Erythromelalgia Remission Associated with GLP-1 Receptor Agonist Therapy

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BACKGROUND

- Erythromelalgia (EM) is a rare neurovascular disorder characterized by episodic burning pain, erythema, and increased skin temperature in the extremities.
- Primary EM: Associated with gain-of-function mutations in the *SCN9A* gene (encoding $Na_v1.7$ voltage-gated sodium channels).
- Secondary EM: Frequently secondary to underlying myeloproliferative disorders, autoimmune conditions, or peripheral neuropathy.
- Lacks standardized clinical management guidelines. Highly refractory to conventional neuropathic pain therapies (e.g., gabapentinoids, topical anesthetics, oral analgesics).
- Pathophysiology: Involves complex interactions between neurogenic inflammation, microvascular dysregulation, and peripheral nerve hypersensitivity.
- Novel Target: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) demonstrate broad systemic anti-inflammatory, neuroprotective, and vascular modulatory properties.
- Objective: Report a novel case of refractory secondary erythromelalgia achieving complete clinical remission following treatment with semaglutide.

METHODS

- **Consent:** Patient informed consent was obtained prior to the presentation of this case report.
- **Privacy:** All patient-identifiable data and protected health information have been de-identified.

CASE PRESENTATION

- 38-year-old female presenting to the outpatient pain clinic.
- PMHx: Psoriatic Arthritis (autoimmune predisposition), Ehlers-Danlos Syndrome, Asthma, Class II Obesity
- Chief Complaint: 3-week history of severe, bilateral lower extremity burning pain, warmth, and intense erythema extending from the calves to the toes.
- Previous Therapy Failures: Prior EM flare-ups were refractory to multiple standard pain interventions: High-dose oral aspirin, Topical lidocaine 5% patches, Gabapentin titrated to therapeutic doses
- Initiated Semaglutide for medical weight management 3.5 years ago with dramatic, rapid improvement in baseline burning pain and erythema.
- Achieved complete clinical remission within 14–21 days of starting GLP-1 RA therapy.
- Treatment included weekly maintenance dose of subcutaneous semaglutide 1.7 mg / 0.75 mL.
- Experienced zero disease exacerbations or flares while maintaining therapy.
- Medication paused abruptly due to a temporary lapse in insurance coverage.
- Within 2–3 weeks of discontinuation: Severe bilateral lower extremity EM flare recurred, matching previous presentations.



Figure 1.Representative Presentation of Lower Extremity Erythromelalgia.

Bilateral erythema and dependent edema extending from the calves to the digits. *(Note: Representative clinical image included for educational purposes; not the actual patient).*

DISCUSSION

- A clear temporal correlation was observed between GLP-1 RA administration, disease remission, and subsequent relapse upon withdrawal.
- GLP-1 receptors are widely expressed on endothelial cells, vascular smooth muscle, and peripheral nerve terminals.
- GLP-1 RAs reduce neuropeptide release (e.g., CGRP, Substance P) and inhibit microvascular hyperpermeability to reduce neurogenic inflammation
- GLP-1 RAs can also attenuate localized endothelial dysfunction and abnormal vasodilation characteristic of EM.
- Downregulation of systemic and peripheral inflammatory cytokines, particularly advantageous given the patient's underlying psoriatic arthritis.

CONCLUSIONS

- Demonstrates the potential utility of GLP-1 RAs as novel therapeutic agents for refractory, inflammatory, or neurovascular pain conditions.
- Warrants further clinical investigation and translational research into GLP-1 pathway targeted therapies for erythromelalgia.

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