Case report

High-Dose Epoprostenol and Adjunct Therapies for Refractory Raynaud's Phenomenon Associated with Anti-Jo Antibodies: a Case Report

Abstract

This case report highlights the use of high-dose Epoprostenol for managing severe digital ischemia associated with antisynthetase syndrome (ASyS) and anti-Jo antibodies, emphasizing its vasodilatory benefits and challenges with tolerability at higher doses.A multi-modal treatment strategy, including calcium channel blockers, phosphodiesterase inhibitors, hyperbaric oxygen therapy, and prostacyclin analogs, was critical for optimizing outcomes in refractory Raynaud's phenomenon.This case underscores the importance of individualized treatment regimens and the need for ongoing monitoring and adjustments to balance therapeutic efficacy with patient safety.The report contributes to the limited literature on the management of severe digital ischemia in ASyS and emphasizes the potential role of adjunct therapies in improving patient outcomes.

Keywords: antisynthetase syndrome, digital ischemia, adjunct therapies, hypotension

Introduction:

Digital ischemia and necrosis are severe manifestations of vascular compromise often seen in autoimmune conditions. Antisynthetase syndrome (ASyS) is a rare autoimmune disorder characterized by the presence of anti-synthetase antibodies, such as anti-Jo-1, which are typically associated with myositis, interstitial lung disease (ILD), arthritis, Raynaud's phenomenon, and "mechanic's hands." [1]While the full spectrum of ASyS includes these features, patients can present with isolated symptoms, complicating diagnosis and management.

Current treatment guidelines emphasize the use of systemic corticosteroids as a first-line therapy to manage inflammation. Methotrexate and other immunosuppressants, such as Azathioprine, are often used as adjuncts.[2] However, in cases resistant to standard treatments for Raynaud's phenomenon, alternative options such as intravenous prostacyclin analogs, including Epoprostenol, are considered. Epoprostenol is known for its potent vasodilatory effects, which can improve blood flow and reduce ischemic symptoms in various conditions. [3]Despite its potential benefits, high-dose Epoprostenol therapy is associated with significant side effects, including hypotension and systemic reactions,

which can limit its utility in certain patients.

This report presents the case of a 71-year-old male with severe digital ischemia and necrosis, anti-Jo antibodies, and a working diagnosis of ASyS without the typical features of myositis or ILD. The patient's treatment course, including the use of high-dose Epoprostenol, is discussed in detail.

Case Presentation:

71-year-old male, living independently was referred to the intensive care unit (ICU) for systemic vasodilators due to digital ischemia. His medical history includes pre-diabetes (HbA1C 6.1% in November 2023, 6.5% in May 2024), dyslipidemia, hypertension, and colonic polyps.

Three months prior to admission, the patient presented to the emergency department with left foot pain, swelling, and erythema, initially treated for cellulitis or gout with Cephalexin and anti-inflammatories. Improvement was noted, but four weeks later, he returned with bilateral inflammatory polyarthritis and new purple discoloration of his fingertips. He also reported a 40-pound weight loss and worsening fatigue, but no fevers or night sweats.

He was admitted to the medical ward, started on prednisone (initially 30 mg daily, increased to 70 mg for 48 hours, then 50 mg daily), and discharged with a referral to the internal medicine clinic. Despite treatment, he experienced worsening acrocyanosis and necrosis of his left fifth fingertip. Rheumatology added methotrexate, and due to further progression, he was referred for systemic vasodilation therapy.

Investigations:

The patient's investigations revealed the following significant findings: elevated IgA (4.3 g/L), positive anti-Jo antibodies, and an ESR greater than 120 mm/hr with CRP levels that improved from 99 mg/L to 12.7 mg/L in June. Rheumatoid factor (RF), anti-CCP, PR3, myeloperoxidase, anti-Ro, EJ, KU, OJ, Mi-2 alpha, Mi-2 beta, NXP-2, PL-7, PL-12, SRP, MDA5, and anti-dsDNA antibodies were negative. Cold agglutinins were positive with a titre of 1 and a thermal amplitude of 22°C. Cryoglobulins and DAT were negative. Additional tests, including UPEP, SPEP, free light chains, hepatitis B and C serologies, and neoplastic workup, were negative or normal. CT angiography of the chest and abdomen was negative

for medium vessel vasculitis, and bilateral hand X-rays showed no erosive changes.

Treatment:

Upon admission to the ICU, the patient's management plan was developed to address his severe digital ischemia and evolving antisynthetase syndrome comprehensively. The treatment regimen initially included systemic corticosteroids, with Prednisone being administered at 50 mg daily. This dose had been adjusted previously, with a temporary increase to 70 mg daily for 48 hours, before returning to 50 mg daily to provide anti-inflammatory and immunosuppressive effects. Alongside Prednisone, Methotrexate was prescribed at a dose of 20 mg weekly, with Folic acid 5 mg supplementation. Regular monitoring of renal function and liver enzymes was planned to assess tolerance and detect adverse effects early.

To address the worsening digital ischemia, the patient's treatment regimen was expanded to include both topical and systemic therapies. Topical nitrate patches were applied to the affected fingertips (2, 3, and 4 of the left hand, and 3, 4, and 5 of the right hand) to promote local vasodilation. Systemically, Epoprostenol, a prostacyclin analogue, was initiated at 2.5 ng/kg/min for refractory Raynaud's phenomenon. The dosage was carefully titrated based on the patient's response and tolerance. Initially, the patient received 2 ng/kg/min for the first 24 hours. On the 2nd day, due to insufficient clinical improvement, the dose was increased to 5 ng/kg/min. Despite slight symptom relief, the dose was further escalated to 7.5 ng/kg/min on the 8th day. After consulting with the rheumatologist, the Epoprostenol dose was increased to 10 ng/kg/min on the 9th day, but the patient experienced significant side effects, including flushing and a presyncopal episode. Consequently, the dose was reduced back to 7.5 ng/kg/min, and then further decreased to 2.5 ng/kg/min over the next 24 hours. Due to the patient's adverse reactions at higher doses and lack of substantial improvement, he was transferred to a tertiary care center on the 12th day of ICU admission for hyperbaric oxygen therapy, aimed at enhancing oxygen delivery to the ischemic tissues and promoting healing.

The patient tolerated the hyperbaric oxygen therapy well and was continued on lower doses of the Epoprosterenol infusion. However, an increase in pain and digital discoloration was noted following the discontinuation of the Epoprostenol infusionprompting

the clinical team to evaluate the long term use of prostacyclin analogues. Sildenafil, a phosphodiesterase type 5 inhibitor, was administered at the maximum dose of 50 mg three times daily. The calcium channel blocker Nifedipine XL was initiated at 90 mg daily, with an option to increase to 120 mg daily based on blood pressure tolerance. Fluoxetine was prescribed at 20 mg daily to promote vasodilation by enhancing nitric oxide bioavailability and improving endothelial function through serotonin receptors. Aspirin, at a dose of 160 mg daily, was included due to the vaso-occlusive nature of the patient's Raynaud's phenomenon. Additionally, Atorvastatin at 40 mg daily was added for its pleiotropic effects on endothelial function.

To continue addressing his ischemic condition, monthly infusions of Iloprost were planned as an outpatient treatment. This decision was made to provide ongoing vasodilatory benefits while minimizing side effects experienced with Epoprostenol. Throughout his stay, regular monitoring of blood pressure, renal function, and liver enzymes was conducted to adjust medication dosages as needed, and consultations with rheumatology and vascular surgery were performed to ensure comprehensive care.

Discussion:

Managing digital ischemia and necrosis in antisynthetase syndrome is complex, as demonstrated by this patient's case. In refractory Raynaud's phenomenon, prostacyclin analogues play a crucial role by promoting vasodilation, providing anti-platelet effects, and protecting endothelial cells. These agents are particularly useful in cases with underlying vascular damage, as they can help compensate for the loss of endogenous prostacyclins caused by the disease. Epoprostenol, a potent vasodilator, has shown effectiveness in improving peripheral blood flow and alleviating severe digital ischemia symptoms. However, the patient's inability to tolerate higher doses of Epoprostenol highlights a significant challenge: while the medication can be beneficial, its side effects and potential adverse reactions at higher doses require careful monitoring and personalized dosing adjustments.

Epoprostenol's effectiveness in enhancing digital blood flow is well-established, but its use can present significant challenges. Early protocols from the 1980s, which involved administering 10 ng/kg/min for 72 hours, were applied to patients without ischemic ulcers.

In Dowd *et al*.'s study, patients tolerated doses of 5-7 ng/kg/min, with only two patients tolerating 10 ng/kg/min. Similarly,Similarly, Rustin *et al*. reported an average tolerated dose of 7 ng/kg/min over 72 hours, starting from 2.5 ng/kg/min and gradually increasing by 1 ng/kg/min up to 10 ng/kg/min.

For our patient, it became evident that higher doses of Epoprostenol, necessary to manage worsening ischemia, resulted in significant side effects, including increased pain and adverse reactions. Other studies have shown that protocols using higher doses (≥7.5 ng/kg/min) administered as intermittent infusions weekly for 4 to 5 hours over three weeks in patients with digital ulcers appear to improve tolerability. This highlights the importance of a tailored approach to dosage and underscores the need for continuous assessment to balance therapeutic benefits with patient safety.

The additions of a calcium channel blockers, such as Nifedipine, and phosphodiesterase type 5 inhibitors like Sildenafil, provided a multi-faceted approach to managing the patient's condition. Calcium channel blockers help reduce vascular resistance and improve blood flow, while Sildenafil enhances vasodilation through its effects on nitric oxide pathways.[1] This combination, along with the addition of Fluoxetine, Acetylsalicylic acid, and Atorvastatin aim to optimize vascular health and address underlying pathophysiological processes contributing to the patient's digital ischemia.[11]

Hyperbaric oxygen therapy was added to the patient's treatment regimen to promote wound healing and improve oxygen delivery to tissues, which is particularly beneficial in cases of severe ischemia. While the therapy was well-tolerated, it was not sufficient to fully resolve the ischemic issues, necessitating the continued use of oral medications and prostaglandin therapy on an outpatient basis. The choice of parenteral prostacyclin analogs for severe Raynaud's Phenomenon is largely determined by their availability, given the lack of comparative studies. Intravenous Iloprost, administered intermittently over 6 to 8 hours for 3 to 5 days monthly, remains a valuable option for outpatient care.

There are limitations to this case report, most notably, the retrospective nature of the study may have impacted the thorough identification, reporting, and documentation in the patient's medical chart. This report is based on a single patient's experience, which may not fully represent the broader population of patients with antisynthetase syndrome and severe digital ischemia. The responses to treatments such as Epoprostenol and hyperbaric oxygen

therapy can vary significantly among individuals, and the findings may not be generalizable. Additionally, the lack of control or comparison groups means that the effectiveness of specific treatments cannot be quantified relative to alternative therapies or placebo. Future research should include larger cohorts and controlled studies to better understand the efficacy and safety profiles of these treatments in diverse patient populations.

Overall, this case underscores the need for a nuanced and individualized treatment strategy, particularly when dealing with severe digital ischemia associated with Raynaud's syndrome. It also highlights the importance of ongoing evaluation and adjustment of therapies to achieve the best possible outcomes while minimizing adverse effects.

Conclusion:

In summary, this case illustrates the complexities of managing digital ischemia in refractory Raynaud's Phenomenom, particularly with high-dose Epoprostenol therapy. While Epoprostenol was beneficial in improving blood flow, its higher doses were poorly tolerated, highlighting the need for careful dose management and alternative therapies. The patient's multi-faceted treatment, including calcium channel blockers, sildenafil, and hyperbaric oxygen therapy, underscores the importance of a comprehensive approach.

Despite these efforts, the case demonstrates that ongoing evaluation and adjustment are crucial, as responses to treatment can vary. This case contributes valuable insights into managing severe digital ischemia and emphasizes the need for continued research to optimize treatment strategies for similar complex conditions.

Declarations

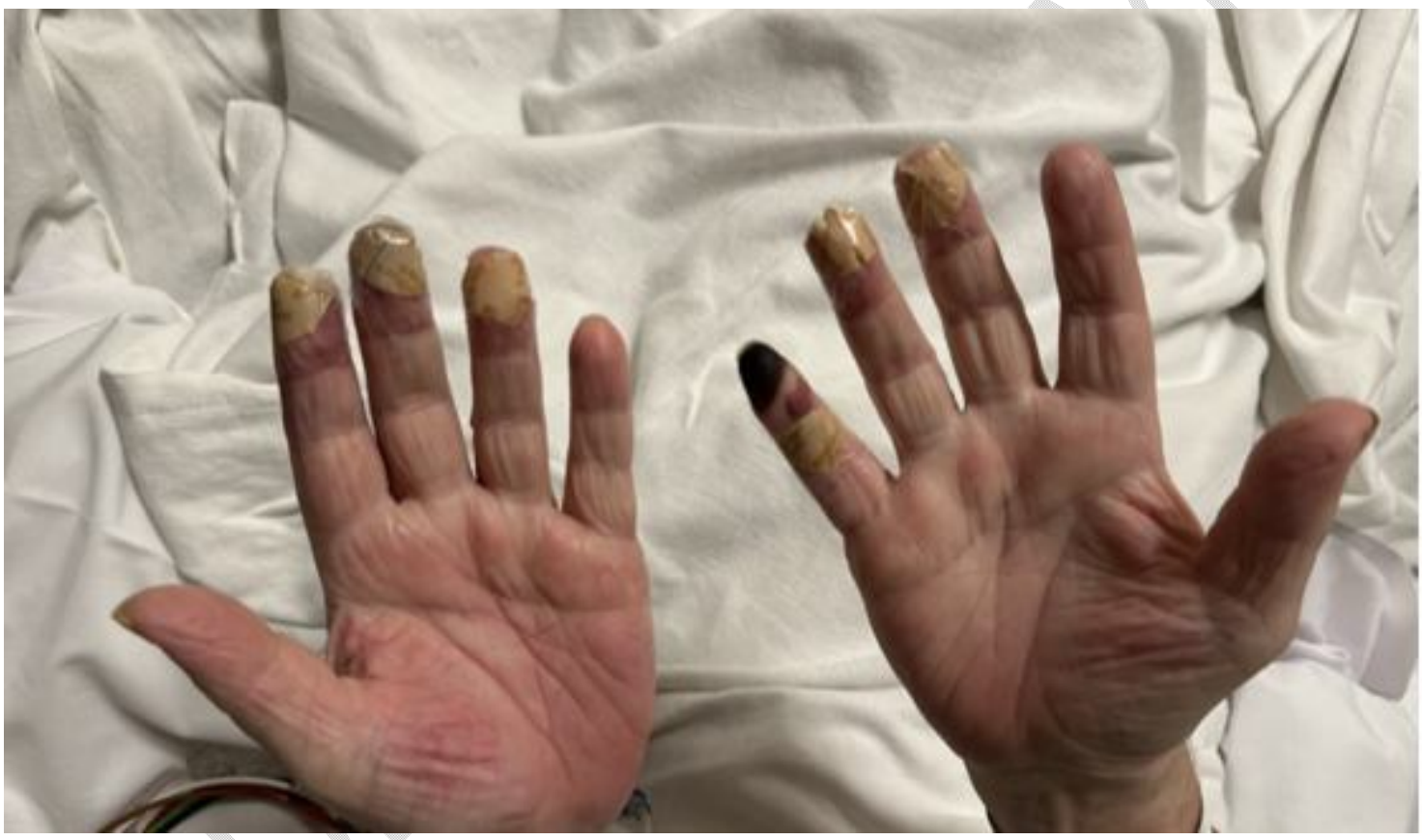
Consent for Publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Availability of Supporting Data: Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Table 1: Epoprostenol Dose and Clinical Effect

Admission	Epoprosterenol dose	Clinical effect/Patient Experience
Day 1	2 ng/kg/min	Initial dose, no significant adverse effects observed.
Day 2	5 ng/kg/min	Increased dose due to insufficient clinical improvement; slight symptom relief.
Day 5	5 ng/kg/min	Continued on same dose and continues to experience symptom relief.
Day 8	7.5 ng/kg/min	Further dose escalation, mild improvement noted.
Day 9	10 ng/kg/min	Increased dose; patient experienced significant side effects including flushing and presyncopal episode.
Day 10	7.5 ng/kg/min	Dose reduced due to adverse reactions; slight improvement in flushing
Day 11	5 ng/kg/min	Continued dose reduction, patient stabilization.
Day 12	2.5 ng/kg/min	Transferred to a tertiary care center for hyperbaric oxygen therapy due to lack of substantial improvement.

Figure 1. Day 3 of therapy: Epoprostenol @ 5 ng/kg/min. Topical nitroglycerin patches in situ.



***All images were obtained with the patient's informed consent, ensuring their privacy and confidentiality were maintained in accordance with ethical standards.*

Figure 2. Day 5 of therapy: Epoprostenol @ 5 ng/kg/min

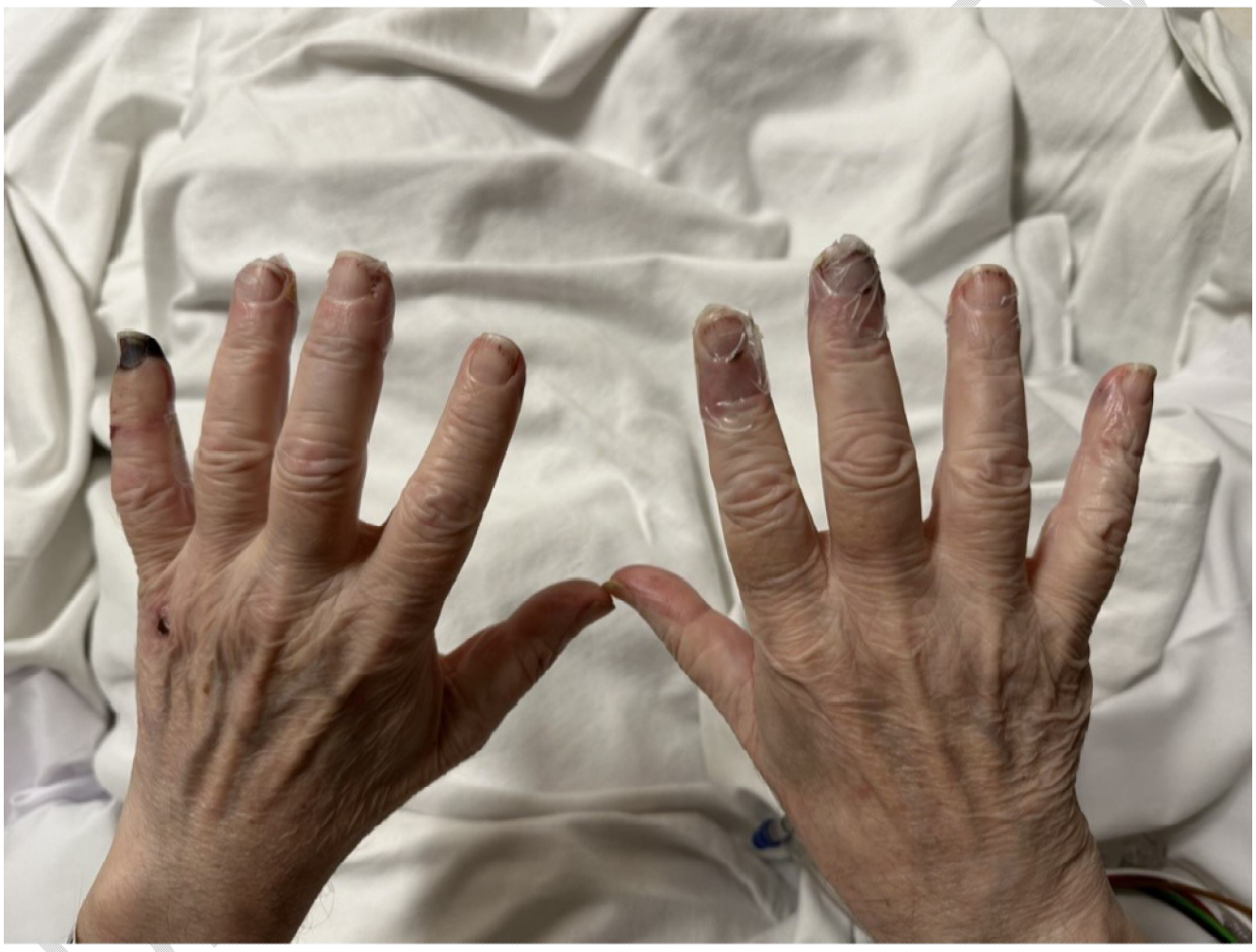


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Figure 3A:Day 11 of therapy. Epoprostenol at 5 ng/kg/min

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Figure 3B:Day 11 of therapy. Epoprostenol at 5 ng/kg/min

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