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Case Report

Frostbite secondary to antimycobacterial-induced peripheral neuropathy: a case report

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Abstract: This case report describes a unique scenario in which antimycobacterial-induced peripheral neuropathy (PN) culminates in severe bilateral foot frostbite. Drug-induced peripheral neuropathy (DIPN) is explored in the context of TB treatment, highlighting the role of medications such as isoniazid (INH) and their potential to cause PN. The report highlights the importance of identifying PN in patients undergoing antimycobacterial treatment. Early recognition and proper management of PN is crucial to prevent complications. Notably, the report advocates for patient education regarding medication side effects and avoiding harmful practices, such as ice immersion, to alliviate neuropathic pain. Emphasis is directed towards the need for a multidisciplinary approach to patient care and a focus on preventative strategies to improve patient outcomes and avoid severe debilitating complications.

Keywords: Frostbite, peripheral neuropathy, isoniazid (INH), drug-induced peripheral neuropathy (DIPN)

Introduction

Frostbite is local tissue damage induced by exposure to temperatures below freezing for several hours [1]. Frostbite is a well-known injury among those living in places with sub-zero temperatures and frigid winters. With the wide acceptance of cooling therapy and the use of ice packs to reduce pain, reports have emerged showing frostbite cases secondary to the use of ice packs for sports injuries or heat strokes [2-5].

Numerous risk factors contribute to increased susceptibility to frostbite, each affecting peripheral circulation and tissue perfusion differently. Risk factors include diabetes mellitus and neuropathy, which can impair cold-induced pain perception and injury detection. Additionally, reduced metabolic heat production is observed in certain groups such as children, older adults, and those with specific endocrine disorders. Furthermore, exposure to substances such as drugs, alcohol, tobacco, and immobilization can increase the risk of frostbite [1, 6, 7].

Peripheral neuropathy (PN) is a painful condition resulting from an insult that affects the nerves and compromises information relay. Multiple causes have been identified that disrupt nerve function, including tuberculosis (TB) infection. Moreover, TB is a well-recognized infection that causes morbidity and mortality worldwide, and it requires multi-drug therapy in addition to a long course of treatment. PN rates vary among TB patients based on whether the mycobacterium is drug-sensitive or drug-resistant [8]. The incidence of PN in drug-sensitive TB patients ranges from 0% to 10%. In contrast, patients with drug-resistant TB tend to experience higher rates, with reported incidences ranging between 13% and 17% [8].

This report presents a case of antimycobacterial-induced peripheral neuropathy that resulted in inappropriate ice use and ultimately caused bilateral foot frostbite. All procedures were performed according to the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in

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2008. Informed consent was obtained from the patient included in the study.

Case presentation

A 32-year-old female with a history of successfully treated pulmonary tuberculosis (PTB) presented with debilitating bilateral foot pain and unexpected progression of complications. The patient completed a six-month regimen of antituberculosis (anti-TB) medications, including rifampicin, ethambutol, linezolid, moxifloxacin, and pyridoxine (vitamin B6), in addition to her prior history of PTB. Her ordeal began one month after initiating anti-TB therapy, when she developed bilateral burning foot pain. She was previously evaluated by Neurology at a different hospital and had clinical and electrodiagnostic findings suggestive of PN. Despite consultation with various healthcare professionals and modifications to her treatment plan, including the administration of Topiramate, Amitriptyline, and Prednisolone, her symptoms continued to escalate. To combat the relentless burning sensation in her feet, the patient resorted to unconventional self-therapy by immersing her feet in ice for extended periods. This desperate measure, taken to alleviate distress, led to frostbite. One week after self-administered cold therapy, the patient developed a rash and discoloration across her lower extremities. A dermatologist consulted for this new development attributed these manifestations to a reaction to pregabalin, which was prescribed to manage her pain. Pregabalin was promptly discontinued, and Tramadol was prescribed for pain management.

Approximately one week after the onset of peripheral neuropathy (PN) symptoms and unconventional cold therapy, the patient was referred to our medical unit. Clinical examination revealed non-blanching, dark mottled skin affecting most toes, bilateral leg swelling (predominantly on the right side), dusky big toes with delayed capillary refill time, ruptured hemorrhagic blisters, full-thickness skin loss, and dry gangrene affecting the right toes and dorsum of the second to fourth toes. Additionally, there were multiple areas of pus discharge and a noticeable limitation in the ankle range of motion (**Figure 1**).

Despite the inability to palpate the dorsalis pedis and posterior tibial artery pulses bilaterally, a Doppler examination confirmed their activity. Lower limb CT angiography showed patency through the common femoral, superficial femoral, and popliteal arteries, ensuring uninterrupted blood flow to the foot. The conclusive diagnosis was frostbite, an unforeseen consequence of anti-TB-induced peripheral neuropathy and unconventional cold therapy. The patient embarked on daily dressing changes and intravenous antibiotics until the wounds began to demarcate (**Figure 2**). Subsequently, she underwent four surgical debridement sessions over three weeks (**Figure 3**). Owing to the advancing gangrenous changes in her toes, a decisive clinical decision was made to perform transmetatarsal amputation. The patient continued to receive adequate postoperative wound care. The dorsal foot wounds showed increased granulating tissue and were ready for skin grafting, whereas the plantar aspect had no residual defects (**Figure 4**). Unfortunately, ambulation was still challenging, considering the development of ankle stiffness and plantar flexion deformity. The patient followed up with orthopedic surgery and underwent thorough physiotherapy to enhance mobility and daily activity. The focus remains on conservative measures, including upper limb strengthening and ankle exercises, before considering surgery.

Discussion

Frostbite is characterized by an intricate pathophysiological interplay governed by four critical factors dictating its degree of severity: the rate of tissue freezing, the duration of exposure to freezing temperatures, the rate at which rewarming occurs, and the extent of tissue exposure [7]. Within the pathophysiological framework, the rewarming phase is linked to reperfusion injury, which is recognized as the peak of inflammatory marker release, leading to heightened tissue damage. Consequently, an oscillatory pattern involving alternating episodes of limb freezing and rewarming represents a hazard that can potentially exacerbate long-term clinical outcomes and impair limb function [7, 9].

The clinical range of manifestations observed in frostbite cases was catigorized using a two-tiered classification system, distinguishing between superficial and deep injuries. Superficial involvement primarily affects the skin, resulting in observable alterations in skin color, suscepti-

Figure 1. Acute frostbite injury. Dark mottled skin, ruptured hemorrhagic blisters, areas of full-thickness skin loss. A. Right foot. B. Left foot. C. Bilateral foot plantar aspect.

bility to deformation upon pressure, and formation of clear-fluid blisters. In contrast, deep involvement extends beyond the skin, frequently culminating in tissue loss, evident through skin necrosis, hemorrhagic blister formation, ulceration, and gangrene [10]. The severity of the long-term consequences of frostbite corresponds to the depth of the tissue damage. Research by Regli et al. revealed that patients assessed four months or more after frostbite often experience various forms of neuropathy, including sensations such as cold allodynia, paresthesia, hypoesthesia, and hyperhidrosis. Additionally, frostbite arthritis, which resembles osteoarthritis, can occur due to impaired circulation during injury. Frostbite can lead to lifelong growth deformities in children by affecting the epiphyseal cartilage [9].

As the body of literature on the association between TB infection and PN expands, three plausible mechanisms have been elucidated. First, TB influences PN through an immune-mediated pathway mainly involves the formation of granulomas. Additionally, TB-associated neurological syndromes, such as spinal tuberculomas or meningeal TB, give rise to clinical presentations that mirror peripheral neuropathy [6]. Second, patients presenting with concurrent comorbidities such as Diabetes Mellitus (DM), Human Immunodeficiency Virus (HIV) infection, hypothyroidism, nutritional deficiency, or substance misuse already exhibit susceptibility to developing Peripheral PN [1, 6]. The third mechanism, recognized in the literature as Drug-Induced Peripheral Neuropathy (DIPN), typically presents as paresthesia resembling a "sock-and-glove" distribution. A limited number of antimycobacterial medications, notably isoniazid (INH), ethambutol (EMB), and linezolid, are acknowledged for their propensity to induce PN [11, 12].

INH is a first-line antimycobacterial medication and is a known cause of reversible DIPN. It interferes with pyridoxine (Vitamin B6) synthesis, which is essential for nerve function. Historically, pyridoxine deficiency has been associated with PN, typically manifesting as loss of proprioception and pallesthesia. Such iatrogenic complications could be prevented using a daily pyridoxine supplement (6-50 mg/day) as a standard for all TB patients undergoing therapy [11, 12]. The risk of INH-induced PN is dose-dependent. Van der et al. published a review that showed 2-12% of those who received low to standard INH doses (3-5 mg/kg/day) experienced symptoms of PN compared to 44% of those who were treated with high INH dose (16-24 mg/kg/mg) [13]. Moreover, it seems that the commencement of neuropathic symptoms exhibits an earlier onset, typically occurring within a span of 3-5 weeks, in individuals receiving higher doses of isoniazid (INH), in contrast to an onset typically observed near the 16th week among those administered lower doses of the medication [13].

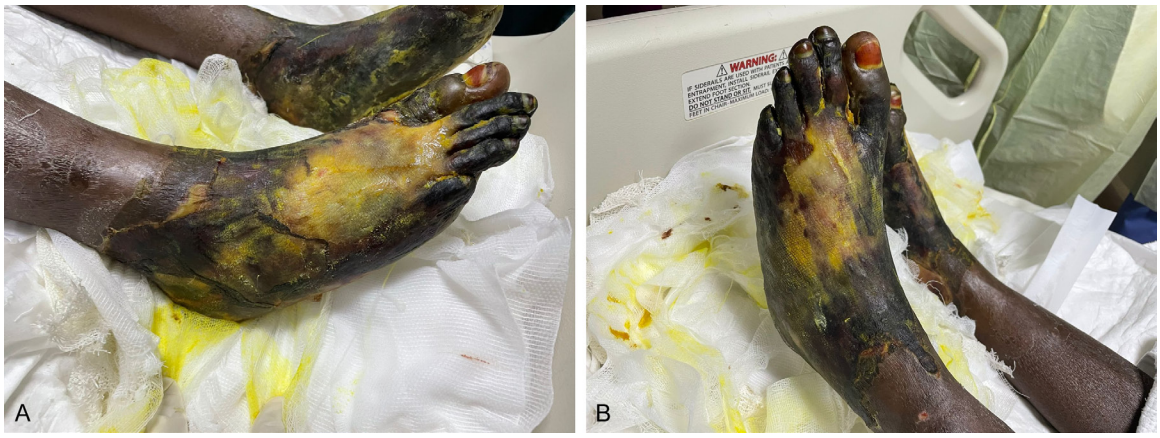

Figure 2. Bilateral foot frostbite injury with signs of demarcation. A. Right foot. B. Left foot.

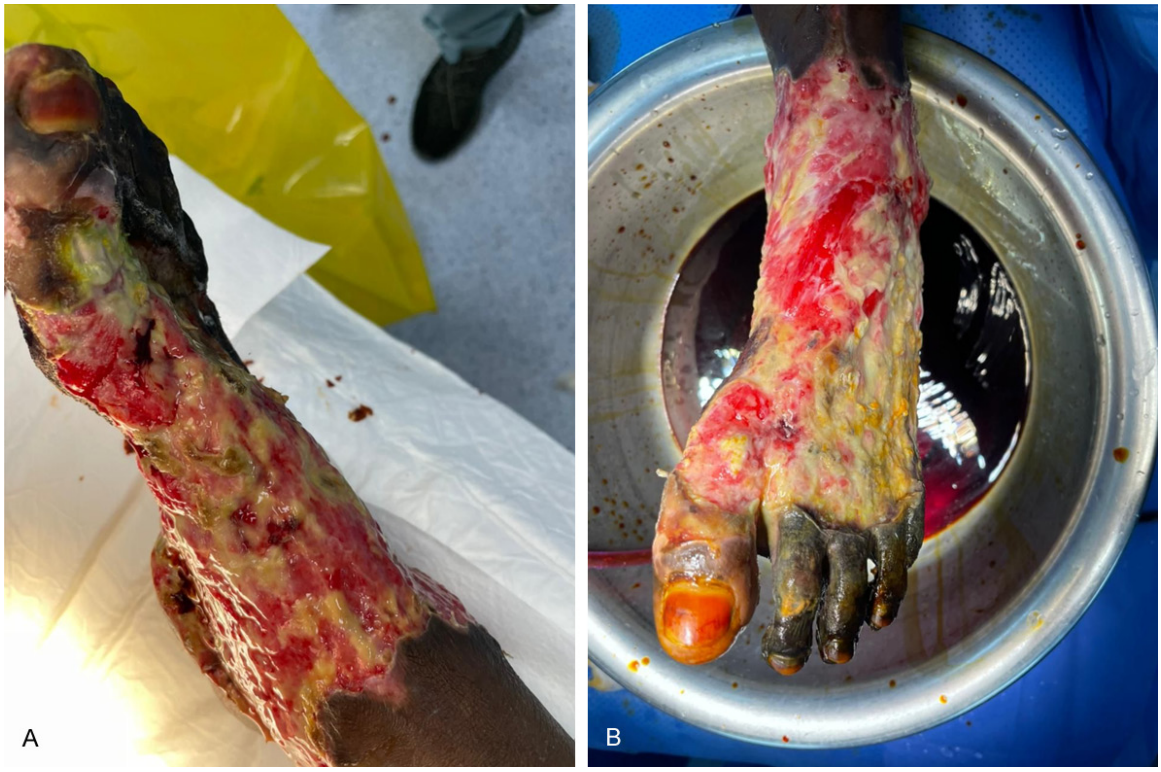

Figure 3. Frostbite wounds following multiple debridement sessions. A. Right foot. B. Left foot.

In addressing DIPN, as illustrated by the current case, early detection and intervention are paramount. The neurotoxic effects of antitubercular agents, notably INH, necessitate vigilant monitoring of neuropathic manifestations to prevent irreversible nerve damage. Therapeutic strategies should prioritize both antimicrobial efficacy and neuroprotection. The adjunctive administration of pyridoxine is advocated to mitigate pyridoxine depletion and confer neuroprotective benefits. Dose modulation of the implicated antibiotic or substitution with an alternative antimicrobial may be necessary based on a rigorous risk-benefit assessment. This balanced approach highlights the importance of adeptly navigating the complexities of

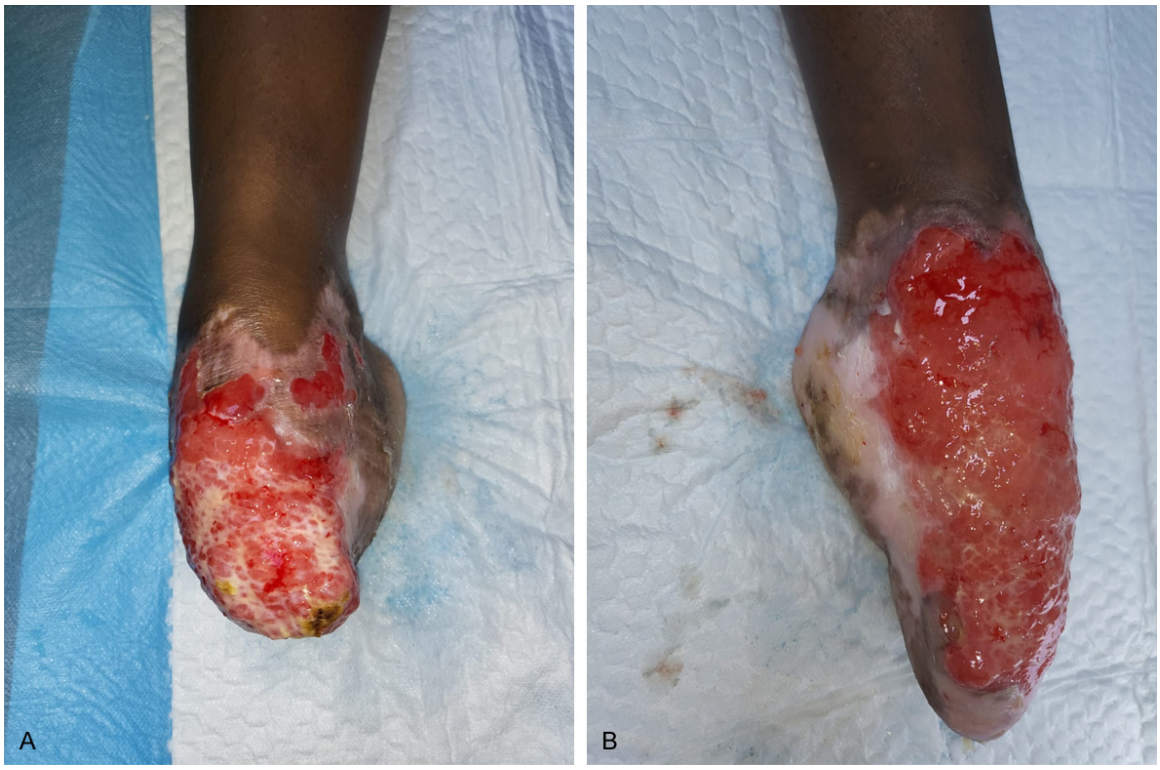

Figure 4. Healing dorsal foot wounds with excess granulation and plantar flexion deformity. A. Right foot. B. Left foot.

DIPN management, ensuring optimal infectious disease control while preserving neurological function.

With the growing number of reported iatrogenic frostbite cases, it is imperative to recognize that the diminishment of sensation during the application of ice packs or ice usage signifies a cautionary sign rather than a relieved symptom. Nerves cease to transmit pain signals owing to their exposure to freezing temperatures, thereby diminishing the capacity to detect ongoing damage [14].

The Wilderness Medical Society (WMS) offers concise advice to prevent frostbite. These guidelines propose strategies such as mitigating the impact of recognized conditions, substances, or medications with a propensity to compromise peripheral perfusion. Additionally, they advocate for the maintenance of core body temperature, adequate fluid and caloric intake, avoidance of articles of clothing or garments that impede peripheral perfusion (e.g., restrictive attire), recommendation of supplemental oxygen for individuals experiencing severe hypoxia, endorsement of exercise as a means to uphold appropriate peripheral tissue perfusion, and the importance of abstaining from smoking [14].

Although peripheral neuropathy induced by antimycobacterial agents has been documented, this report introduces a distinctive case wherein antimycobacterial-induced peripheral neuropathy resulted in bilateral foot frostbite. This highlights the importance of a multidisciplinary approach in managing DIPN by combining targeted antimicrobial treatment with neuroprotection measures. Prompt recognition of peripheral neuropathy and timely implementation of appropriate interventions are paramount for mitigating potential adverse outcomes.

The primary limitation of this case report is its narrow focus on a rare complication of DIPN frostbite, which constrains broader applicability and future research prospects. The anticipated direction for future endeavors centers on improving awareness and creating detailed protocols for the early detection and management of DIPN. This approach aims to prevent adverse outcomes by enhancing healthcare professionals' ability to efficiently identify and address

DIPN, underscoring the importance of clinical vigilance and proactive intervention strategies. Furthermore, it is crucial to educate patients on the potential side effects of their medication regimens and emphasize the importance of regular clinical follow-ups.

Conclusion

This case report describes a complex interplay of antimycobacterial-induced peripheral neuropathy leading to unconventional self-administered cold therapy, which tragically culminated in bilateral foot frostbite in a previously treated tuberculosis patient. The agony of the peripheral neuropathy compelled the patient to seek relief through ice immersion, a desperate measure that exacerbated her condition. Frostbite manifested as non-blanching, dark mottled skin, delayed capillary refill, and eventually gangrene, necessitating transmetatarsal amputation. This retrospective narrative underlines the unforeseen repercussions of DIPN, highlighting the need for comprehensive patient education and attentive monitoring during anti-TB therapy to avert similar manifestations. Furthermore, it accentuates the essential role of prompt recognition and intervention in managing peripheral neuropathy to prevent severe complications such as frostbite. This case serves as a stark reminder for clinicians to exercise caution and uphold a high index of suspicion for peripheral neuropathy in patients receiving antimycobacterial therapy. This case report amplifies the call for a multidisciplinary approach to managing such patients, ensuring holistic care, and averting severe debilitating outcomes.

Disclosure of conflict of interest

None.

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References

[1] Kraincuk P, Keck M, Lumenta D and Kamolz LP. Frostbite. In: Handbook of Burns. Vienna: Springer; 2012. pp. 479-483.

[2] Rivlin M, King M, Kruse R and Ilyas AM. Frostbite in an adolescent football player: a case report. J Athl Train 2014; 49: 97-101.

[3] Orak M, Üstündağ M, Güloğlu C, Doğan H and Altunci YA. Frostbite a case report. Am J Case Rep 2007; 8: 128-31.

[4] Tobalem M, Modarressi A, Elias B, Harder Y and Pittet B. Frostbite complicating therapeutic surface cooling after heat stroke. Intensive Care Med 2010; 36: 1614-5.

[5] Brown WC and Hahn DB. Frostbite of the feet after cryotherapy: a report of two cases. J Foot Ankle Surg 2009; 48: 577-80.

[6] Joshi K, Goyary D, Mazumder B, Chattopadhyay P, Chakraborty R, Bhutia YD, Karmakar S and Dwivedi SK. Frostbite: current status and advancements in therapeutics. J Therm Biol 2020; 93: 102716.

[7] Millet JD, Brown RK, Levi B, Kraft CT, Jacobson JA, Gross MD and Wong KK. Frostbite: spectrum of imaging findings and guidelines for management. Radiographics 2016; 36: 2154-2169.

[8] Mafukidze AT, Calnan M and Furin J. Peripheral neuropathy in persons with tuberculosis. J Clin Tuberc Other Mycobact Dis 2015; 2: 5-11.

[9] Regli IB, Strapazzon G, Falla M, Oberhammer R and Brugger H. Long-term sequelae of frostbite-a scoping review. Int J Environ Res Public Health 2021; 18: 9655.

[10] Zhao JC, Fan X, Yu JA, Zhang XH, Shi K and Hong L. Deep frostbite: clinical characteristics and outcomes in northeastern China. J Tissue Viability 2020; 29: 110-5.

[11] Jones MR, Urits I, Wolf J, Corrigan D, Colburn L, Peterson E, Williamson A and Viswanath O. Drug-induced peripheral neuropathy: a narrative review. Curr Clin Pharmacol 2020; 15: 38-48.

[12] Vilholm OJ, Christensen AA, Zedan AH and Itani M. Drug-induced peripheral neuropathy. Basic Clin Pharmacol Toxicol 2014; 115: 185-92.

[13] Van der Watt JJ, Harrison TB, Benatar M and Heckmann JM. Polyneuropathy, anti-tuberculosis treatment and the role of pyridoxine in the HIV/AIDS era: a systematic review. Int J Tuberc Lung Dis 2011; 15: 722-8.

[14] McIntosh SE, Freer L, Grissom CK, Auerbach PS, Rodway GW, Cochran A, Giesbrecht GG, McDevitt M, Imray CH, Johnson EL, Pandey P, Dow J and Hackett PH. Wilderness medical society clinical practice guidelines for the prevention and treatment of frostbite: 2019 update. Wilderness Environ Med 2019; 30: S19-S32.