Received: 17 November 2023 | Revised: 3 January 2024 | Accepted: 22 January 2024

DOI: 10.1111/jocd.16206

JCD Journal of Cosmetic Dermatology WILEY

CLINICAL COMMENTARY

Skin necrosis after intradermal injection of lyophilized exosome: A case report and a review of the literature

Weeratian Tawanwongsri MD[1] | **Vasanop Vachiramon MD**[2]

[1]Division of Dermatology, Department of Internal Medicine, School of Medicine, Walailak University, Nakhon Si Thammarat, Thailand

[2]Division of Dermatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Correspondence
Weeratian Tawanwongsri, Division of Dermatology, Department of Internal Medicine, School of Medicine, Walailak University, Nakhon Si Thammarat 80161, Thailand.
Email: weeratian.ta@gmail.com

Abstract

Background: Exosomes have gained attention for their potential in skin rejuvenation. Currently, most exosome products are available for topical administration, and the use of subdermal injection as a route of administration has not been approved.

Aims: The purpose of this case report is to describe a case of skin necrosis that occurred following an intradermal injection of lyophilized exosomes.

Materials and Methods: We hereby report a case of a middle-aged man who experienced adverse effects after receiving an intradermal injection of lyophilized exosomes. Multiple injections of an exosome product were administered to treat enlarged facial pores. Shortly after the injection, the patient felt pain and noticed several dark red bumps. Three days after injection, the lesions transformed into palpable, painful, non-blanchable purplish papules and nodules, accompanied by central, tiny crusted erosions. The residual product was injected into the upper arm using an intradermal method. Similar lesions also appeared, and a skin biopsy showed necrotic keratinocytes, leukocytoclastic vasculitis, and eccrine necrosis.

Results: There are few reports available regarding complications, especially those related to intradermal exosomes. These complications include multiple foreign-body granulomatous reactions at the injection sites. In our case, oral prednisolone was administered for a duration of 7 days. After the treatment, the lesions exhibited notable improvement, eventually leaving post-inflammatory hyperpigmentation.

Conclusion: Utilizing exosomes through unapproved methods should be avoided due to the possibility of adverse reactions that could cause aesthetic issues.

KEYWORDS
eccrine necrosis, exosome, intradermal, skin necrosis, vasculopathy

1 | INTRODUCTION

Exosomes, which are lipid bilayer vesicles ranging in size from 30 to 150 nm, play a crucial role in intercellular communication. A major source of exosomes is mesenchymal stem cells, found in bone marrow, umbilical cord blood, and adipose tissue.[1] These vesicles are adorned with diverse surface proteins and encapsulate a range of biologically active cargo, including proteins, DNA, messenger RNA, microRNA, metabolites, and lipids.[2–4] They have gained increasing attention among researchers in various fields,

including dermatology and regenerative medicine.[5–7] The studies assessing the safety and efficacy of exosome treatments include chronic ulcers, wound healing, dystrophic epidermolysis bullosa, inflammatory skin disorders (e.g., psoriasis, atopic dermatitis, lichen planus, bullous pemphigoid, psoriasis, systemic lupus erythematosus, etc.), age spots, acne, and cutaneous malignancies. According to anti-aging benefits, the exosomes have the potential to augment the effectiveness of other active components, including hyaluronic acid, peptides, and antioxidants. This mechanism operates by reducing the presence of reactive oxygen species and TNF-alpha, while simultaneously increasing the levels of TGF-beta, ultimately leading to heightened MMP-1 and pro-collagen type I.[8] Consequently, there is an increase in the production of collagen, an improvement in elasticity, and a reduction in the appearance of wrinkles.[8,9] Currently, most exosome products are available for topical administration, and the use of subdermal injection as a route of administration has not been approved.[5,10] There exists a mounting inclination towards the utilization of cellular derivatives, particularly exosomes, as a preferred choice for therapeutic interventions as opposed to conventional stem cells. Nevertheless, the imperative of evaluating the safety parameters associated with these exosomes remains insufficiently investigated.[11]

2 | CASE PRESENTATION

A 36-year-old man presented at the university-based outpatient dermatology clinic with recently developed painful facial rashes on both cheeks 3 days after receiving multiple intradermal injections of an exosome product, manufactured in Korea, to treat facial enlarged pores at a private clinic. He had been otherwise healthy and had been denied concurrent oral medications and supplements. He has no history of food or drug allergies. He reported that the set of products consisted of two vials: one containing a lyophilized exosome powder-like material and another containing a clear liquid solvent. The ingredient details are shown in Data S1. Two vials were then mixed by gently swirling. After the application of topical anesthesia (10 grams of 2.5% lidocaine-2.5% prilocaine cream) to the face for a duration of 30 min, the product was intradermally injected into both sides of his cheeks using 1 mL gauge 33 syringes with 1 cm intervals and in the amount of 0.1 mL. A total of 1.8 mL of the product was injected, but the injection was stopped due to pain and notable erythematous-to-purplish papules. According to his past history, he received incobotulinumtoxinA under the same topical local anesthesia for wrinkle reduction 3 months ago without experiencing any complications.

On examination, his temperature was 37°C, pulse rate was 75 beats per minute, his blood pressure 115/70 mm Hg, and his respiratory rate was 18 breaths per minute. A dermatologic examination revealed multiple palpable, painful erythematous-to-purplish papules and nodules, accompanied by some tiny erosions (Figure 1A,B). The remainder of the general examination was normal. Laboratory tests including complete blood count, liver function test, blood urea nitrogen, and creatinine were all within normal limits. A small amount of the product was tested for acidity using litmus paper, and the result was pH 7. Oral prednisolone (30 mg/day) was commenced for 7 days. Three days after the treatment, his facial rashes resolved remarkably. At the 2-week follow-up, no recurrent skin lesions or other systemic involvements were observed. However, multiple atrophic scars with residual erythema and hyperpigmentation were still present.

A volume of 0.1 mL of the residual product was intradermally injected into the right inner upper arm. Subsequently, severe pain and erythema were immediately observed, similar to previous occurrences in the facial injection sites. The patient was asked about their comfort during and after the injection. At the moment of needle insertion, the patient reported mild pain, describing it as a sharp sensation and rating it 1 out of 10. While the product was being administered, the patient experienced a moderate level of pain, marked by a burning sensation and rated as 5 out of 10. This burning sensation continued even after the needle was withdrawn, intensifying to what the patient described as severe pain, scoring it 7 out of 10. This severe discomfort persisted for about 30 minutes before it gradually diminished spontaneously. The patient noted that this pattern and intensity of pain were similar to their previous experiences with facial injections at a private clinic. After 3 days, the lesion transformed into a purplish papule, displaying a central dusky

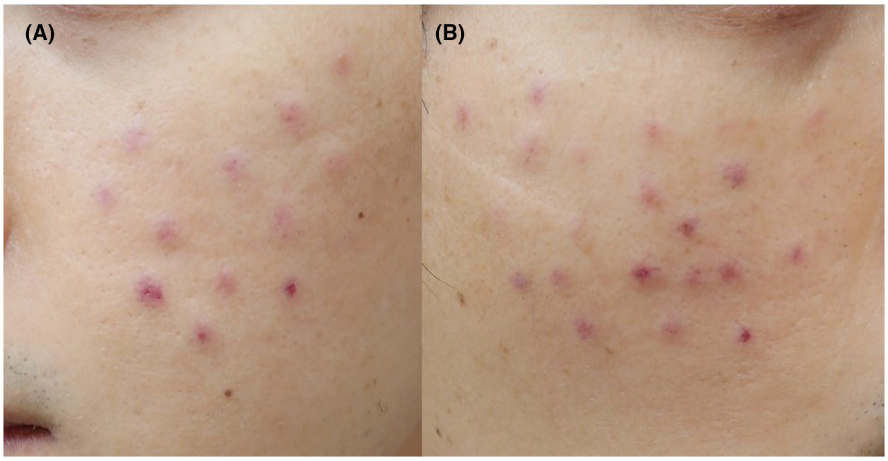

FIGURE 1 Multiple palpable, painful erythematous-to-purplish papules and nodules, accompanied by some tiny erosions on left cheek (A) and right cheek (B).

macule with a serrated edge. A 3-mm punch biopsy was performed on the right arm and sent for routine histopathological examination. The result revealed early changes of skin necrosis with interstitial inflammatory cell infiltrate composed of neutrophils, nuclear debris, necrosis of small blood vessels, and eccrine gland within the dermal tissue (Figure 2B). Moreover, the patch test on the left arm was conducted using the Finn chamber, which has a diameter of 8 mm, and the exosome product mixture (as is) with a volume of 15 microliters. Test results at 48- and 96-h post-application were all negative. A patch test with metal screening was also performed with a negative result. In addition, a repeat open application test with topical anesthetics (2.5% lidocaine–2.5% prilocaine cream) showed normal results. He underwent a single session of fractional carbon dioxide laser treatment for the atrophic scars on his face. During the 8-week follow-up, the scars exhibited a reduction in depth with the presence of residual post-inflammatory hyperpigmentation.

3 | DISCUSSION

Currently, intradermal botulinum toxin injection, low-cross-linked hyaluronic acid, collagen bio-stimulators (e.g., polynucleotides, poly-L-lactic acid, poly-D-L-lactic acid, calcium hydroxylapatite, etc.), platelet-rich plasma, laser, and energy-based devices are increasingly popular treatment options for facial rejuvenation and the improvement of skin quality. However, there are some limitations with certain modalities. No single option can address all problems related to skin quality. Therefore, various methods have been introduced for a better outcome.

In this report, we present a case of early skin necrosis, which is probably due to a pathologic change in the dermal vasculature as a result of an exosome-containing product. This is supported by the presence of non-blanchable, painful purpuric papules and central dusky macules with a serrated edge at the injection site. Cutaneous vasculitis are associated with some antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs). Among antibiotics, beta-lactams, quinolones, and macrolides are the most frequently implicated.[12–14] Additionally, drugs such as levamisole, heparin, and doxorubicin are well-recognized for their association with vasculopathy.[15] While the majority of reported cases with skin necrosis are linked to the subcutaneous injection of low-molecular-weight heparin, there is a growing number of instances where cosmetic materials administered intradermally or subcutaneously have been associated with vasculitis or vasculopathy (Table 1).[16–29] Regarding eccrine necrosis, although the common systemic drugs linked to this condition include barbiturates, benzodiazepines, and tricyclic antidepressants,[30–33] medication with intradermal or subcutaneous injection associated with eccrine necrosis has never been reported. Alterations within the sweat glands can exhibit a spectrum of variability, extending from subtle inflammatory infiltration with or without metaplasia to overt necrotic features. These changes are attributable to several causative factors, which encompass inflammatory diseases, infections, cutaneous lymphoproliferative disorders, trauma, prolonged pressure, leukocytoclastic vasculitis, disseminated intravascular coagulation, microwave radiation therapy, and drugs.[34–36] In these cases, eccrine gland necrosis could be explained by pathologic changes in the dermal blood vessel. Eccrine necrosis, particularly the secretory portion, is vulnerable to hypoxic damage when vascular compromise occurs, which can result from various factors such as inflammation, thrombosis, or obstruction.[34,37]

Based on the biological characteristics of exosomes derived from mesenchymal stem cells, they contribute to tissue regeneration and repair by diminishing inflammatory reactions, fostering cell proliferation, preventing apoptosis, and aiding in the process of angiogenesis.[38] There are still few reports available regarding complications, particularly those related to intradermal exosomes. Yang HJ et al.[39] presented a case involving multiple foreign body granulomatous reactions at injection sites where a conditioned medium obtained from human umbilical cord blood-derived stem cells was administered to reduce neck wrinkles. The lesions manifested 3 days after the injection and persisted chronically for 7 months. These cutaneous reactions were attributed to non-allergic chronic inflammation in granulomas triggered by injecting substances. The findings in our case may be explained by factors such as arterial inflammation, acute vasospasm, and micro-embolic obstruction.[40] This could resulted in local tissue hypoxia led to the necrosis of eccrine glands and the skin. Regarding the severe pain experienced, the exact mechanism behind it remains unclear. However, it appears unrelated to the product's acidity, as evidenced by a pH test result of 7. We hypothesize that the pain may be attributable to the solution's inherent stinging properties.

There is a growing fascination with employing cellular derivatives like exosomes in therapeutic approaches. Nevertheless, further well-designed long-term clinical studies are essential to elucidate

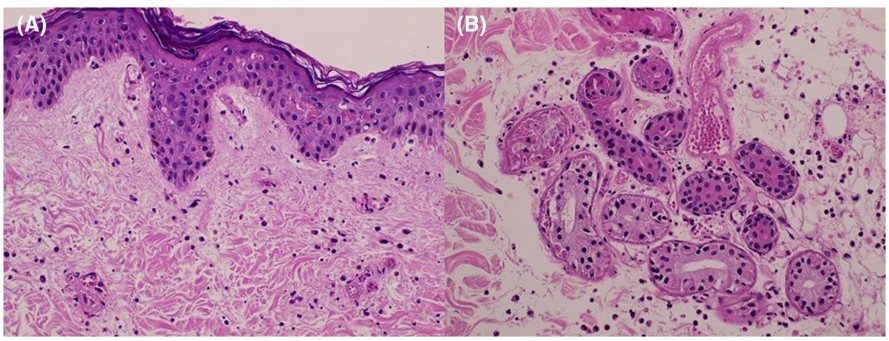

FIGURE 2 (A) Necrotic keratinocytes accompanied by an interstitial inflammatory-cell infiltrate composed of neutrophils, nuclear debris, and necrosis of small blood vessels within the upper dermis (hematoxylin & eosin, ×400). (B) Necrosis of sweat coils and distal ducts with partially preserved nuclei in the outer layer (hematoxylin & eosin, ×400).

TABLE 1 Skin necrosis with vascular involvement following administration of injected materials*.

Author (year) Country (Ref)	Study design	Patient description	Injected materials	Route of administration	Onset	Adverse events	Histopathology	Treatment/Clinical outcomes
Alijotas-Reig J (2009) Spain[16]	CR	A 45-year-old female	Non-animal stabilized hyaluronic acid filler	NA	3 weeks	Pruritus, facial angioedema, fever, and urticarial lesions spreading across the body	Involvement of small vessels, lymphomonocytic infiltrates, and fibrin deposition were observed. Additionally, small foci of C3 deposits were found in the capillaries	A short course of oral prednisone treatment led to clinical resolution. The product was rechallenged 26 months later without any complications.
Ghattaura A et al. (2009) UK[17]	CR	A 12-year-old female	BCG vaccination	Intradermal	NA	Extensive ulceration on the left upper arm and disease progression to the forehead, starting as pustules and evolving into ulcerative areas	Inflammation characterized by numerous histiocytes in ill-defined granulomas with central microabscesses, and multinucleate giant cells surrounding small blood vessels	Initial dosing of 60 mg/day, gradually reduced over 4 weeks to a maintenance dose of 30 mg/day for 1 year, plus split skin grafting for the wounds.
Handschin AE et al. (2005) Germany[18]	Systematic review	11 females and 10 males (mean age 62 ± 13 years)	LMWHs	Subcutaneous	7.6 ± 3.4 days	Erythematous, subcutaneous lesions with swelling and pain at the injection sites, often progressing to blistering and eventually full-skin necrosis	Epidermal necrosis, inflammatory cell infiltration, and microvascular thrombosis in the dermal vessels.	Discontinuation of LMWHs and surgical therapy
Namazi N et al. (2020) Iran[19]	CR	A 60-year-old female	Botulinum toxin A	NA	6 h	Edema, erythema and purpura at the site of injections with dissemination to lower face and neck	Transmural eosinophilic and neutrophilic infiltration with fibrinoid necrosis of the vessel walls, leukocytoclastic vasculitis and extravasation of red blood cells	Oral prednisolone (20 mg/day) was administered for 2 weeks and then tapered over the next 2 weeks, leading to clinical remission.
Namazi N et al. (2016) Iran[20]	CR	A 45-year-old female	Botulinum toxin A	NA	2 h	Prominent edema, purpuric papules and erythema in periorbital region and at the sites of injection in the forehead	Transmural infiltration of neutrophils and eosinophils with endothelial swelling and fibrinoid necrosis of the vessel walls and leukocytoclasia, extravasation of red blood cells, and infiltration of neutrophils and eosinophils in the subcutis	Oral prednisolone at a dose of 0.5 mg/kg and hydroxyzine 25 mg were administered daily. The prednisolone was continued for three consecutive days and then tapered over 2 weeks, resulting in clinical remission.
Li J et al. (2019) US[21]	CR	A 54-year-old female	Enoxaparin	Subcutaneous	8 days	Non-palpable purpura with surrounding erythema on both sides of the lower abdomen	Thrombotic vasculopathy with minimal vasculitis	The medication was changed to fondaparinux, followed by a switch to warfarin, resulting in clinical resolution.
Katsourakis A et al. (2011) Greece[22]	CR	A 76-year-old male	Enoxaparin	Subcutaneous	10 days	Progressive, painful erythematous lesions, later evolving into central necrosis	Necrosis of the surface skin as well as clots in small blood vessels with inflammatory changes of the deeper skin	Upon switching therapy to Nadroparin, the necrotic plaques resolved within a week.
Haffner M et al. (2018) US[23]	CR	A 60-year-old male	Enoxaparin	Subcutaneous	10 days	A large necrotic skin reaction over the abdominal injection site	NA	Enoxaparin was discontinued, intravenous bivalirudin and dabigatran were started; the wound healed in 7 months.

TABLE 1 (Continued)

Author (year) Country (Ref)	Study design	Patient description	Injected materials	Route of administration	Onset	Adverse events	Histopathology	Treatment/Clinical outcomes
Tampaki M et al. (2020) Greece[24]	CR	A 73-year-old female	Enoxaparin	Subcutaneous	11 days	Two painful erythematous lesions resembling injection site hematomas rapidly evolved into necrotic blisters.	NA	Enoxaparin was discontinued, replaced with fondaparinux, and later switched back to warfarin. At the 2-month follow-up, the necrotic areas had completely healed.
Yang C-H et al. (2002) Taiwan[25]	CR	A 40-year-old male	INF-β-1b	Subcutaneous	3 months	A necrotic ulcer on the right upper arm covered with eschar at the injection site and surrounded by wide, irregular erythema	Cutaneous necrosis down to the subcutaneous fat with vessel thrombosis	The wound underwent surgical excision and was repaired with a flap.
Brauer DL et al. (2019) US[26]	Case series	1. A37-year-old female	SCIT	Subcutaneous	48 h	Swelling in the arm, initially painful, later subsided into two small necrotic papules	NA	SCIT was discontinued, scarring persisted for over 6 years.
		2. A56-year-old female			1 day	A triangular, erythematous, swollen, and hyperpigmented patch at the injection site		After applying topical clobetasol, the lesion subsided. The patient then continued SCIT for over a year without similar complications, and the lesions gradually faded over several months.
		3. A73-year-old male			2–3 days	Injection-site pain with ecchymosis		The patient eventually stopped receiving SCIT. After 1 month, the site was healing, but long-term scarring ensued.
Crouse E et al. (2022) US[27]	CR	A 35-year-old male	Buprenorphine	Subcutaneous	1 day	Ulceration down to the subcutis	NA	Debridement; injection site healed with scar formation.
Pérez DLC et al. (2016) Mexico[28]	CR	A 33-year-old man	Nadroparin	Subcutaneous	7 days	A heart-shaped blistering skin lesion with central necrosis and surrounding erythema at the injection site	NA	NA
Surendiran A et al. (2012) India[29]	Case series	1. A 12-year-old male	Cloxacillin	Intradermal	30 min	Intense pain, itching and rash over the site of injection	NA	Pain subsided spontaneously
		2. A 28-year-old male						
		3. A 52-year-old male						

Note: *Hyaluronic acid-associated vascular occlusion was excluded from the table.

Abbreviations: BCG, Bacillus Calmette-Guerin; CR, case report; INF-β-1b, recombinant interferon beta-1b; LMWHs, low molecular weight heparins; NA, not available; Ref, reference, SCIT, subcutaneous immunotherapy; UK, the United Kingdom; US, the United States.

the immunogenicity, immunotoxicity, biodistribution, persistence, metabolism, excretion, administration route, dosage, concentration, and adverse effects.[7,41] Our case highlights the harmful effects of malpractice and the utilization of unapproved administration methods. It acts as a crucial reminder to physicians that patient safety and adherence to the medical ethic of nonmaleficence must always be paramount.[42] This entails rigorously following the approved and recommended routes for administering medications. It is important to note that the use of subdermal injection as a route of administration lacks approval.[5,10] Engaging in such harmful practices can result in not just cosmetic physical damage but also mental distress, profoundly affecting the patient's quality of life.[43,44]

In the absence of a standard treatment for this phenomenon, a treatment based on pathologic changes is the most appropriate. In our case, oral prednisolone was administered for a duration of 7 days. After the treatment, the lesions exhibited a notable resolution, ultimately leaving atrophic scars and post-inflammatory hyperpigmentation. Since the risk of adverse effects from intradermal injection as a route of administration may not be predicted by the topical application or patch test. Therefore, we recommended that the mode of delivery should strictly comply with the manufacturers' recommendation.

4 | CONCLUSIONS

We present a case of skin necrosis as a result of cutaneous vascular compromise due to exosome injection. Practitioners should perform cosmetic procedures based on the manufacturers' guidelines and recommendations. In addition, further well-designed clinical studies are required to clarify several aspects, including immunogenicity, immunotoxicity, biodistribution, persistence, metabolism, excretion, preferred administration routes, optimal dosage, concentration, potential side effects, as well as, drug–drug and drug-fluid compatibility of certain injection products.

CONFLICT OF INTEREST STATEMENT

No conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Walailak Ethics Committee (WUEC-23-237-01). The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case presentation and any accompanying images.

ORCID

Weeratian Tawanwongsri https://orcid.org/0000-0002-1949-7323

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tawanwongsri W, Vachiramon V. Skin necrosis after intradermal injection of lyophilized exosome: A case report and a review of the literature. *J Cosmet Dermatol*. 2024;23:1597-1603. doi:10.1111/jocd.16206