extremities [4]. Cooling and elevation are the most effective ways to relieve pain symptoms. Patients often immerse affected limbs in ice water, uncover their feet during sleep or walk barefoot in winter. Affected extremities can develop ulceration and gangrene which are not directly attributable to PE but are results of excessive exposure to low temperature in an attempt to relieve pain [5].

Differential diagnoses can include Fabric disease, cellulitis, Raynaud phenomenon, frostbite, vasculitis, cellulitis, erysipelas, dermatitis, osteomyelitis, complex regional pain syndrome, Systemic Lupus Erythematosus (SLE), peripheral neuropathy, arterial or venous insufficiency, and gout [6].

The diagnosis of PE depends on the clinical history and physical examinations of the patient. There is no diagnostic test to confirm the diagnosis. The triad of recurrent redness, burning pain, and warmth of the extremities is the diagnostic hallmark of erythromelalgia. Auxiliary tests such as complete blood count, imaging studies, and thermographs can be given for exclusion of other differential diagnoses. Histological analysis is not typically useful because of its limited specificity [7].

There is no cure for PE as of 2019. The goal of current treatments is to attempt to make the condition bearable. Frequently used pain-relieving drugs include NSAIDs, opiates and opioids, and sodium channel blockers such as lidocaine, carbamazepine, and mexiletine. Other reported medications include capsaicin cream, magnesium, amitriptyline, sertraline, gabapentin, nifedipine, propranolol, and misoprostol. These treatments have been shown to have limited success. IV infusions of nitroprusside, lidocaine, prostacyclin, and cyclosporine have been reported with minimal efficacy. Patient's symptoms often worsen over time [8].

The Mesenchymal Stem Cell (MSC) is an adult stem cell found throughout the vascular system (known as a pericyte), in adipose tissue, and also in the bone marrow. The MSC has many functions, including powerful anti-inflammatory capabilities and the ability to modulate the immune system. The MSC is able to

accomplish these functions *via* paracrine release of active Growth Factors (GFs) and exosomes. The exosome is a 30 to 150-nanometer bi-phospholipid membrane-enclosed structure created by the endosome [9]. The exosome contains active GFs but, most importantly messenger and micro RNA. The exact type and quantity of anti-inflammatory and immune modulation RNA is dependent on the micro-environment surrounding the MSC. Exosomes are released into the extracellular matrix and taken up by a receptor cell where its GF and RNA contents can restore a physiologic environment. Extensive research is currently being conducted to evaluate the safety and efficacy of utilizing MSC exosomes to treat various autoimmune conditions [10]. This is a case report of the first erythromelalgia patient treated with an IV infusion of bone marrow derived Mesenchymal Stem Cell (MSC) Extracellular Vesicle Isolate Product (EVIP) containing active GFs and exosomes [11].

Case Presentation

The patient is a 65-year-old white female suffering from Fabris disease of the kidney and Erythromelalgia of the bilateral palms. She has suffered severe symptoms for several years. Her progressive condition has resulted in significant debility. It severely affected all of her activities of daily living. She found it difficult to perform simple tasks such as dressing herself, personal hygiene, or preparing meals. She was forced to ultimately take a disability retirement from being a nearly tenured professor at a local state university.

She failed extensive conservative treatment with Tylenol, oral NSAIDs, topical NSAIDs, oral steroids, Station enter Palmer injections, nerve blocks, cold treatments, acupuncture, and numerous other therapies. She experienced no improvement with IV steroids. Eventually she became a habitual opiate user. She developed tolerance to her narcotic medication and occasionally experienced side effects such as over sedation and withdrawal symptoms. She presented to our clinic after having been terminated for opioid contract violations by her previous provider. We agreed to take on her case with the understanding that we would search for better treatments [12].

Her workup included an antinuclear antibody level, CBC sedimentation rate, electrolytes, liver function tests, all of which were normal. She underwent an inpatient hospital evaluation with multiple specialties. It was felt that she would best be managed by chronic pain management for her autoimmune condition and was discharged [13].

Her physical exam always revealed generalized intense palmer erythema. Her palms were extremely hypersensitive to touch. She had mild palmer edema without actual induration. The erythema did not blanch with pressure. She maintained flexion at the MCP, PIP, and DIP joints for maximum comfort. She was unable to perform a grip strength test due to her pain [14].

The intravenous exosome infusion

After expanded informed consent, intravenous access was established in the antecubital fossa. At this point 5 cc of the frozen EVIP exosomes (ExoFlo-Direct Biologics, St. Louis MO) was thawed to room temperature and infused over 30 seconds. The patient experienced no adverse reactions. Her vital signs remained stable, and she was released. The entire procedure took 15 minutes [15].

One week following the 5cc EVIP exosome infusion, the patient noticed a significant reduction in pain increased function of her hands, and a taper of her methadone was initiated. Figure 1 shows pre-procedure photographs, and the photographs in Figure 2 show the results of infusion at eight weeks post-procedure. These document the improvement in her chronic palmar erythema. Her pain and hypersensitivity to touch were markedly improved (**Figures 1 and 2**).

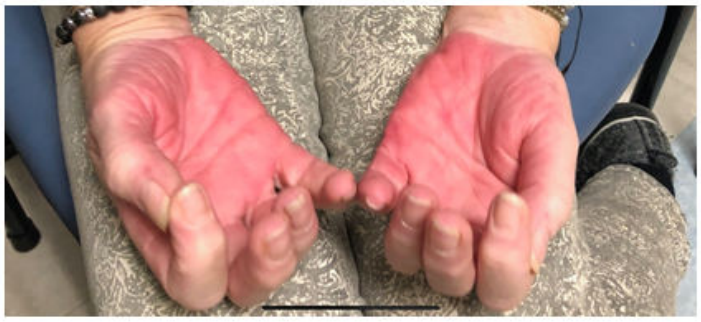

Figure 1: Before infusion, hands bright red, unable to extend fingers secondary to pain.

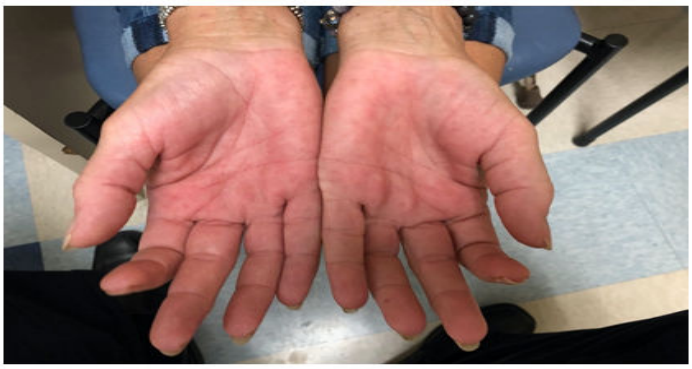

Figure 2: After infusion, hands light pink, able to extend fingers.

Discussion

Erythromelalgia is a rare autoimmune disorder with no current cure. The same is true with all other autoimmune diseases. This is a case study of a college professor with a long history of severe erythromelalgia manifested primarily in her palms. She had tried numerous treatments without success. She became addicted to opioids and was forced to retire due to her severe impairments and disability. She was treated with a single intravenous 5 cc dose of bone marrow derived MSC extracellular vesicle isolate product containing active GFs and exosomes (ExoFlo-Direct Biologics, St. Louis MO). This resulted in a dramatic improvement in her palmar erythema, pain, and hypersensitivity within days after the infusion [16].

Extensive research is being conducted to evaluate the safety and efficacy of using IV infusions of allogeneic cellular MSCs to treat and potentially cure numerous autoimmune diseases. Replacing cellular allogeneic IV infusions with acellular bone marrow-derived MSC exosomes has numerous advantages [17]. It has become increasingly understood by researchers and

clinicians that the clinical efficacy of using MSCs for regenerative medicine is not dependent on the living cells but entirely on their paracrine release of Growth Factors (GFs) and exosomes. Living MSCs are not required to accomplish the signaling of GFs and exosomes. The future of regenerative medicine will be the use of acellular products. Acellular exosomes derived from bone marrow MSCs provide a consistent product that has extensive characterization, which includes advanced particle analysis, proteomic evaluation, and USP<71> sterility assurance. Think of acellular bone marrow derived MSC exosomes as a therapeutic quality product that is consistent, standardized, and quality tested regarding dose and activity [18].

Conclusion

Infusions of bone marrow derived MSC acellular exosomes result in down regulation of systemic inflammation and appear to restore autoimmune diseases to physiologic homeostasis. This type of therapy is being extensively studied as a possible safe and efficacious treatment and potential cure for autoimmune diseases.

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