Use of plasma rich in growth factors for symptoms of diabetic neuropathy

S J Roman and Zach Broyer

RegeneSpine Regenerative Spine and Joint Institute, New Jersey, USA and Advanced Relief Institute, Florida, USA

Summary

Painful peripheral polyneuropathy is a common complication of diabetes mellitus (DM) and is a significant source of chronic disability and remains a challenging condition with no available disease-modifying treatment. In the present case report, we describe the treatment of a patient featuring painful diabetic neuropathy with perineural injections of autologous plasma rich in growth factors (PRGF). At one-year post-procedure, the patient exhibited improved scores on the neuropathic pain scale and improvement in the activity level.

Learning points

- Plasma rich in growth factors (PRGF) is an autologous product that can be prepared and administered in a physician's office.
- PRGF can be infiltrated as a liquid, creating a three-dimensional gel scaffold in the body.
- PRGF releases growth factors involved in nerve healing.
- PRGF may be established as a potent alternative treatment of painful diabetic polyneuropathy.

Background

Peripheral neuropathy is a common complication of diabetes mellitus, with a wide spectrum of clinical manifestations that encompass focal and multifocal forms resulting in an impaired quality of life, as well as in increased morbidity and mortality with no available disease-modifying treatments (1). Platelet-rich plasma (PRP) has been used in the treatment of diabetic neuropathy (2) and neuropathic pain (3). Plasma rich in growth factors (PRGF) is a subtype of PRP that stimulates tissue regeneration and may promote neuronal healing and survival. A case report demonstrated clinical improvement in the treatment of nerve injury with PRGF (4). This is the first reported case, we are aware of, utilizing PRGF in the treatment of diabetic neuropathy.

Case presentation

A 74-year-old white non-smoking female patient presented for consultation per her podiatrist due to upper and lower extremity pain. She had a history of coronary artery disease with myocardial infarction, a twenty-eight-year history of diabetes mellitus type II, and a five-year history of seronegative rheumatoid arthritis. She reported progressive deterioration of her symptoms with pain, numbness, and tingling in the upper and lower extremities bilaterally including complete numbness of the toes. She reported dropping objects and instability due to decreased sensation of the lower extremities. She was homebound except for trips to the store due to severe pain while walking. She reported an inability to differentiate warm and cold sensations and slept with three comforters.
on her feet due to the sensation of coldness of her feet. She was taking pregabalin 100 mg twice daily, with little clinical benefit. Her antihyperglycemic medications included metformin 500 mg once daily and sitagliptin 100 mg once daily, and for rheumatoid arthritis, she was taking tocilizumab 690.1 mg once a month. Her other diabetic complications included renal insufficiency, which began with an anaphylactic reaction to the dye used for angiography at the time of a myocardial infarction 4 years prior.

**Investigation**

The conducted physical examination revealed deep tendon reflexes of 1/4 at the bilateral biceps, triceps, and patellar tendons, and 0/4 at the bilateral Achilles tendons. No plantar response was featured. Decreased light touch sensation was noted in the hands, lower legs, and feet, with the absence of light touch sensation in the toes. There were no foot deformities. The BMI was 31.9 corresponding to adiposity grade I WHO. Electromyogram and nerve conduction studies of the upper and lower extremities bilaterally demonstrated mild to moderate sensorimotor peripheral polyneuropathy as well as mild left ulnar neuropathy at the elbow. Laboratory studies included HbA1C 5.9% (normal value below 5.9%), and the estimated glomerular filtration rate was 31 mL/min (normal value over 59 mL/min). There was no family history of diabetes mellitus.

**Treatment**

After informed consent, the patient wished to proceed with treatment using PRGF (Endoret® PRGF®, BTI Vitoria-Gasteiz, Spain). For PRGF preparation, 72 mL of peripheral blood was withdrawn and put into 9 mL tubes containing 3.8% sodium citrate. Afterwards, the blood was centrifuged (BTI System IV, Vitoria, Spain) at 580 g for 8 min, and the plasma column was fractioned into Fraction 1 (F1) and Fraction 2 (F2). F2 is defined as the 2 mL of platelet-rich plasma just above the leukocyte buffy coat, and F1 is defined as the remaining plasma volume above F2. This process yielded 12 mL of the F1 fraction with approximately a 1–1.5 fold increase in platelets and 12 mL of the F2 fraction with approximately a 2–3 fold increase in platelets. To increase the volume of injectate, we combined 12 mL of the F2 fraction with 6 mL of the F1 fraction for a total of 18 mL of product which was activated with 20 µL of calcium chloride per milliliter PRGF prior to injection. The Konica Minolta Sonimage® HS-1 ultrasound unit with a 4–18 MHz high-frequency linear transducer was used to scan selected nerves (Konica Minolta Wayne, NJ, USA). 1.5 mL was injected perineurally under live ultrasound guidance using a 25-gauge 1.5” needle adjacent to the median and ulnar nerves proximal to the wrist, as well as the tibial, deep peroneal, superficial peroneal, and sural nerves at or proximal to the ankle.

**Outcome and follow-up**

Neuropathic pain was measured using the Neuropathic Pain Scale (5) at baseline and at 7 months and 12 months post therapeutically. Scores were 71, 39, and 29, respectively (Fig. 1). One-month post-treatment, the patient discontinued pregabalin. She was able to differentiate among walking surfaces, sense warm and cold, and reported an improved sense of balance and overall activity level. She was able to sleep comfortably with one comforter on her feet. Follow-up physical exam demonstrated nearly normal light touch sensation in the hands, lower legs, and feet, with the return of partial light touch sensation in the toes. By her seven-month follow-up, she was gainfully employed and had returned to her normal activities including walking without limitation, training and showing dogs, and traveling internationally.

**Discussion**

PRGF may be infiltrated as a liquid-to-gel injectable three-dimensional scaffold to assist in nerve repair. Fibrin is then broken down via fibrinolysis, thereby releasing cell signaling molecules such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF) (6, 7).
Evidence suggests that the therapeutic effects of PRP on nerve regeneration are due to neuroprotection and prevention of cell apoptosis, stimulation of angiogenesis, enhancing axonal outgrowth capacity, overcoming the inflammatory microenvironment, and decreasing denervated target muscle atrophy (8).

Painful peripheral diabetic polyneuropathy is challenging to treat and affects many people. Further investigation is warranted into treatments for this disorder utilizing regenerative medicine techniques.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
Written informed consent for publication of clinical details was obtained from the patient.

Author contribution statement
S J Roman is the treating physician who designed and drafted the manuscript. Z Broyer contributed to the design of the manuscript as well as the analysis of data, critically revised the article, and approved the version to be published.

References
8 Sánchez M, Garate A, Delgado D & Padilla S. Correction: Platelet-rich plasma, an adjuvant biological therapy to assist peripheral nerve repair. Neural Regeneration Research 2017 12 338. (https://doi.org/10.4103/1673-5374.202914)