Case report

Administration of Exosome-Based Treatment for Exogenous Ochronosis Caused by Prolonged Use of Topical Hydroquinone

ABSTRACT

Objective:
Exogenous ochronosis is a rare but challenging skin condition caused by prolonged misuse of hydroquinone-containing creams, with limited effective treatments. This study aimed to evaluate the effectiveness of exosome-based therapy as a novel therapeutic approach for this condition.

Materials and Methods:
A 39-year-old Indonesian woman with stage 2 exogenous ochronosis, characterized by discolorationand skin dullness following eight months of hydroquinone misuse, was treated with plant-derived exosomes administered via intradermal injection and topical serum application.

Results:
After 36 days of treatment, the patient showedmarked improvements in skin texture, hydration, and a reduction of hyperpigmentation and telangiectasia, with no adverse effects observed.

Conclusion:
This case highlights the potential of exosome therapy as an effective and minimally invasive intervention for exogenous ochronosis. The findings highlight the need for further research to validate this approach and reinforce the importance of stricter regulations to prevent dermatological complications from harmful skincare ingredients.

Keywords: exosome; hydroquinone; ochronosis; plant-derived exosome

1. INTRODUCTION

The distribution of drugs and skincare products in Indonesia is regulated and supervised by the Indonesian Food and Drug Authority. However, many skincare products containing harmful ingredients remain freely available and easily accessible, particularly on e-commerce platforms. One of the skincare products widely sold over the counter is skincare containing 4% hydroquinone, claimed to brighten the skin in a short time. Hydroquinone, also referred to as benzene-1,4-diol or quinol, is an aromatic organic compound and a form of phenol derived from benzene. The FDA has approved 4% hydroquinone for the treatment of conditions such as melasma, freckles, senile lentigines, and hyperpigmentation; however, it must be used under medical supervision. Its mechanism of action includes modifying melanosome formation, interacting with copper at the active site of tyrosinase, and inhibiting the synthesis of DNA and RNA(Ishack & Lipner, 2022).

Prolonged and unsupervised use of topical products containing hydroquinone can lead to exogenous ochronosis, which was first described in 1906 by L. Pick and is characterized by bluish-gray patches with a coarse texture and "caviar-like" papules(Qorbani et al., 2020). Epidemiologically, exogenous ochronosis is more common in patients with darker skin, such as Hispanic or African descent, due to the increased use of skin-brightening skincare products over extended periods(Ishack & Lipner, 2022).

Although it is difficult to fully restore the skin to its original condition, skin affected by ochronosis can be improved by reducing pigmentation and providing a healthier appearance. Various treatment modalities, such as peeling, laser therapy, and skin booster injections, are used to fade ochronosis. Currently, exosomes are a highly sought-after treatment modality due to their important role in various biological functions, such as cell communication and signaling processes, cell regeneration, and immune system regulation. Exosomes are nano-sized vesicles, ranging from 30 to 150 nm in diameter, that contain a variety of biological molecules such as proteins, nucleic acids, and metabolites(Sreeraj et al., 2024). Exosomes can originate from human, plants, or prokaryotic cells (such as *Lactobacillus* bacteria)(Liu, 2024; Yi et al., 2023). In the field of dermatology, exosomes can provide benefits such as anti-aging effects, accelerating wound healing, addressing hyperpigmentation, preventing hair loss, and stimulating new hair growth(B. Zhang et al., 2022).

2. CASE PRESENTATION

A 39-year-old Indonesian woman presented to our clinic with complaints of dark patches appearing all over her face. The patient had a history of prolonged use of an over-the-counter facial cream containing 4% hydroquinone for eight months. Initially, during the use of the cream, her skin appeared brighter. However, after three weeks of use, redness started to develop across her facial skin. Despite this, the patient continued using the cream for eight months due to testimonials from her friends. Eventually, she noticed her facial skin darkened, with many spots appearing, prompting her to stop using the cream. On a daily basis, the patient also never uses sunscreen at all.

On physical examination, the skin appeared dull and dry, accompanied by multiple hyperpigmented macules on both cheeks, the nose, chin, and forehead. Hypopigmented patches and telangiectasia were also observed on both cheeks. The patient underwent an intradermal injection treatment with a 6cc plant-based exosome skin booster, administered to all areas of the face. This was followed by a facial treatment and the application of exosome serum as much as 1.2cc topically and PDT light therapy using two types of light, each applied for 10 minutes. After the first treatment, the patient received a topical regimen consisting of a skincare set that included a facial wash, toner, serum, and a morning cream containing niacinamide, alpha arbutin, 3-O-ethyl ascorbic acid, and tranexamic acid, as well as a night cream containing retinol. The patient also used a hybrid sunscreen with SPF 50 PA++++.

Thirty-six days later, the patient returned to the clinic for follow-up treatment. The skin appeared brighter, healthier, and more hydrated. Dark patches, particularly on both cheeks, had significantly reduced.

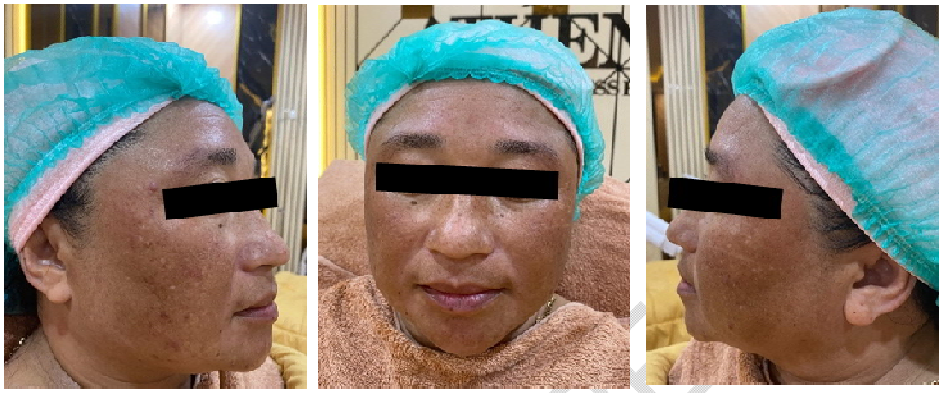

Fig 1. Skin condition before exosome treatment

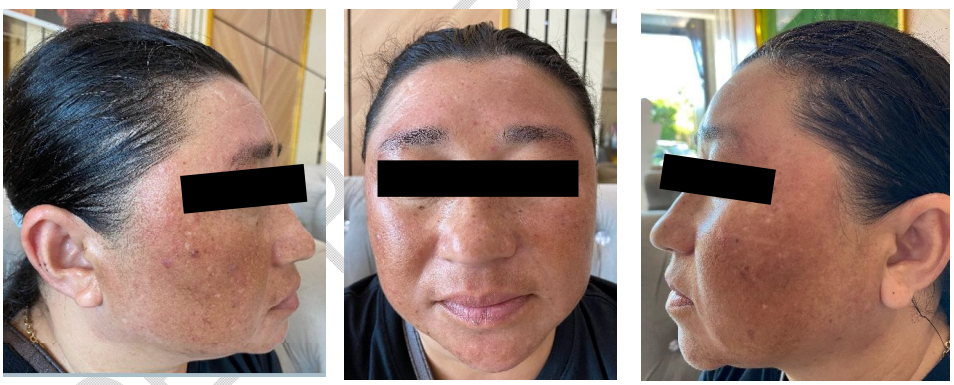

Fig 2. Skin condition 36 days after the initial exosome treatment

3. DISCUSSION

The use of 2-4% topical hydroquinone for 3-5 months is indeed the primary treatment for hyperpigmentation. However, several considerations must be taken into account during hydroquinone use, including the need for dermatological supervision and the requirement for the patient to use sunscreen in daily activities(Fabian et al., 2023). Currently, many skincare products contain topical hydroquinone for skin bleaching cream, causing patients to apply hydroquinone to their entire face for long periods without medical supervision.In cases of prolonged use, hydroquinone accumulates in the papillary dermis and is subsequently absorbed by fibroblasts. Its degradation products, particularly phenolic compounds, bind to collagen and elastic fibers. If this process persists, it can cause structural changes in collagen and elastic fibers, leading to hyperpigmentation, skin discoloration, and a loss of skin elasticity(Bhattar et al., 2015).

Ochronosis is classified into endogenous ochronosis (alkaptonuria), a rare autosomal recessive disease characterized by a deficiency of the enzyme homogentisic acid oxidase, and exogenous ochronosis, which results from prolonged use of topical medications containing phenols, most commonly hydroquinone(Bhattar et al., 2015). Various explanations have been proposed for the mechanism behind hydroquinone-induced ochronosis. A leading hypothesis posits that elevated levels of hydroquinone suppress the activity of the homogentisic acid oxidase enzyme in the skin, causing a buildup of homogentisic acid and benzoquinone acetate, which subsequently polymerize to produce ochronotic pigmentation. This effect is exacerbated by sun exposure without the protection of sunscreen. Exogenous ochronosis progresses through three clinical stages: First, is the onset of erythema and subtle pigmentation changes, second is the development of hyperpigmentation, black colloid milia, and skin atrophy, and lastly is the appearance of papulonodules in the final stage(Bhattar et al., 2015).

When the patient first came to our clinic, hyperpigmented macules were visible on the skin, particularly on both cheeks. Previously, the patient had experienced an episode of erythema across the entire face. Therefore, upon arrival at the clinic, the patient had already progressed to stage 2 exogenous ochronosis. The patient's skin also showed signs of discoloration and telangiectasia, indicating that damage had occurred in the dermis, particularly to the collagen and elastic fibers.

Among the many treatment options available, our clinic chose an exosome-based treatment because exosomes are believed to promote skin regeneration by influencing cell proliferation, migration, and differentiation. Exosomes are one of the nano-sized extracellular vesicles that function as intracellular communication tools. Exosomes are composed of two lipid layers that can interact with both hydrophobic and hydrophilic drugs(Huda et al., 2021; Marjani et al., 2024). Exosomes are selective extracellular vesicles because their surface contains immune regulatory molecules, membrane proteins, and membrane trafficking molecules, which enable the exosomes to attach specifically only to the site of interest(McBride et al., 2017). Exosomes are capable of carrying mRNA, nucleic acids, or proteins, which are subsequently transferred to target cells via various pathways, including ligand-receptor interactions that activate signaling pathways, pinocytosis, phagocytosis, and fusion with the plasma membrane(Tamon, 2024; Thakur et al., 2023). These processes ultimately result in changes to the pathological or physiological functions of the target cells(McBride et al., 2017).

Currently, exosomes are widely used in dermatology for skin health and rejuvenation. In the skin, exosomes can inhibit melanogenesis, accelerate wound healing, act as anti-aging agents, and reduce inflammation by reducing the expression of pro-inflammatory cytokine such as IL-6, IL-2, TNFα(Sreeraj et al., 2024; Zhou et al., 2023). Exosomes can be administered topicallyor intradermally through injection. Intradermal exosome injections involve directly injecting these vesicles into the skin, a process that has been shown to stimulate neocollagenesis and promote skin regeneration. Today, neocollagenesis has become a key focus of various treatments and interventions aimed at improving skin health and appearance. Optimal neocollagenesis can enable the rebuilding of the dermal structure (Tamon, 2024; Thakur et al., 2023).

Based on their origin, exosomes are classified into human exosomes, plant-derived exosomes, and lactobacillus-derived exosomes(Liu, 2024; Nemati et al., 2022). Human exosomes have good regenerative capacity and stability, but are limited by the risk of immune reactions and legal regulatory issues(Girón et al., 2022; Huang et al., 2024). Lactobacillus-derived exosomes are a newer approach and are considered relatively stable with low immunogenicity risk(Liu, 2024). However, to this day, the methods for isolation and purification are still not perfected(Yi et al., 2023). Plant-derived exosomes are widely used today because they are relatively stable, low immune reactions, and cruelty-free, while still retaining the regenerative and anti-inflammatory functions of exosomes (Nemati et al., 2022; Sarasati et al., 2023; Yi et al., 2023; Z. Zhang et al., 2022).

Potential side effects include pain, redness, swelling, and discomfort. Serious side effects, particularly with the administration of human-derived exosomes, include allergic reactions such as anaphylactic shock.One case report describes a side effect involving painful, multiple purple erythematous papules on both cheeks following intradermal exosome injection. The punch biopsy revealed early signs of skin necrosis, with interstitial infiltration of inflammatory cells, including neutrophils, nuclear debris, as well as necrosis of small blood vessels and eccrine glands within the dermal tissue (Tawanwongsri & Vachiramon, 2024). Another case report describes the appearance of multiple asymptomatic flesh-colored papules and nodules on both cheeks, which developed 7 weeks after intradermal exosome injection. The punch biopsy showed histopathological signs of a granulomatous reaction (Choi et al., 2024).

In this case, we applied an intradermal exosome treatment using 6cc of plant-derived exosomes, which is evenly injected across all areas of the face, including both cheeks, temples, forehead, nose,chin, and upper neck. This was followed by the application of 1.2 cc of topical exosome serum, completed with the use of a sheet mask, and PDT light therapy using two types of light, each applied for 10 minutes: green light to repair damaged skin and soothe sensitive skin, and red light to enhance skin cell regeneration and improve the absorption of topical exosomes into the skin.In addition to being administered intradermally to stimulate neocollagenesis, we also applied topical exosomes to increase collagen deposition, accelerate wound healing, and improve overall cosmesis, ensuring that the regeneration and neocollagenesis processes occur optimally(Ash et al., 2024). Within 36 days after the exosome treatment, the patient's skin became brighter and more hydrated. Hyperpigmentation and telangiectasia also decreased significantly. The patient showed no signs of side effects or complications. Most importantly, the patient is satisfied with the results achieved so far and she is determined to continue the treatment to achieve more optimal results.

4. CONCLUSION

The widespread availability of skincare products containing harmful ingredients remains an ongoing issue. Ochronosis is a pathological skin condition frequently caused by the misuse of hydroquinone-containing creams. Various treatment modalities are available to address ochronosis, with exosome treatment being one of the most effective. This treatment has been shown to enhance skin regeneration, reduce inflammation, and stimulate neocollagenesis, all with minimal downtime.

It is hoped that stricter regulations on skincare distribution will be implemented in the future to prevent potential skin damage caused by harmful products.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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