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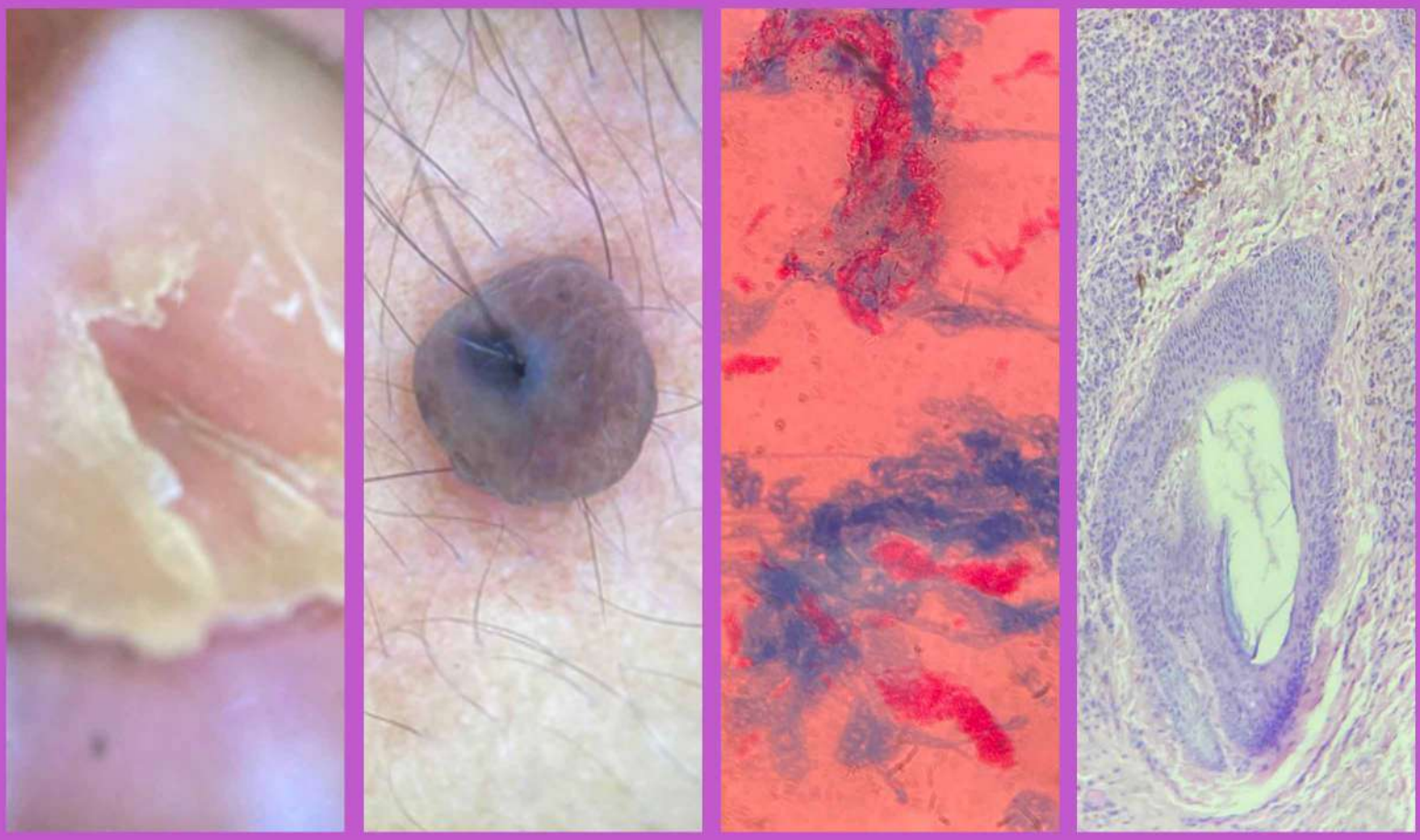
# Bali Dermatology Venereology and Aesthetic Journal



Volume 6, Issue 2 (December 2023)

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Department of Dermatology and Venereology, Medical Faculty, Universitas Udayana, Bali - Indonesia

Department of Dermatology and Venereology, Medical Faculty, Universitas Udayana, Bali - Indonesia
Bali Dermatology Venereology and Aesthetic Journal

# LETTER OF NOTIFICATION

**No. 01/BDVAJ/DENPASAR/2023**

Date:6th of November, 2023

Dear authors, readers, and editorial team of Bali Dermatology Venereology and Aesthetic Journal (BDVAJ)

We certify that **Bali Dermatology Venereology and Aesthetic Journal (BDVAJ)** has previously been registered under the name Bali Dermatology and Venereology Journal (BDVJ) with P-ISSN number: 2622-5417; E-ISSN: 2715-694X and website: https://balidv.org (inactive) and has stopped publishing periodicals.

**The periodical journal has become Dermatology Venereology and Aesthetic Journal (BDVAJ)** with the new website at **https://balidv.id/**.

Historically, the editions of Bali Dermatology and Venereology Journal (BDVJ) and Bali Dermatology Venereology and Aesthetic Journal (BDVAJ) are as follows:

**Previous volume (BDVJ):**
Volume 1 Issue 1, June 2018
Volume 1 Issue 2, December 2018
Volume 2 Issue 1, June 2019
Volume 2 Issue 2, December 2019
Volume 3 Issue 1, June 2020
Volume 3 Issue 2, December 2020
Volume 4 Issue 1, June 2021
Volume 4 Issue 2, December 2021
Volume 5 Issue 1, June 2022
Volume 5 Issue 2, December 2022
Volume 6 Issue 1, June 2023

**Recent volume (BDVAJ):**
Volume 6 Issue 2, December 2023
Volume 7 Issue 1, January 2024
Volume 7 Issue 2, July 2024
and so on.

This notification is to provide information about changes to the journal for the benefit of authors, reviewers, and the editorial team.

Warm Regards,
Editor in Chief
Bali Dermatology Venereology and Aesthetic Journal

**Dr. dr. A. A. G. P. Wiraguna, Sp.KK(K), FINSDV, FAADV**

# Bali Dermatology Venereology and Aesthetic Journal

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## Editorial Board

# Bali Dermatology Venereology and Aesthetic Journal

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## Reviewer

# Bali Dermatology Venereology and Aesthetic Journal

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# Clinical features of allergic contact dermatitis to sandals: a case series

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## ABSTRACT

**Background:** Allergic contact dermatitis (ACD) is a skin inflammation caused by a type 4 delayed-type hypersensitivity reaction. One of the most common types of ACD is shoe dermatitis, characterized by pruritic or painful bilateral and symmetrical erythema, papules, vesicles, scaling, crusting, lichenification, or fissures at the site of footwear contact.
**Case series:** We present seven patients with allergic contact dermatitis caused by rubber flip-flop sandals who presented with acute to chronic eczema and leukoderma. Patients range in age from 4 to 65 years old, with symptoms lasting from 5 months to 2 years. Two of the seven patients had a history of atopy.
**Conclusion:** Flip-flop sandals are the most common offending footwear in Indonesian ACD patients because they are appropriate and comfortable in hot and humid climates like Indonesia. Rubber and rubber chemicals, preservatives, shoe adhesives, and leather materials are the most common offending allergens.

**Keywords:** ACD, flip-flop sandals, rubber, shoe dermatitis.
**Cite This Article:** Gotama S, Hapsari Y, Kusuma DR, Clinical features of allergic contact dermatitis to sandals: a case series. *Bali Dermatology Venereology and Aesthetic Journal*. 2023;6(2):20-25

## INTRODUCTION

Allergic contact dermatitis (ACD) is an inflammatory skin condition caused by type 4 delayed-type hypersensitivity reaction. It is caused by interacting irritating or antigen chemical agents with the skin, followed by a T-cell-mediated reaction.[1,2] Allergic contact dermatitis caused by footwear is termed shoe dermatitis or footwear dermatitis.[3]

Allergic contact dermatitis is a common condition that affects approximately 15-20% of adults in the general population.[1,4,5] Allergic contact dermatitis is responsible for 20% of contact dermatitis, and allergens vary greatly depending on location, personal habits and interests, and the types of preservatives legally permitted.[6] In Dr. Mohammad Hosein General Hospital Palembang, the prevalence of ACD was 13.42% in 2008.[7] The prevalence of footwear ACD in patch-tested individuals for foot dermatitis is between 3-24.2%.[3,8] An epidemic-allergological study by Chowduri and Ghosh in India showed that footwear dermatitis comprises 24.22% of contact dermatitis cases.[9] Footwear ACD affects both sexes and any age group, including children.[8]

The prevalence of shoe allergic contact dermatitis (ACD) is approximately 1.5% to 24.2% of all patch-tested positive patients.[10] ACD of the feet is characterized by bilateral and symmetrical erythema, vesicles, papules, oozing, scaling, or crusting on the skin in contact with the footwear. Lichenification, fissuring, and scaling are more prevalent in chronic ACD. Blistering, oozing, and crusting can also occur in chronic ACD with further exposure to the hapten. Hypopigmented lesions (leukoderma) may also be found and are commonly associated with hydroquinone.[11] The most commonly reported symptoms are pruritus, burning, and pain. Any part of the foot can be affected, but the dorsum of the foot is the most commonly affected due to its larger surface area, thin stratum corneum, and constant contact with the upper portion of the footwear.[6,10,12–14]

Major risk factors for footwear dermatitis are heat, friction, occlusion, hyperhidrosis, and atopy.[12,15,16] The prevalence of footwear ACD is highest in warm-climate countries such as Indonesia, where heat and humidity cause sweating, increased pressure, and skin occlusion.[12,14] In a study of 64 patients suspected of having shoe dermatitis in Indonesia, Febriana et al. discovered that rubber slippers or sandals are the most common footwear (50.7%) causing footwear ACD.[14]

There are over 3,700 substances that can trigger ACD.[17,18] The prevalence of a particular antigen in causing ACD depends on its sensitizing potential and the frequency and duration of exposure.[18] Globally, the most common sensitizers of footwear ACD are rubber and rubber chemicals such as mercaptobenzothiazole, thiuram mix, and black rubber mix.[9,14,19] A study of 46 shoe dermatitis patients in Indonesia found that the most common sensitizers are rubber allergens, preservatives, shoe adhesives, and leather materials.[14] This corresponds well with Indonesians' preference for rubber slippers or sandals.

The only effective treatment for footwear ACD is preventing contact with the sensitizers.[10,12,20] Therefore, characterizing footwear ACD, especially one caused by sandals, is important to provide an effective treatment plan for ACD patients. The objective of our case series is to highlight the characteristics of shoe dermatitis caused by rubber flip-flops often worn by Indonesians.

## CASE REPORT

### Patient characteristics

There were 7 patients from 2019 to 2021 attending Mataram University Hospital's Dermatology Outpatient Clinic were suspected of having allergic contact dermatitis to flip-flop sandals (Figure 1). Four of 7 patients (57%) were females, and the remaining 3 were males (43%). All patients complained of pruritus and erythema, followed by lichenification, blisters, and leukoderma in some other patients. In all cases, the lesion was located on the dorsal foot, and flip-flops sandals can be easily identified as the causative agent because the morphological lesions resembled this agent. Two patients had a history of atopy and a history of family atopy. The age of the patients varied from the youngest at 4 to the oldest at 65 years old. The duration of the symptoms varied from 2 months to 5 years (Table 1). The manifestations of ACD caused by flip-flops sandals in our patients are shown in Figure 1. All of our cases presented with pruritus and erythema except Case 7 who only reported pruritus without erythema. Case 1 also showed blisters and hyperpigmented crusts in the shape of the rubber flip-flops sandals that they used. Case 2, 4 and 5 had lichenification on the dorsum aspect of both feet. Case 3 was the only case that showed leukoderma in the shape of the rubber strap of her sandal. In addition to pruritus and erythema, case 6 complained of blisters and skin erosion. Case 7 was the only patient who showed skin atrophy and desquamation.

## DISCUSSION

Allergic contact dermatitis (ACD) is a cell-mediated, type IV hypersensitivity reaction caused by repeated and direct skin exposure to contact allergens.[1,2,5,17] Allergic contact dermatitis caused by footwear (shoe dermatitis) may present as acute, subacute, intermittent, or chronic disease and appear superimposed on endogenous eczema or other skin diseases.[3,12] Three criteria must be met to generate an A: a genetic predisposition, an intact immune system, anlow molecular weight substances that can penetrate the skin.[17,21] Most allergens are haptens, simple chemicals that require proteins to be a

**Table 1. Characteristics of patients diagnosed with ACD to flip-flop sandals**

| Case | Age | Gender | Sign & Symptoms | Location of lesion | Duration of symptoms | History of atopy | History of family atopy |
|---|---|---|---|---|---|---|---|
| 1 | 18 | Female | Pruritus, erythema, blister, hyperpigmented crust | Medial anterolateral dorsum pedis resembling flip-flops and dorsal part of digiti pedis | Swallow® flip flop sandals, fashion flip-flop sandals | 4 months | No | No |
| 2 | 60 | Male | Pruritus, erythema, fissure lichenification | Medial anterolateral dorsum pedis resembling flip-flops | Swallow® flip flop sandals | 1 year | No | No |
| 3 | 47 | Female | Pruritus, erythema blister, leucoderma | Medial anterolateral dorsum pedis resembling flip-flops and dorsal part of digiti pedis | Swallow® flip flop sandals | 5 years | Yes | Yes |
| 4 | 65 | Female | Pruritus, erythema, lichenification | Medial anterolateral dorsum pedis resembling flip-flops, dorsal part of digiti pedis and anterior part of the ankle | Swallow® flip flop sandals | 2 years | No | No |
| 5 | 56 | Male | Pruritus, erythema, lichenification | Medial anterolateral dorsum pedis resembling flip-flops, dorsal part of digiti pedis and anterior part of the ankle | Swallow® flip flop sandals | 5 years | No | No |
| 6 | 4 | Male | Pruritus, erythema, blister, erosion | Medial and anterior dorsum pedis, dorsal part digiti pedis I, II | Fashion flip-flop sandals | 2 months | Yes | Yes |
| 7 | 54 | Female | Pruritus, skin atrophy desquamation | Medial anterolateral dorsum pedis resembling flip-flops, dorsal part of digiti pedis | Swallow® flip flop sandals | 2 years | No | No |

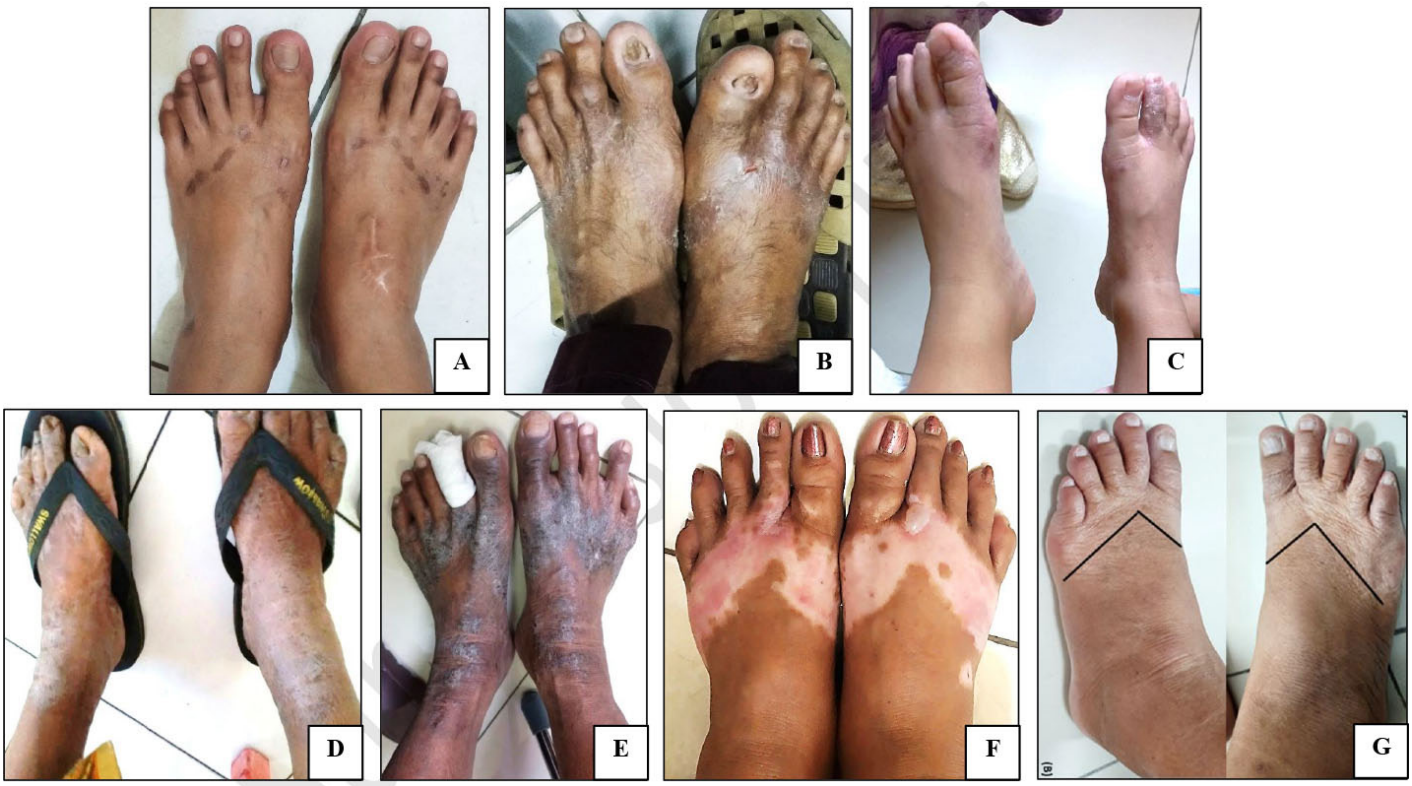


**Figure 1.** The manifestations of ACD in our patients. All of the cases showed skin lesions on the dorsal parts of their feet that were in contact with the rubber straps of their sandals **(A-G)**. Case 1 showed blisters and hyperpigmented crusts **(A)**; Case 2 showed fissure lichenifications **(B)**; Case 3 showed blisters and leukoderma **(C)**; Case 4 and 5 both showed lichenification that extended beyond the dorsal part of the feet **(D, E)**; Case 6 showed blisters and erosions **(F)**; and Case 7 showed skin atrophy and desquamation **(G)**.

complete antigen before sensitization.[17] ACD is a two-stage process that starts with T-cell sensitization to low-molecular-weight allergens (haptens), aided by dermal dendritic cells (Langerhans cells) in the proximal draining lymph node. During the sensitization phase, effector T-cells (CD8+ cytotoxic T-cells) are produced. Subsequent contact with the specific hapten results from the elicitation phase through activating the previously induced T-cell population. These T-cells are recruited in the skin and activated by skin cells that present the hapten on MHC class I and II molecules. The activated T cells produce type 1 cytokines (IFN-γ, IL-2, IL-17). These cytokines are cytotoxic and can destroy various skin cells, including keratinocytes. Apoptosis of skin cells causes inflammation, which leads to eczema lesions 72 hours after re-exposure to the offending hapten. This hypersensitivity response is primarily mediated by TH1 cells, but TH2, TH17, and TH22 cells may also be involved.[6,13]

Furthermore, the absence of dermatitis when patients wear substitute footwear and patch test reactions to one or more allergens found in the footwear are both indicators of footwear ACD.[5,12,14] The onset of shoe dermatitis is often sudden, with a history of a reaction to a new pair of footwear.[12] All of our patients presented with pruritus. Intense pruritus, pain, or burning sensation are the most common complaints of patients with footwear ACD.[12,21,22] At the sites of allergen contact, clinical manifestations include erythema, vesicles or blisters, papules, scaling, oozing and crusting. Lichenification and hyperpigmentation with cracks and fissures may develop in chronic cases.[1,10,12,22] Three of our patients (Cases 2, 4, and 5) had chronic manifestations of footwear ACD, which manifested as lichenifications. These patients have had ACD for 1 to 5 years. The lesions of footwear ACD usually have distinct lines and borders that outline the shape of the footwear or sandals.[22] This characteristic is evident in 6 out of 7 patients (Cases 1, 2, 3, 4, 5, and 7) whose lesions were in the shape of their flip-flop sandals. Another important diagnostic parameter in footwear ACD is the presence of normal skin that is not in contact with the footwear between eczematous areas.[20]

Atopic dermatitis (AD) has been linked to an increased probability of ACD. Individuals with AD have skin-barrier disruptions, which increases the absorption of irritants and contact allergens two-fold. Irritants cause further skin barrier breakdown, increased transcutaneous penetration of contact allergens, and an increased risk of contact sensitization and presentation. The skin barrier disruption is thought to be caused by inflammatory cytokines released during AD. During the acute and chronic phases of AD, Th2 cells stimulate the release of IL-4, IL-5, IL-13, and IL-31, whereas Th1 cells contribute during the chronic phase. Two of these cytokines, IL-4 and IL-5, are known to disrupt the skin barrier. This establishes a link between inflammation and skin barrier disruption, even in patients who have never had defects. Furthermore,

during the acute phase, studies have found increased IL-17 (secreted by Th17) and IL-22 (secreted by Th22). Bacterial colonization, common in AD, has also been linked to increased contact sensitization by creating an inflammatory environment. These mechanisms show that AD and ACD might share immune pathways, especially those involving Th1, Th2, Th9 and/or Th17. Despite these mechanisms, studies show varying results regarding the relationships between atopy and ACD.[16,23] In our study, only 2 patients (28.6%) had a history of atopy. A low prevalence of atopy in footwear ACD patients was also found in a study of 276 patients in India, in which only 24.64% of patients had a history of atopy. The relationship between atopy and ACD has not been well-established, and studies have shown varying results.[16]

The prevalence of footwear ACD is highest in warm-climate countries such as Indonesia, where heat and humidity cause sweating, increased pressure, and skin occlusion.[12,14] In a study of 64 patients suspected of having shoe dermatitis in Indonesia, Febriana et al. discovered that rubber slippers or sandals are the most common footwear (50.7%) causing footwear ACD.[14]

Four out of seven patients (57.1%) presented in our study were females. This is similar to the results of various other studies. A study by Chowduri and Ghosh (2007) in 155 shoe dermatitis patients in India found that 61.93% of their patients were females.[9] Similarly, an Indonesian study conducted in 2015 also found that 68.8% of shoe dermatitis patients were females.[14] These studies show that women are more frequently affected by footwear ACD athey often wear more varieties of footwear, exposing them to more haptens. Women are also generally more concerned about their health and seek medical assistance more often.[16,19] Furthermore, women have higher levels of immunoglobulin (IgM and IgG) than m, hence stronger cell-mediated immune responses.[24] Indonesian housewives are more susceptible to footwear ACD because they are constantly exposed to water, household detergents, and cleaning agents while performing household chores barefoot or in sandals. These agents may impair epidermal function, allowing allergens to penetrate deeper into the skin.[9,14]

One of our patients is a child aged 4 years old. Although ACD is more common in productive age groups, children can also be diagnosed with ACD.[12,25] The prevalence of ACD in the pediatric population has been estimated to be between 14,5%-70%. The highest sensitization rate is found in children between 0-3 years old. Pediatric ACD most commonly affects the skin of the legs, feet, hands, and face caused by metals, footwear, topical medications, and cosmetics. Children have a higher risk of ACD due to their thinner stratum corneum, incomplete epidermis layers, and higher skin surface area to body weight ratio, all of which cause increased absorption of substances in contact with the skin.[26] Although ACD is more common in productive age groups, children can also be diagnosed with ACD.[12,25] Allergic contact dermatitis is a close differential diagnosis for juvenile plantar dermatosis (JPD) and often aggravates the pre-existing JPD that mainly affects children aged 3-14 years. Juvenile plantar dermatosis is characterized by shiny, dry, fissured dermatitis of the plantar surface of the forefoot.[25] Atopic children and those suffering from juvenile plantar dermatosis (JPD) may become sensitized to footwear chemicals.[12] Patch testing should be performed on children with sole dermatitis to rule out ACD caused by rubber additives, adhesives, and/or chromates (found in leather shoes).[21] A study by Perumbil et al. analyzed the role of footwear allergy in JPD and found that 52.5% of the subjects used plastic footwear, 25% used leather footwear, and 12.5% used rubber footwear, with most patients presented with erythema and fissuring. The study found that footwear causes flare-ups of JPD in 20% of the patients.[25]

Rubber comes in both natural and synthetic forms, and sandals may contain a combination of the two.[10] In Indonesia, the straps of flip flops or sandals are frequently made of natural rubber latex, while the insoles are made of neoprene rubber covered with fabric.[14] Lazzarini et al. found that rubber was the most common component of footwear that tested positive in ACD patients (55.2%), with positive results for carba mix, thiuram mix, PPD mix, 1,3-diphenyl guanidine, para-phenylenediamine, and 4,4-dithiomorpholine. In sandals, rubber can be found in soles and elastics.[19] When rubber chemicals are considered a group, they are the most common allergen in footwear. According to North American Contact Dermatitis Group Study in 2001-2004, the most common allergens found in footwear are carba mix, thiuram mix, mercapto benzothiazole, mercapto mix, mixed dialkyl ureas, and rubber mix. Thioureas are chemical accelerators used to manufacture neoprene and foam rubber, frequently associated with footwear ACD.[10,12,14,15] Black or gray rubber contains para-phenylenediamine, a common cause of occupational dermatitis.[9,10,16] Black rubber mix was the most common allergen found in a study of 276 patients with footwear dermatitis by Thyvalappil et al.[16] ACD is also associated with the aromatic diamine 4,4'-diamino-diphenylmethane (DDM), which is commonly used in the production of rubber, plastics, diisocyanates, dyes, and adhesive. DDM is particularly associated with Asian-made footwear.[10]

The rubber antioxidant and depigmenting agent hydroquinone monobenzylether may also cause sensitization.[10] Hydroquinone monobenzylether used in footwear has a dispigmentary mechanism that leads to leucodermic lesions manifesting as confetti-like or hypopigmented macules.[14,27] Hydroquinone causes depigmentation by inhibiting the tyrosinase enzyme, DNA replication, and RNA transcrip, directly cytotoxic effect on melanocytes, and causing melanosome degradation. Several studies have reported the occurrence of leucodermic skin lesions following the application of hydroquinone monobenzylether or monomethyl ether.[11,27] Leucoderma was observed in one of our patients (Case 3) who had suffered from ACD for 5 years, implying that her flip-flop sandals may have contained hydroquinone monobenzylether. However, patch testing is required to confirm this hypothesis. Cyclohexylthiophthalimide has also been found through patch testing as a common rubber allergen.[10] In a Study by Freeman, rubber was the most common cause of allergic shoe

dermatitis (43.1%), followed by potassium dichromate (23.6%), 4-tert-butylphenol formaldehyde resin (PTBFR) (20%), and colophonium (9%).[28] Similarly, a study of 64 shoe dermatitis patients in Yogyakarta discovered that rubber allergens, specifically 2-mercaptobenzothiazole and 1,3-diphenyl guanidine, were the most common sensitizers of allergic shoe dermatitis. Most rubber-allergic patients had hyperkeratotic skin lesions frequently associated with rubber.[14]

Footwear ACD has also been linked to adhesive sensitivity, although the frequency remains undetermined.[10] Adhesives are importanfootwear components to attach various shoe or sandals components.[15] An adhesive most often used in footwear production is p-tertiary-butyl-phenol formaldehyde resin (PTBFR)often added in rubber glues and a component of neoprene adhesive used to attach shoe linings and insoles.[10,15,16] PTBFR accounts for approximately 10-20% of footwear allergies.[15] Colophony, a sap from pine or spruce trees added to natural rubber latex cement, is another common adhesive in footwear. A resin acid known as abietic acid is a key component of colophony. ACD sensitizers are produced during the oxidation of abietic acid.[3,10,20] Dodecylmercaptan and epoxy resins are two other known allergens in footwear adhesives. Polymerization of diglycidyl ether of bisphenol A (DGEBA) or polymerization of diglycidyl ether of bisphenol F (DGEBF) results in the production of epoxy resins, both of which are associated with ACD of the foot. Foot dermatitis after wearing plastic flip-flops due to the presence of bisphenol A (1% petrolatum) was reported in a study.[10]

All of our patients presented with bilateral, symmetrical lesions on the dorsum of the feet and none on the soles. Our findings are consistent with those of other studies. A study by Febriana et al. found that foot eczema most frequently occurred on the dorsum of the feet in 47.6% of patients in Yogyakarta.[14] Similarly, Lazzarini et al. found that the most common location was the dorsum of the feet and toes, as these areas are in closer and longer contact with the shoes, have larger surface areas and have thinner stratum corneum.[12,14,19] The most frequent location of ACD of the feet is the dorsum pedis with interdigital sparing and the sole.[10,12,14,19] The interdigital spaces are often the sites of microbial or fungal infections.[12] Most of the patients observed had skin lesions on the dorsum of their feet where the sandal/slipper strap came into contact with them.[14] ACD of the foot often appears as bilateral and symmetrical dermatitis, although in some cases, patchy and unilateral lesions may be found.[12,29] These differences might be due to different percutaneous penetration in various anatomical regions.[12] Footwear ACD might also expand beyond the originaexposure site through inadvertent contact or auto sensitization.[12,17] This is demonstrated in Cases 4 and 5, where the lesions extend cranially beyond the dorsum of the feet.

The most important part of footwear ACD treatment is determining the sensitizers and subsequently avoiding them by substituting patients' footwear with ones that do not contain materials that trigger the ACD.[10,12,20] Patients should be advised to wear hypoallergenic substitute footwear, such as ordering custom footwear that does not contain sensitizers. Injection-molded plastic shoes, wooden shoes, or vinyl shoes may be an alternative for patients allergic to rubber.[12] Patients may reduce contact by using barriers such as barrier socks.[10] Patients may also be educated to avoid re-dyed footwear because they have a higher probability of causing dye leakage.[14,20] Patients allergic to colophony or 4-tert-buthylphenolformaldehyde resin should be advised to wear footwear without or with stitched rather than glued linings.[12,14]

There are several limitations to our study. Patch-test results were not used to diagnose ACD to flip-flop sandals in our patients. We decided against performing the patch test because all of the patients had clinical manifestations related to using rubber flip-flops. In addition, patch testing kits were difficult to come by in rural areas like ours.

## CONCLUSION

We present 7 cases of ACD to flip-flop sandals that manifested as pruritic acute or chronic lesions on the dorsum of the feet after wearing flip-flop sandals. Although patch testing was not performed, the signs and symptoms developed by all of our patients indicated a strong link between ACD and flip-flop sandals. However, patch testing is still necessary to determine the exact components of the sandals that cause allergic reactions in each patient to provide the most effective management.

## ETHICS IN PUBLICATION

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have consented for their images and other clinical information to be reported in the journal. The patient understands that their name and initials will not be published.

## CONFLICT OF INTEREST

No conflict of interest.

## FUNDING

None.

## AUTHOR CONTRIBUTIONS

Authors and co-author are responsible for taking care of, following up with the patients, manuscript preparation, and publication.

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CASE REPORT
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# Dermatomyositis with multiple organ involvement: a case report and literature review

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## ABSTRACT

**Background:** Dermatomyositis (DM) is a chronic autoimmune disorder characterized by muscle and skin inflammation, a part of the idiopathic inflammatory myositis (IIM). Even though the disease is idiopathic, there are multifactorial factors related to dermatomyositis. This care report aimed to describe a DM case in a male patient to increase the knowledge and management of DM patients.

**Case description:** A 44-year-old Filipino male was referred to the emergency department (ED) of Siloam Hospital Mataram complaining of muscle pain and weakness with skin rashes 3 weeks before admission. Before the skin rash started, he had enlarged femoral lymph nodes in both thighs. The patient was afebrile with normal vital signs and was prescribed ibuprofen and amoxicillin. After that, he experienced skin rashes around his neck and the back of his ears with minimal pruritus. The symptoms worsened, making him unable to open his mouth and hard to breathe. In the ED, he also threw up dark-colored blood twice. Supporting examination showed elevated transaminase, increased LDH, and creatinine kinase. Biopsy results showed a histologic pattern of dermatomyositis. During hospitalization, he received a high-dose systemic steroid, antibiotic, and symptomatic treatment. He was discharged with a good outcome and planned to continue medical treatment in his country.

**Conclusion:** Dermatomyositis is an idiopathic autoimmune disease involving skin and internal organs. It is a multifactorial disease yet with unclear etiopathogenesis. Specific treatment guidelines for DM are not yet established, but initial systemic corticosteroid and additional steroid-sparring agents may exhibit good outcomes.

**Keywords:** autoimmune, dermatomyositis, idiopathic, myositis, skin rash.
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## INTRODUCTION

Dermatomyositis (DM) is a chronic autoimmune disorder characterized by muscle and skin inflammation, a part of the idiopathic inflammatory myositis (IIM).[1] Although the disease is idiopathic, there are multifactorial factors related to dermatomyositis, such as genetic, environmental, and immunologic factors. The disease presents with proximal skeletal muscle weakness and skin manifestation, which differ from other types of myositis clinically and histopathologically.[2,3] However, around 20% of cases present without muscle weakness, which is then referred to as clinically amyopathic dermatomyositis (CADM). The CADM is further classified into two subcategories: hypomyopathic and amyopathic dermatomyositis.[4] The cutaneous findings include violaceous erythema in different sites such as elbows, knees, lateral hips, upper chest and back, multiple papules over the finger, heliotrope rash around the eyelid, telangiectasia, and proximal nail fold capillary dilatation.[3,4] Moreover, the pathognomonic manifestations consist of Gottron's papule, Gottron's sign, V-neck sign, shawl sign, Holster sign, calcinosis, and mechanic's hand may occur in patients with DM.[4]

Dermatomyositis usually occurs in children or adults with a bimodal distribution and affects two to three times more women than men. The first age peak is 5-14, and the other group is 45-64. Nonetheless, the prevalence of DM is not quite representative of the true population because comprehensive data are lacking. A 32-retrospective study from Minnesota showed the incidence of DM based on age adjustment was 9.63 per 1,000,000 per decade, and the prevalence was 21.42 per 100,000 people. Meanwhile, juvenile dermatomyositis in the United States among children 2-17 years old was 2.1 – 4.5 per million.[4,5]

The length of inflammation in dermatomyositis could affect internal organs such as the pulmonary, cardiovascular, and gastrointestinal systems. Furthermore, 10-20% of cases are associated with underlying malignancy, which could alter the prognosis.[3,4] The most common pulmonary manifestation is interstitial lung disease (ILD), the leading cause of death in patients with dermatomyositis.[6]

Establishing the diagnosis of dermatomyositis requires clinical judgment based on the patient's history and physical examination, thus making it challenging because some cases are not classical. Detection of several specific autoantibodies could help diagnose DM, such as anti-melanoma differentiation-associates genes 5 (MDA5), which is correlated with an increased risk of

interstitial lung disease.[4] However, there are no specific well-established diagnostic criteria for diagnosing dermatomyositis. Therefore, this case will explain a dermatomyositis case in our hospital with several internal organ involvements.

## CASE REPORT

A 44-year-old Filipino male was referred to the emergency department of Siloam Hospital, Mataram, via the hospital ambulance call facility, complaining of muscle pain and weakness with skin rashes (Figure 1A-E). The symptoms started to appear 3 weeks before admission when the patient felt weak and muscle pain in both of his thighs and upper arms with stiffness and limited movement.

Along with his symptoms, there was a significant appearance of enlarged femoral lymph nodes in both of his inner thighs. The patient was afebrile with normal vital signs. The patient was prescribed ibuprofen and amoxicillin. The next day, he still felt pain and weakness but started to experience skin rashes around his neck and the back of his ears. The rashes were slightly painful and pruritic. Additional symptoms, such as diarrhea and stomachache, were denied. Two weeks before admission), the swelling of his femoral lymph nodes began to improve. However, the rashes spread to his upper chest, back, and face even more. He then received cetirizine taken orally once before bedtime. The muscle pain and weakness began to worsen with spreading rashes. One day before admission, he experienced facial pain and difficulty opening his mouth, thus making him unable to eat properly. Oedema occurred in both of his arms with stiffness. He also complained of breathing difficulty because he felt pain in both of his side chests. His blood pressure started to increase but without fever.

On his arrival at the ED, he felt nauseous and threw up dark-colored blood vomit twice. He had no history of cough or flu. His blood pressure was 130/90, heart rate 82 times per minute, temperature 36.7°C, and respiratory rate 16 times per minute. According to his previous medical history, he had high blood pressure and had routinely taken 10 mg of amlodipine before bedtime. He had no history of diabetes, food or medication allergy, asthma, or history of surgery. He did notice slight weight loss just because he had been eating a little. He had been working on the ship as a helmsman for 3 years and had been exposed to moderate ultraviolet exposure ever since. Despite this, he wore a full-body suit during his work. According to his familial history, both his mother and father were deceased due to leukemia and stroke, respectively. Based on the physical examination result, he had edema around the buccal area, limitation to open his mouth fully, normal cardiopulmonary examination, and generalized ill-defined

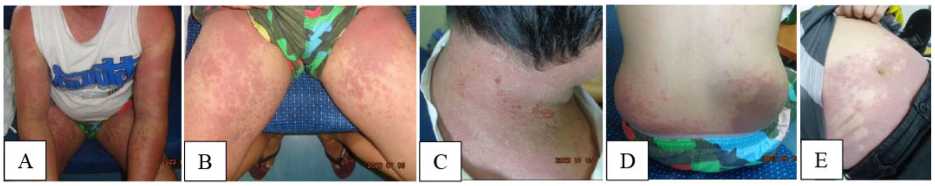


**Figure 1.** Generalized violaceous and erythematous patches, varying from ill to well-defined border, with thin scales (**A**) on both arms (**B**), on the thighs (**C**), and the presence of multiple erosion and thin scales on the lower back (**D**). Note the finger marks on the patient's stomach blanched with pressure (**E**).

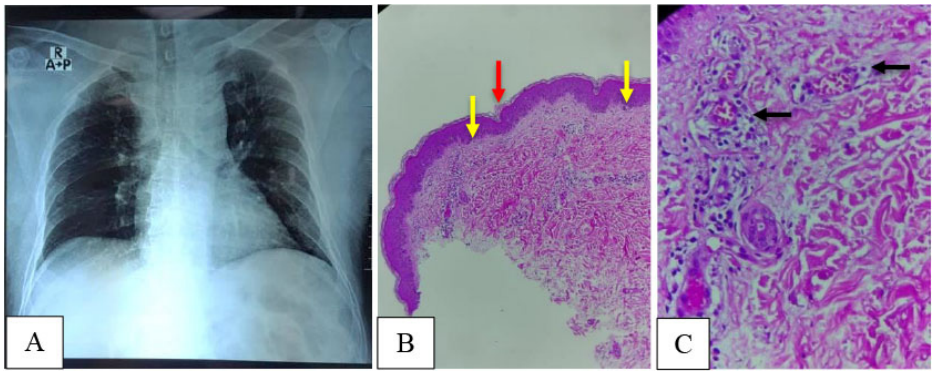


**Figure 2.** Supporting examination results. Chest X-ray showing increased bronchovascular pattern (**A**). Histopathology examination. Histopathological results show focal vacuolar interface dermatitis (yellow arrow) and mild hyperkeratosis (red arrow) (hematoxylin & eosin staining, 100x objective magnification) (**B**). Perivascular lymphocyte infiltrate (black arrow) (hematoxylin & eosin staining, 400x objective magnification) (**C**).

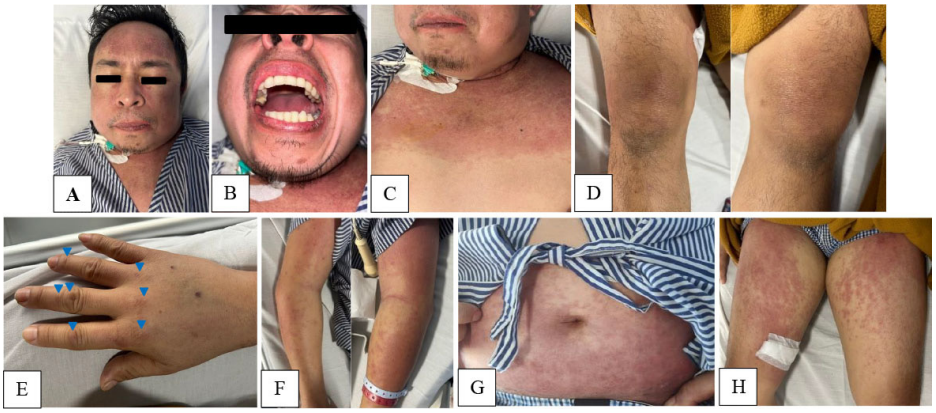


**Figure 3.** Clinical manifestation on the 6th day of hospitalization. Macular violaceous erythema on the face with perioral bright pink rash and thin scales (**A**) and jaw stiffness (**B**). V-neck sign (**C**); Gottron sign or slight ill-defined erythema on the knees (**D**); Gottron papules (multiple light erythema, ill-defined, multiple papules over the metacarpophalangeal, proximal, and distal interphalangeal joints shown in blue head arrow) (**E**); and violaceous erythema on the upper arms (**F**), thighs (**G**), and lower abdomen (**H**) were observed.

macular rashes on his face, neck, upper arms, thighs, back, and lower abdomen with slight scaling on top of his rash and multiple erosions. The rash was blanched with pressure (Figure 1E). In the ED, the patient received fluid resuscitation with 1L of ringer lactate for 2 hours, a loading dose of 80 mg pantoprazole, and 1 gr of meropenem.

Supporting examination was carried out for the patient in the ER. His electrocardiography (ECG) result was normal. Laboratory results showed hyperhemoglobinemia, increased hematocrit, hyperleukocytosis, elevated liver enzymes, hypoalbuminemia, and electrolyte imbalance. His urinalysis showed mild ketonuria, positive urobilinogen, and occult blood in the urine. Several radiological examinations were done. Abdominal ultrasound showed non-specific hepatomegaly (suspected parenchymal liver disease), cholelithiasis 0.6 cm with sludge, suspected bowel inflammation, and non-specific lymphadenopathy of bilateral inguinal. Neck ultrasound revealed non-specific lymphadenopathy at the submental, bilateral submandibular, bilateral carotid space, and posterior bilateral cervical space regions. Edema in the sternocleidomastoid and trapezius muscles was found, and dermatomyositis was suspected.

His chest X-ray showed an increased bronchovascular pattern (Figure 2A). Next, a lumbosacral X-ray was done with paralumbal muscle spasms without any compression. Doppler ultrasound revealed valve incompetency at the median cubital vein. Furthermore, musculoskeletal ultrasound showed signs of myositis, tendinosis, and subcutaneous edema. The patient was then screened for COVID-19 infection with an antigen swab test. However, the result was positive. Polymerase chain reaction (PCR) was done twice to confirm the COVID-19 infection. Both PCR results were detected as negative. This case was handled by a multidisciplinary team, which included the internal medicine doctor, neurologist, dermatologist, and pulmonologist.

Furthermore, a blood culture was done with negative bacterial growth. Since he had leukocytosis and a familial history of leukemia, a blood smear morphology test was carried out. The result was interpreted as a sign of inflammation without any suspicion of malignancy. The level of creatinine kinase (7,519 U/L) and lactate dehydrogenase (593 U/L) was highly elevated. Moreover, the patient was screened for thyroid disease. The TSH level appeared normal. The ANA profile was conducted to rule out any underlying autoimmune disease, revealing mild positive for AMA-M2, Scl-70, and DFS70 antigens. A punch biopsy was also executed. The biopsy result showed mild hyperkeratosis in the epidermis, mild perivascular lymphocyte infiltrates, collagen thickening, and erythrocyte extravasation (Figure 2B-C). Those findings established the diagnosis of dermatomyositis with transaminitis, electrolyte imbalance, hypoalbuminemia, hematemesis due to probable erosive gastritis, controlled hypertension, and lung involvement. Electromyography (EMG) and muscle biopsy were planned to be conducted; however, the patient was not suitable as the EMG candidate, and he did not give his consent for muscle biopsy.

During hospitalization, the patient received a high dose of steroid (1 gr of methylprednisolone intravenously (IV) per day) for 3 days, albumin transfusion for correction, furosemide IV 20 mg per day, diphenhydramine IV twice per day, pantoprazole IV 40 mg twice a day, meropenem IV 1 gr thrice a day, IVFD 3% normal saline with 0.9% saline for maintenance, topical ceramide, and topical antibiotic for his skin. On the 4$^{th}$ day of his admission, the patient was put on a central venous catheter because his extremities had become too swollen to put on a peripheral IV line. The rashes started to be less pruritic and painful. The jaw stiffness and erythema around the face remained (Figure 3A-B). Besides, the generalized rash, V-neck sign, Gottron papules, and Gottron sign could still be observed (Figure 3C-H).

He was hospitalized for 9 days, and his condition improved. There was no additional appearance of skin rash, and the rashes started to darken compared to the initial condition, with significant muscle strength improvement. The swelling had diminished, and his electrolyte level, as well as liver enzymes, improved better. There was no adverse event from the treatment. After his condition was stabilized, he was discharged from the hospital to continue further medical examination and treatment in his country. He was prescribed an oral antibiotic, steroid, topical antibiotic, and symptomatic medication.

## DISCUSSION

Dermatomyositis is a chronic acquired immune-mediated disease that presents muscle weakness and skin rash. In around 50-70% of cases, patients with DM have myositis-specific autoantibodies. Nonetheless, the etiopathogenesis of dermatomyositis remains questionable.[3] The risks of developing dermatomyositis are multifactorial and include genetics, immunology, and environmental factors.[2] Genetics plays a role in the etiology of dermatomyositis. Human leukocyte antigen (HLA) polymorphism increases the risk of developing the disease. The first identified allele was HLA-B8, harbored in 75% of juvenile dermatomyositis patients. Several high-risk haplotypes of HLA also contribute to disease occurrence. These haplotypes include HLA-A*68, HLA-DRB1*0301, HLA-DQA1*0104, HLA-DRB1*07, DQA1*05, and DQB1*02.[2,4] Besides, the innate and adaptive immune response also partake in the pathogenesis of DM. The histological and molecular features of the disease prove this evidence. The activity of CD4+, CD8+ T cells, B cells, dendritic cells, and macrophages causes the direct inflammatory effect. In contrast, the indirect effect involves several cytokines such as interferons (IFNs), interleukins (ILs), and tumor necrosis factors (TNF).[7] Higinterferon (IFN) levels can induce DM-autoantigen, such as MDA5, which then accounts for humoral response-producing autoantibodies.[4] Those autoantibodies help identify the diagnosis of dermatomyositis and are associated with the risks of systemic disease. For example, anti-tRNA synthetase and anti-melanoma differentiation-associated gene 5 (MDA5) are associated with an increased risk of interstitial lung disease; anti–transcriptional intermediary factor (TIF1)-g and anti-nuclear matrix protein 2 (NXP2) are correlated with cancer risks.[4,6] More than 80% of patients with myositis present with autoantibodies.

Furthermore, viral infection may also trigger the disease, including coxsackie B, enterovirus, and parvovirus. Several drugs, such as antineoplastic drugs, antibiotics (penicillin, sulfonamide, isoniazid), NSAIDs (diclofenac), and radiation could contribute to disease development.[3]

Dermatomyositis is two times more prevalent in women compared to men, and it affects approximately 1-6 persons per 100,000 people. This disease is recognized as a disease with a bimodal age distribution.[1,7] In adults, the mean age at diagnosis is 44 ± 18.3 years.[2] Since the disease is one of the rare diseases, estimating the incidence and prevalence of true dermatomyositis becomes quite challenging. In addition, establishing the diagnosis of dermatomyositis requires precision and specific standardization. Several countries, such as Japan and Taiwan, used the insurance claims database for the data analysis. According to the study, DM cases' approximate annual incidence rate was 10-13 and 6-10 per million, respectively.[8,9] Moreover, studies from the few-based and largest populations approximated similar results for the incidence and prevalence of dermatomyositis. The prevalence was estimated at 10-20 cases per 100,000 people, while the incidence was 5-10 per 1,000,000 per year.[5] Based on age-adjusted incidence, there was 13.98 per 1 million (95% CI, 8.08-19.89) and 4.68 per 1 million (95% CI, 1.15-8.20) for women and men respectively. In the United States, the black race is more prevalent with dermatomyositis compared to the white race.[7]

Most cases were termed classic dermatomyositis by means of patients with particular muscular and cutaneous manifestations of DM. Sontheimer proposed diagnostic criteria for cutaneous findings. The major criteria of DM cutaneous manifestation include heliotrope sign (violaceous erythema hue on the upper eyelid), Gottron papules (papules over metacarpophalangeal (MCP) and interphalangeal (IP) joints), Gottron sign (erythema over the elbows, knees, or IP joints). Furthermore, the minor criteria include V-neck sign (erythema around the V-neck area of the upper chest), shawl sign (erythema over the posterior neck or shoulder), holster sign (erythema at the lateral thigh or hips), mechanic's hands (hyperkeratosis along the medial part of the thumb, lateral second, and third finger), pruritus, and violaceous erythema on the malar eminences.[4] However, around 20% of cases were defined as clinically amyopathic dermatomyositis (CADM).[1] These patients have the classical cutaneous rash of DM yet without muscle weakness. Clinically, amyopathic dermatomyositis has two subcategories: hypomyopathic and amyopathic dermatomyositis. The two subtypes are determined based on supporting examinations such as magnetic resonance imaging (MRI), electromyography, muscle biopsy, and laboratory results of muscle enzymes. Muscle enzymes can be measured through creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and aldolase.[2,4] Hypomyopathic dermatomyositis will result in at least one abnormality in those tests, while the results of amyopathic DM will be negative in all tests.[4] Thus, acknowledging all spectrums of dermatomyositis is important because this disease is related to malignancy and internal organ involvement, which could cause morbidity and mortality. Additionally, clinically amyopathic dermatomyositis patients have the same risk of developing systemic disease as classic dermatomyositis. Dermatomyositis may involve extracutaneous pulmonary, gastrointestinal, cardiovascular, and musculoskeletal manifestations. In our case report, the patient had classic dermatomyositis with gastrointestinal, musculoskeletal, and pulmonary involvement based on clinical approach and supporting exams.

## Internal Organ Involvement

### *Gastrointestinal (GI) manifestation*

The most common GI symptom is dysphagia in juvenile dermatomyositis; meanwhile, in adults, patients complain of abdominal pain (65%), vomiting (16.6%), diarrhea (4.5%), and bleeding 12.5%). The symptoms may appear acute or subacute, ranging from 2 days to 6 months, and are mostly present in women. Even though GI tract involvement is rare in DM patients, it can cause life-threatening problems. The manifestation includes perforation and ulcer formation. Moreover, upper and lower GI tracts are commonly affected. If perforation occurs, the duodenum is the most prevalent affected site. Some studies explained the main cause of GI manifestation was vascular compromise. Histopathologically, several patients also presented with vasculitis. The vascular compromise happens due to chronic arteriopathy, caused by an activated complement and membrane attack complex that destroys the capillary system. Several studies also found that myositis-specific autoantibodies (MSA) (e.g., NPX-2) were likely positive in DM patients with GI manifestation. However, there was no clear explanation regarding the key role of MSA in DM patients with GI complications. The treatment for DM patients with GI involvement should consider more aggressive treatments because of the tendency for life-threatening events. Pulsed intravenous corticosteroids may be considered initially for patients with GI complications. Moreover, additional intravenous immunoglobulin (IVIG) or immunosuppressant medication such as methotrexate and azathioprine may be good choices for treatment.[2,4,10] Our patient presented with nausea and hematemesis, which is a high suspicion of GI involvement of dermatomyositis.

### *Pulmonary manifestation*

In patients with DM, interstitial lung disease (ILD) is the common manifestation that causes morbidity and mortality in patients. In addition, ILD mostly occurs as an internal organ complication in DM patients and is a leading cause of hospitalization and cause of death, with a mortality rate between 7.5%-44%. Patients mostly complain of Interstitial lung disease, which may occur at any point of the disease course, with the median time ranging from 16.9 to 18 months. Several MSA also correlate with ILD occurrence. For example, anti-Mi-2, anti-TIF-1-gamma, and NXP-2 lower the risk of developing ILD, while anti-MDA-5 increases the risk. Additionally, palmar papules, punched-out ulcers, and skin necrosis are the pathognomonic manifestations of the presence of MDA-

5. In some cases, interstitial lung disease will progress and cause pulmonary hypertension with symptoms of increased fatigue, shortness of breath, dyspnea on exertion, palpitation, chest pain, edema, and lightheadedness. Along with anti-synthetase syndrome, it will decrease the chance of survival. Usually, the pulmonary screening must be conveyed for all DM patients, regardless of the symptoms. Pulmonary function test (PFT) may be useful but not an adequate screening tool for ILD detection. The common finding is a restrictive pattern with decreased forced vital capacity (FVC). Moreover, a high-resolution CT scan may be considered a valuable diagnostic test that may present with nonspecific interstitial pneumonia.[2,4,6] In this case, the patient had an increased bronchovascular pattern on the chest X-ray without obvious pulmonary symptoms. During treatment, he never had breathing difficulty or cough

*Musculoskeletal manifestation*

Typically, DM patients complain of muscle weakness in the extensor muscle forming the shoulder, pelvic girdle, and proximal limbs. Myositis in DM presents symmetrically in the proximal extremities. However, around 20% of patients are clinically amyopathic without evidence of muscle weakness. Furthermore, several patients with muscle pain may be present without muscle weakness. Respiratory muscles may also be affected, causing significant respiratory insufficiency and failure. Arthralgia also occurs in 30-40% of DM patients. It commonly affects small joints such as the wrist, MCP, IP, elbows, shoulder, and ankles. The symptoms should be distinguished from rheumatoid arthritis.[4]

### Malignancy

Various cancers, such as breast, lung, ovarian, hematologic, and nasopharyngeal cancers, are linked to dermatomyositis. Malignancy in dermatomyositis occurs in around 10-20% of DM cases and usually happens at 1-2 years of disease onset. Myositis-specific autoantibodies related to increased risk of malignancy include anti-(TIF1)-g and anti-(NXP2). Several risk factors for developing malignancy in dermatomyositis involve male gender, older age, absence of ILD, presence of specific autoantibodies, severe skin manifestation, and dysphagia. Protective factors of malignancy include ILD, Raynaud phenomenon, and arthritis.[4]

### Treatment

The first line of initial treatment for classic dermatomyositis is a systemic corticosteroid, prednisone, at a dose of more than 0.5 mg/kg/day. However, corticosteroid sparring agents may be necessary to treat myositis and extracutaneous manifestation. Besides, these agents are important to minimize the side effects of systemic corticosteroids, which may cause induced myopathy.[4] Antimalarial medication (e.g., hydroxychloroquine) is considered the first-line treatment of DM. However, patients treated with antimalarial drugs are more likely to have flare-ups.[11] The first-line treatment for cutaneous disease includes photoprotection and topical steroids. Topical steroids help reduce erythema, pruritus, and scales, and they are in adjunct with systemic corticosteroids.[4] Common corticosteroid-sparring agents are methotrexate and azathioprine.[6] Intravenous immunoglobulin is effective for severe manifestations such as dysphagia and respiratory muscle involvement.[4] As observed in this patient, a high dose of corticosteroid and other treatments gives a good outcome.

## CONCLUSION

Dermatomyositis is an idiopathic autoimmune disease that involves the skin and internal organs. Classic dermatomyositis presents with muscle weakness, and it is a multifactorial disease with unclear etiopathogenesis. Several myositis-specific autoantibodies are associated with the increased risk of internal organ manifestation and cancers. Extracutaneous manifestations of DM include pulmonary, gastrointestinal, cardiovascular, musculoskeletal, and malignancy. Interstitial lung disease is the leading cause of mortality in DM patients. Moreover, gastrointestinal involvement also increases the risk of morbidity and mortality due to GI perforation or ulcer. Specific treatment guidelines for DM are not yet established, but initial systemic corticosteroid and additional steroid-sparring agents may exhibit good outcomes.

## CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

## ETHICS IN PUBLICATION

The patient had agreed to and signed an informed consent form for the study's purpose and publication while maintaining the patient's confidentiality. This study was approved by the Research Ethics Committee of the Faculty of Medicine of Universitas Mataram (No: 310/UN18.F8/ETIK/2023).

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## AUTHOR CONTRIBUTION

The first and second authors contributed substantially to the case report concept and carried out the working draft, data acquisition, data analysis, manuscript preparation, and review. For final approval, the third, fourth, and fifth authors conducted data acquisition, analysis, and manuscript review. The sixth author was responsible for data analysis.

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# Characteristics of skin aging at the Dermatology and Venereology Outpatient Unit at Prof. dr. I Goesti Ngoerah Gde Ngoerah General Hospital, Denpasar from January to December 2019

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## ABSTRACT

**Background:** Skin aging is a complex biological process influenced by intrinsic and extrinsic factors. In addition, national data regarding skin aging is still scant. This research was carried out to learn the characteristics of skin aging at the Dermatology and Venereology outpatient unit of Prof. Dr. I G. N. G. Ngoerah General Hospital, Denpasar, in January-December 2019.
**Methods:** This research is a quantitative descriptive study with a cross-sectional design. Sampling was carried out by total sampling with research subjects consisting of skin-aging patients at the Dermatology and Venereology Outpatient Unit of Prof. dr. I G. N. G. Ngoerah General Hospital in January-December 2019. The data collected consists of age, gender, smoking history, alcohol consumption history, body mass index, usage of sunscreen, duration of sun exposure, and Glogau scale classification. Descriptive analysis was carried out using SPSS ver. 23.
**Results:** Twenty cases of skin aging were included. Most cases of skin aging were in the age group of 36-45 years old, all of whom were female, all of whom had no history of smoking, all of whom had no history of alcohol consumption, most body mass index classification was overweight, most do not use sunscreen, the duration of the sun exposure is mostly 30 minutes-6 hours, and the highest classification of the Glogau scale is group III.
**Conclusion:** In this study, body mass index, usage of sunscreen, and duration of sun exposure are the main factors affecting skin aging.

**Keywords:** characteristics, extrinsic factor, intrinsic factor, skin aging.
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## INTRODUCTION

Aging is inevitable and is experienced by everyone. As aging occurs, the skin also undergoes an aging process. The skin is the largest organ covering the body's external surface.[1] One of the most important extracellular matrix (ECM) is collagen. Collagen plays a role in determining the tensile strength of the skin. It contributes to the aging process.[2] Skin aging is a complex biological process influenced by various factors that cause physical and histological changes.[3] Some experts claim that signs of skin aging begin to appear after the age of 25 because the production of collagen in the body decreases so that the skin becomes less elastic.[4] Physically, there are several signs of skin aging, which include dry skin, wrinkles, and dyspigmentation or discoloration of the skin.[5] Histologically, physical signs can arise due to atrophy of collagen.[2]

Skin aging is triggered by a combination of two components consisting of intrinsic aging and extrinsic aging.[6] About 10% of skin aging is caused by intrinsic factors, and extrinsic factors cause 90%. Different factors trigger intrinsic and extrinsic skin aging. Skin aging triggered by intrinsic factors, also called chronological aging, occurs as a result of the natural aging process of the body, which is influenced by age, gender, ethnicity, anatomical variations, and hormonal changes.[7] Extrinsic skin aging, also known as photoaging, involves environmental factors such as sun exposure, nutritional status, smoking history, and alcohol consumption history. Exposure to the sun's ultraviolet (UV) radiation can cause skin changes, such as the breakdown of the matrix structure of the dermis. However, extrinsic aging can be avoided in contrast to intrinsic aging, which is inevitable.[6,7]

The skin aging process causes changes in appearance that could decrease confidence. According to previous research, the impact of skin aging can cause social anxiety and low levels of self-confidence. In some others, manifestations of skin aging can cause psychological disorders such as eating and body dysmorphic disorders.[8] Currently, data on skin aging is still scant. In addition, judging from the impact caused by skin aging, which is quite significant and could

impact the quality of life, this study aimed to evaluate the characteristics of skin aging at the Dermatology and Venereology Outpatient unit at Prof. dr. I G. N. G. Ngoerah General Hospital, Denpasar Between January - December 2019.

## METHODS

This research is a quantitative descriptive study with a cross-sectional design to determine skin aging characteristics at the Dermatology and Venereology Outpatient unit at Prof. dr. I G. N. G. Ngoerah General Hospital, Denpasar between January-December 2019. Data was collected in one month using secondary data from the patient's medical record. The sampling technique is carried out using total sampling. Subject criteria included in this study were all patients who attended the Medical Cosmetic Division and complained of skin aging as the primary or secondary concern. The data collected includes age, gender, body mass index (WHO classification for Asia), history of smoking, history of alcohol consumption, usage of sunscreen, duration of sun exposure, and Glogau scale classification. Exclusion criteria if the data were not recorded completely. Data were analyzed descriptively using SPSS version 23 to obtain frequency and proportion for each characteristic.

## RESULTS

The total number of subjects seeking treatment at the Medical Cosmetic Division of the Dermatology and Venereology Outpatient Unit of Prof. dr. I G. N. G. Ngoerah General Hospital has 110 patients. Patients who came with complaints of skin aging accounted for 22 cases or 20% of the total 110 patients seeking treatment. Two cases were excluded from a total of 22 cases due to incomplete medical record data, so a total sample of 20 cases was obtained, consisting of all women who had met the inclusion and exclusion criteria. Research findings showed that (Table 1) the age group that experiences skin aging is the 36-45 age group, with 11 cases (55%). The youngest subject was 33 years old, and the oldest subject was 48 years old. With an average age of 40.10 ± 4.87 years old. All skin-aging patients are female and without any history of smoking. Most cases were overweight (23-24.9 kg/m2) in the body mass index group, with 10 cases (50%). Most skin-aging patients did not use sunscreen, with 14 cases (70%). Most of the duration of sun exposure in the range of 24 hours was 30 minutes to 6 hours, with 16 cases (80%). Most cases were in the Glogau III group, with 18 cases (90%).

**Table 1. Age distribution of skin aging subjects**

| Characteristic | | Frequency | Proportion (%) |
|---|---|---|---|
| Age classification | Age group (years) | | |
| Late adolescents | 17-25 | 0 | 0% |
| Young adults | 26-35 | 5 | 25% |
| Late adults | 36-45 | 11 | 55% |
| Young elderly | 46-55 | 4 | 20% |
| Late elderly | 56-65 | 0 | 0% |
| Senior | >65 | 0 | 0% |
| Mean ± SD | 40.10 ± 4.87 | | |
| | Total | 20 | 100% |
| Gender | | | |
| Male | | 0 | 0% |
| Female | | 20 | 100% |
| Total | | 20 | 100% |
| Smoking history | | | |
| Yes | | 0 | 0% |
| No | | 20 | 100% |
| Total | | 20 | 100% |
| Alcohol consumption history | | | |
| Yes | | 0 | 0% |
| No | | 20 | 100% |
| Total | | 20 | 100% |
| BMI classification | BMI range | | |
| Underweight | <18.5 kg/m$^2$ | 0 | 0% |
| Ideal | 18.5-22.9 kg/m$^2$ | 7 | 35% |
| Overweight | 23-24.9 kg/m$^2$ | 10 | 50% |
| Obesity I | 25-29.9 kg/m$^2$ | 3 | 15% |
| Obesity II | >30 kg/m$^2$ | 0 | 0% |
| Total | Total | 20 | 100% |
| Sunscreen usage | | | |
| Yes | | 6 | 30% |
| No | | 14 | 70% |
| | Total | 20 | 100% |
| Duration of sun exposure | | | |
| <30 minutes | | 4 | 20% |
| 30 minutes - 6 hours | | 16 | 80% |
| >6 hours | | 0 | 0% |
| | Total | 20 | 100% |
| Glogau classification | | | |
| I (mild) | | 0 | 0% |
| II (moderate) | | 2 | 10% |
| III (advanced) | | 18 | 90% |
| IV (severe) | | 0 | 0% |
| | Total | 20 | 100% |

SD: standard deviation; BMI: body mass index

## DISCUSSION

Skin aging is a complex biological process influenced by various factors that cause physical and histological changes. Early signs of skin aging begin to appear at the age of 25 years. The ratio of collagen composition will change with age. At a younger age, the skin comprises 85% type I collagen and 15% type III collagen. With chronological aging, the ratio of type III collagen will increase compared to type I

collagen.[9] Each year, the signs of aging will become more significant due to decreasing collagen production, causing the skin to be less elastic. In addition, several major components of the extracellular matrix, such as elastin and hyaluronic acid, undergo structural changes.[10,11]

Cases of skin aging for <26 years old were 0 cases (0%) can be caused as the early signs of skin aging only begin to appear after the age of 25 years. In this study, most age groups that experience skin aging were between 36-45 years old. Most patients in a productive age range are more susceptible to external factors such as UV radiation and pollutants. Previous epidemiological research stated that air pollution from motor vehicle emissions such as particulate matter (PM), NO2, and soot is associated with premature skin aging because it contains polycyclic aromatic hydrocarbons (PAHs), which bind to aryl hydrocarbon receptors (AHR); thus damaging the skin barrier.[12]

Early manifestations of skin aging appear earlier in women because the dermal thickness and collagen density are lower in women. At the time of menopause in women, changes in hormone levels, such as lower estrogen levels, will cause the thickness of the skin to decrease significantly, making the signs of aging more visible. Meanwhile, men have a thicker dermal thickness, causing manifestations of skin aging to appear later.[13] In this study, most patients had not experienced menopause, so the incidence of skin aging was not caused by a decrease in hormones due to menopause.

Smoking and alcohol are both risk factors for skin aging. Nicotine in cigarettes can cause a decrease in blood supply, causing a lack of oxygen and wrinkles. Previous studies show that matrix metalloproteinase (MMP)-1 in smokers is higher than in non-smokers. High MMP levels can degrade collagen, elastic fibers, and proteoglycans and cause an imbalance between the synthesis and degradation of dermal connective tissue.[14] Research also shows that smokers have a thicker epidermis and low dermal density and elasticity.[15]

Previous research showed a significant correlation between alcohol consumption and the formation of eye bags, midface volume loss, and fine blood vessel appearance. The literature states that alcohol damages carotenoid antioxidants in the skin, which increase UV sensitivity. Excessive alcohol consumption is also reported to cause eye bags due to reduced suborbital fat pads.[16] However, there were no cases recorded regarding the history of smoking and alcohol consumption; hence, this study is unable to conclude the correlations between smoking and alcohol consumption in skin-aging patients.

Previous study shows that patients with overweight body mass index show earlier signs of aging significantly due to various mechanisms. At higher body mass index, changes in the epidermal barrier cause trans-epidermal water loss (TEWL) and increased erythema compared to control subjects with ideal body weight. Some subjects with severe obesity also have dry skin and damaged skin barrier. An in vivo experiment showed that the skin's mechanical strength was weaker in obese patients than in the control group due to the failure of collagen deposition to accommodate the increased surface area of the skin. Another study showed that excess body mass index correlates with increased type III collagen turnover.[17] Conversely, in a previous study involving 128 subjects, low body mass index causes skin wrinkles to be visible due to xerosis and reduced skin elasticity.[18] This is consistent with the findings in this study, which discovered that most skin-aging patients are classified as overweight (23-24.9 kg/m$^2$).

Sunscreen application on skin exposed to sun from the sun can protect the skin from damage caused by UV radiation. There are 2 mechanisms of action for sunscreen products depending on the UV filter used. Chemical sunscreens work by absorbing UV radiation.[19] Physical sunscreens work by reflecting or scattering UV radiation.[20] The results of previous observational studies prove that proper sunscreen prevents the formation of free radicals such as ROS, thus preventing signs of photoaging such as wrinkles, hyperpigmentation, and telangiectasia.[21] This is consistent with the findings in this study, which discovered that most skin-aging patients did not use sunscreen protection. The distribution of smoking habits and alcohol consumption habits of as much as 0 cases (0%) can also support that in this study, skin aging is caused by intrinsic and extrinsic factors in the form of exposure to UV of the sun without optimal protection.

Exposure to UV is an extrinsic factor that has the biggest role in causing premature aging. Direct sun exposure for more than 15 minutes without protection can cause premature skin aging. Caucasian women showed that the impact of exposure to UV rays increased with age. The impact of sun exposure can vary between individuals depending on the skin type. Despite the major role of extrinsic factors, chronological aging and photoaging have complex and inseparable correlations. Therefore, detailed quantification of the duration of direct sun exposure on aging is difficult to obtain.[22]

There are 3 spectrums of UV radiation, namely UVA, UVB, and UVC. Ultraviolet radiation will activate reactive oxidative stress (ROS), which correlates with the activation of the mitogen-activated protein kinase (MAPK) pathway, which causes cellular inflammatory activity. The ozone layer has absorbed most UVC. Most of the UV radiation that enters the earth's surface is UVA. Ultraviolet B has greater energy than UVA but can only reach the skin's epidermis. Ultraviolet-B can carry out broader oxidation modifications to proteins that cause molecular changes in carcinogenesis processes. UVA can reach the dermis and hypodermis of the skin. Ultraviolet-A radiation reduces transforming growth factor (TGF)-β1, causes dysfunction of the G1 arrest phase and increases the expression of MMPs and degradation of ECM such as glycosaminoglycans, collagen, and elastin.[23–25]

Glogau classification is used to determine the degree of severity of photoaging. Glogau classification III usually occurs at 50-65 with signs of wrinkles at rest. Research findings show that skin aging patients recorded are in the age range of 33-48 years. The age classification specified in the Glogau photoaging classification may shift to earlier or later depending on exposure to extrinsic factors of each subject.[6,8,16] In this study, a shift in aging was found to be premature. In the distribution of duration

of sun exposure and sunscreen usage, it was found that most cases were exposed to sunlight for a duration of >30 minutes per day and did not use sunscreen. These factors can affect the shift in the age of Glogau classification, which may occur earlier than it should be. The weakness of this study is the small number of samples, the fact that it only used recall memory and the possibility of recall and selection bias. In addition, the classification of skin aging only uses Glogau photoaging classification, which only shows skin aging due to UV exposure factors, so it cannot provide an overview of skin aging due to internal factors.

## CONCLUSION

Based on the results of this study, it can be concluded that the main precipitating factors that play a role in skin aging in this study are body mass index, sunscreen usage, and duration of sun exposure.

## ETHICS IN PUBLICATION

This research has been through the Ethics Committee review in the Research Ethics Committee Faculty of Medicine, Universitas Udayana (643/UN14.2.2.VII.14/LT/2022).

## CONFLICT OF INTEREST

All authors declare there are no conflicts of interest in this study.

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## AUTHORS CONTRIBUTION

The author and co-authors contributed equally to this research.

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CASE REPORT
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# Steatocystoma multiplex suppurativa: a case report

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## ABSTRACT

**Introduction:** Steatocystoma multiplex (SM) suppurativa is an inflammatory variant of SM, a benign hamartomatous disorder of pilosebaceous unit that usually occurs in early adulthood. Treatment responses are often disappointing due to widespread lesions and late diagnosis. This case report aimed to describe a male diagnosed with SM suppurativa to increase the knowledge and management of SM suppurativa.

**Case:** A 23-year-old male came with multiple lumps on his neck, chest, back, and extremities over the last four years. On dermatological examination, yellow to skin-colored papules, nodules, and cysts, 0.3 to 2 cm in diameter, were observed with erythematous-to-hyperpigmented macules and scars over the lesions. Histopathological examination of the lesion showed cysts with pilosebaceous-like lining and sebaceous glands adhered to the cyst's wall. The patient diagnosed with steatocystoma multiplex SM suppurativa was treated only with a topical antibiotic and corticosteroid.

**Discussions:** Although the histopathological findings showed pathognomonic findings for SM, SM suppurativa was established as the working diagnosis based on the clinical and dermoscopic findings of inflammatory lesions. The biopsy of noninflammatory lesions might cause no sign of inflammation in the histopathological findings.

**Conclusions:** Dermoscopic findings showed a yellow structureless area with diffuse erythematous borders and histopathological findings of a pilosebaceous-like layer with sebaceous glands adhering to the cyst wall and chronic inflammation is the hallmark of SM suppurativa.

**Keywords:** dermoscopy, diagnosis, histopathology, steatocystoma multiplex suppurativa.
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## INTRODUCTION

Steatocystoma multiplex (SM) suppurativa is an inflammatory variant of SM, a benign hamartoma developing from a pilosebaceous duct. Adolescents or early adulthood often suffer from this disorder without gender predominance. In most cases, the sporadic occurrence can be observed despite being inherited with an autosomal dominant pattern. The incidence of SM suppurativa has not been reported due to its rare occurrence. The treatment's responses are often disappointing due to the widespread lesions, so early diagnosis and correct approach should be conducted to obtain the best outcome.[1] This case report will discuss a case of SM suppurativa in a 23-year-old man.

## CASE DESCRIPTION

A 23-year-old man came with lumps on the neck, chest, back, and extremities. The first lump appeared on the arm four years ago. They were yellow-colored, which subsequently turned red-colored. Some ruptured and leaked yellow fluid. The patient did not feel itch or pain. He had never sought medication. There was no similar history in his family. On dermatological examination, there were yellow to skin-colored papules, nodules, and cysts, 0.3 to 2 cm in diameter, on the left side of the neck, chest, lateral aspect of the chest, back, and both arms, with erythematous-to-hyperpigmented macules and scars over the lesions (Figure 1). A dermoscopic examination showed a yellow structureless area with a diffuse erythematous border (Figure 2). Laboratory examination showed hypertriglyceridemia. The histopathological examination showed cysts with pilosebaceous-like lining with sebaceous glands adhered to the cyst's wall (Figure 3). Based on the clinical and histopathological findings, the patient was diagnosed with steatocystoma multiplex suppurativa. There was no specific treatment available. Thus, the patient was treated with topical corticosteroid and antibotic.

## DISCUSSION

SM usually appears in early adulthood, with a mean age of 26.[1] Early adulthood is associated with strong hormonal influences that stimulate pilosebaceous activity.[2] Although the familial form is the most common, our patient reported no similar history in his family, pointing to the sporadic form.[1]

The predilections of SM are neck, proximal extremities, trunk, and intertriginous area.[3,4] The diameter of lesions was 3 mm to 2 cm, per the literature, reporting 3 mm to 3 cm. The lesions are usually asymptomatic, as seen in our patient.[2] The lesions were subsequently ruptured and produced a yellow discharge. This showed the progression of SM into

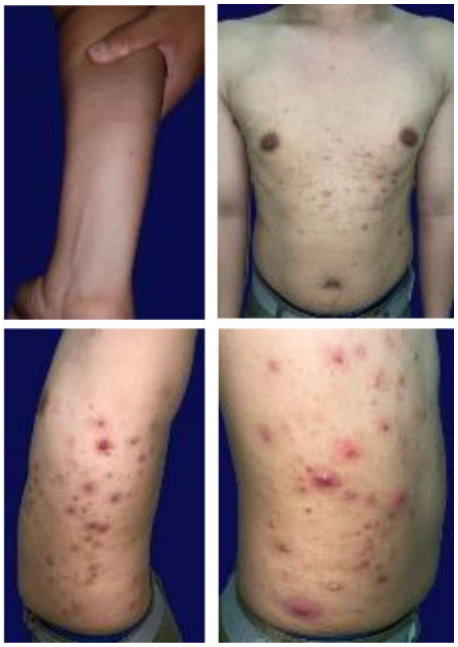

**Figure 1.** Papules, nodules, and cysts on the arm and chest.

SM suppurativa. Steatocystoma multiplex suppurativa can be secondarily infected and associated with poor compliance and low socioeconomic conditions.[1] The patient visited a hospital after four years because it became a cosmetic concern for the patient. However, the lumps had increased significantly. Multiple yellow to skin-colored papules, nodules, and cysts with erythematous-to-hyperpigmented macules and scars were observed on the neck, trunk, and extremities.

As SM suppurativa can have similar manifestations to pyoderma, nodulocystic acne, infected fibroadenoma, tubercular abscess, and acne conglobate, histopathological examination should be performed to establish the diagnosis.[1,2] We found pilosebaceous-like lining with sebaceous gland adhered to the cyst's wall which is pathognomonic for SM. On the other hand, SM suppurativa usually showed chronic or granulomatous inflammation.[2] We did not find this finding, which might be due to a biopsy of a noninflammatory lesion. A dermoscopic examination was also performed. The yellow structureless area represented the sebum inside the cyst, while the diffuse erythematous border represented inflammation.[4,5] The clinical findings of inflammatory lesions supported the diagnosis of SM suppurativa in this case.

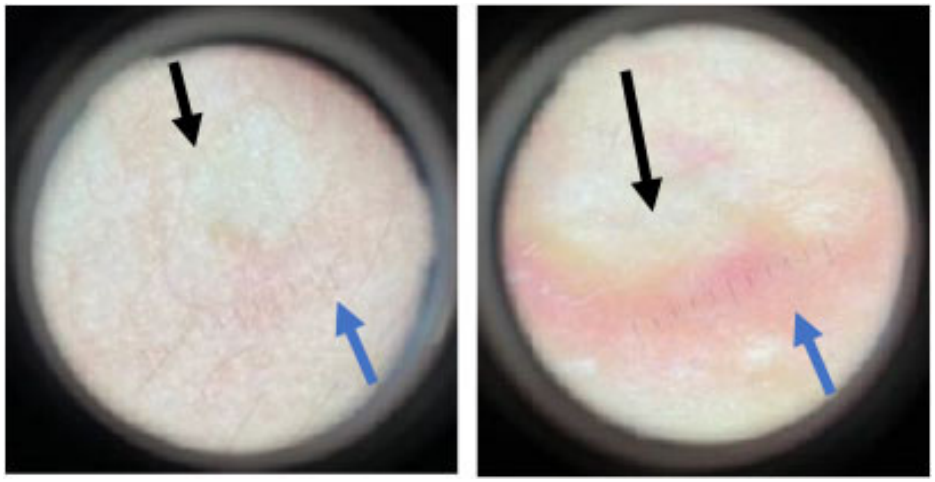

**Figure 2.** Dermoscopic examination showed a yellow structureless area (black arrow) with a diffuse erythematous border (blue arrow).

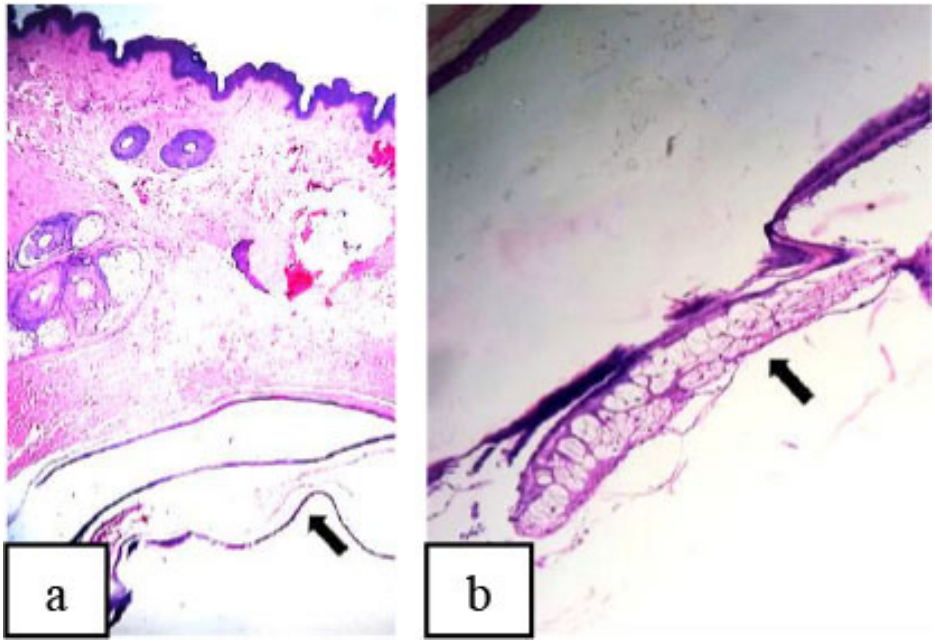


**Figure 3.** Cyst (Hematoxylin-eosin (HE), 100 times magnification) (A) with sebaceous gland adhered to the wall (black arrow) (HE, 400 times magnification).

## CONCLUSION

Steatocystoma multiplex suppurativa is a rare benign hamartomatous disorder in early adulthood with a manifestation of a longstanding asymptomatic papulonodular lesion. Dermoscopic findings showing a yellow structureless area and diffuse erythematous border and histopathological findings showing pilosebaceous-like lining with sebaceous gland adhered to the cyst's wall and chronic inflammation are characteristic of SM suppurativa.

## ETHICS IN PUBLICATION

The patient received informed consent and agreed to share the clinical image and medical history for educational and publication purposes.

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## AUTHORS' CONTRIBUTIONS

Author AR contributed substantially to the work's conception and data analysis and interpretation. Author IAK

contributed to the final approval of the version to be published and agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Author RR contributed to the final approval of the version to be published. Author NS contributed to drafting or revising the work critically for important intellectual content. Author DS contributed to drafting or revising the work critically for important intellectual content.

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ORIGINAL ARTICLE

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# *Cyclooxygenase-2* as potential intervention target of leprosy reactions: a systematic review

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## ABSTRACT

**Background:** Leprosy reaction is an acute inflammatory of leprosy complication that potentially cause disability. Prompt and appropriate treatment is needed to prevent this permanent neurological complication. As inflammation of this reaction is mediated by cyclooxygenase-2 (COX-2), therefore targeting this substance may potential to prevent disability. This systematic review aimed to define COX-2 as a potential target of intervention in leprosy reaction.
**Method:** Medline, Cochrane library, PubMed, and Google scholar databases were searched for articles published at any time. Observational study and clinical trial, comparative, prospective, retrospective, and descriptive study were extracted, analyzed, and discussed.
**Results:** We found 6 studies that met the inclusion and exclusion criteria, with 104 participants with leprosy reactions and 143 comparators included in this review. In leprosy reactions, COX-2 expression was found in the vessels and nerves of the dermis and subcutis. Macrophages are cell mostly abundantly expressing COX-2. The COX-2 expression was found higher in the leprosy reaction compare to the non-leprosy reaction. Genetically, genes PTGS2 and TNFAIP6 encode COX-2 production also tend to increase especially in type 1 reaction.
**Conclusions:** Preclinically and genetically, COX-2 is a potential target for intervention of leprosy reaction.

**Keywords:** COX-2, cyclooxygenase-2, leprosy, reaction.
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## INTRODUCTION

Leprosy is a high-morbidity neuro-dermatologic disease caused by Mycobacterium leprae.[1] A complex complication with difficulties in the clinical management of this disease is leprosy reactions.[1-3] These reactions are characterized by acute inflammatory episodes, which are precipitated by pharmacology and non-pharmacology. Therefore, it can occur before, during, or after complete treatment.[2] It's about 50% of leprosy patients develop this immune-mediated complication.[4]

Two types of leprosy reactions are known, categorized as type 1 reactions (T1R) or reversal and type 2 reactions (T2R) or erythema nodosum leprosum (ENL).[5] The T1R is a cell-mediated immunity reaction that leads to skin or nerve inflammation at the infection site. The lesion becomes erythema and edema, paraesthesia, pain, tenderness, or sudden deterioration of its function.[3,6] Meanwhile ENL is immune complex-mediated, which is characterized by diverse symptoms such as painful, erythematous subcutaneous nodules associated with fever, lymphadenitis, neuritis, arthritis, orchitis, or iridocyclitis. In some cases, ENL may develop into a chronic or recurrent course leading to neuropathy and disability.[3]

Both reactions potentially cause nerve damage and leads to disabilities. But, prompt and appropriate treatment significantly prevents this permanent neurological complication. As observed in TR1, 60-70% of cases recover after being treated within six months of onset.[5] Classically, a corticosteroid is the standard treatment for this condition. However, the optimal dose and duration of treatment remain unclear.[7,8] In addition, chronic course and recurrences occurred in 62,5% of patients.[9,10] So, a new modality with better performance is needed to manage this reaction.

Inflammation of this reaction is mediated by various substances including cyclooxygenase-2 (COX-2). Some studies revealed increase expression of COX-2 in lesions, micro-vessels, nerve bundles, and nerve fibers.[11,12] Therefore, this enzyme may be a new insight target of treatment. The objective of this study is to review COX-2 as potential in managing leprosy reactions.

## METHODS

Two researchers conducted the literature search independently, and any doubts and disagreements were solved by negotiation with the corresponding author. The data search on Medline, Cochrane library, PubMed, and Google scholar for articles published any time using keywords 'Cyclooxygenase-2' AND 'leprosy' AND 'reaction' OR 'reversal' OR 'erythema nodosum leprosum'. The criteria of the studies included in the review were as follows: an observational study and clinical trial, a comparative, prospective, retrospective, and descriptive study reported in English. Duplicate publications, reviews, and animal research were excluded (Figure 1).

## RESULTS

The online literature search resulted in 57 citations (Figure 1), 6 studies met the criteria and were included in this review. The total sample size was 104 subjects with leprosy reactions and 143 comparators. Each study includes between 6 to 57 subjects for the case and 6 to 90 subjects for comparators. All studies were comparative studies (Table 1).

The COX-2 expression in leprosy disease and leprosy reactions may be observed in several types of tissues. In leprosy reactions, especially T1R, COX-2 expression was found in the vessels and nerves of the dermis and subcutis. Vessel type mostly expressing COX-2 is microvessels which contributed to vascular dilation and tissue edema. Nerve bundles and isolated nerve fibers were also distinctly positive for COX-2.[11] Vascular endothelial growth factor (VEGF) inducing prostaglandin (PG) production through COX-2 stimulation and PG synthase expression was also upregulated.[13] The pro-inflammatory products leukotriene B4 (LTB4), prostaglandin D2 (PGD2) and lipoxin A4 (LXA4) catalyzed by COX-2 are also increased in T1R.[12] This causes vascular changes leading to tissue edema in T1R and potential nerve damage.[13]

Specific cell analysis, studies on lepromatous lesions, and tuberculoid leprosy found most positive COX-2 cells were macrophages and occasionally immunostained in fibroblasts and endothelium (seen only 3-4%).[14] The study of Malhotra et al., using skin biopsy specimens, found that COX-2 expression was higher in the leprosy reaction than without either reaction only in dermal macrophage cells while in vascular endothelium was not different. According to the type of reaction, T1R had higher

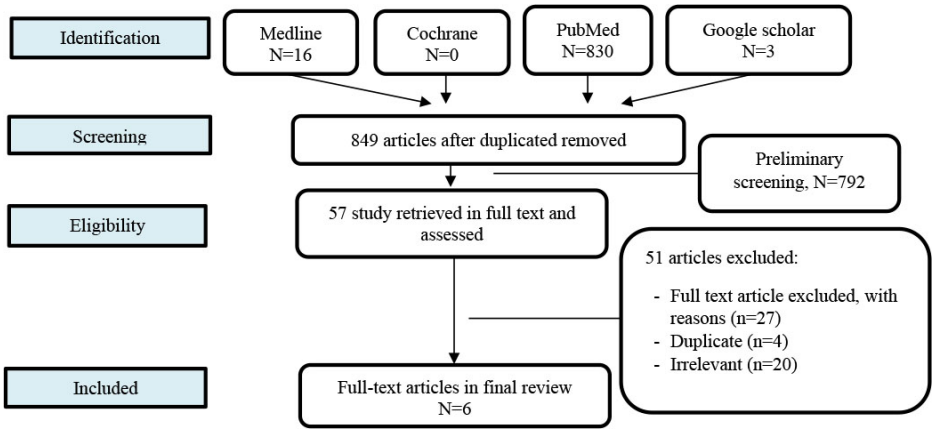


**Figure 1.** Flow chart study selection process.

**Table 1. Studies found analyzed in the review**

| Author, year | Study design | n | Finding |
|---|---|---|---|
| Pesce, Grattarol, Menini, & Fiallo, (2006) | Comparative study of skin biopsy findings between patients with RR (six BT and one BL) and BT patients (three BL and four LL) without reactionary leprosy. | 7 T1R patients and 7 comparators | Only T1R showed additional COX-2 expression in microvessels and nerve bundles and isolated nerve fibers. The same sites also express vascular endothelial growth factor (VEGF). Possibly a relation between VEGF and COX2 expression, with VEGF enhancing prostaglandin production through COX2 stimulation and prostaglandin synthase expression. |
| Malhotra, Suvirya, Malhotra, Kumar, Kumar, Husain (2021) | Case-control study evaluating expressions of *Cyclooxygenase 2* and *Vascular Endothelial Growth Factor* in skin biopsies. | 57 cases and 90 controls | Both COX-2 and Vascular Endothelial Growth Factor (VEGF) expression were significantly higher in type 1 reaction followed by type 2 reaction as compared to controls. |
| Silva, Webb, Andre, Marques, Carvalho, de Macedo, Pinheiro, Sarno, Pessolani, & Belisle, (2017) | Comparative study of a patient with and without T1R by metabolomics-based analyses via liquid chromatography-mass spectrometry | 7 patients T1R and 9 comparators | Proinflammatory leukotriene B4 (LTB4), prostaglandin D2 (PGD2), and lipoxin A4 (LXA4) in patients with T1R were significantly increased. Theoretically, PGD2 production is catalyzed by COX-2. |
| Orlova, Cobat, Thu Huong, et al, (2013) | A retrospective study comparing gene set signature between T1R and non T1R | 6 T1R patients and 6 non-T1R patients | *PTGS2*, encoding COX-2 preferentially upregulated genes in the T1R gene set signature. In addition, *TNFAIP6* highly expressed in the early onset T1R samples, encoded *TNF-stimulated gene 6 (TSG6).* |
| Kiszewsk, Becerril, Baquera, Ruiz-Maldonado, Hernández Pando, (2003) | A comparative study comparing COX-2 expression between LL and TL leprosy patients. | 20 LL leprosy and 20 TL leprosy | Dominant COX-2-positive cells identified were macrophages located in the papillary dermis, reticular dermis, and peri adnexal. The COX-2 was significantly higher in LL than in TL ($P < 0.001$) |
| Fiallo, Clapasso, Favre, Pesce (2002) | A comparative study comparing VEGF produced through COX-2 between T1R and non-T1R leprosy | 7 T1R and 14 comparators | Vascular endothelial growth factor (VEGF) induces prostaglandin (PG) production through COX-2 stimulation and PG synthase expression. This causes vascular changes leading to tissue edema in T1R and potential nerve damage. |

COX-2 macrophage levels than T2R, leprosy without reaction, and healthy control ($p<0.001$). Based on their treatment status, patients who were on medication had a higher risk of COX-2 expression than non-on-treatment patients (191.50 ± 56.76 vs 141.98 ± 78.85).[15]

Genetic studies have also shown that the PTGS2 gene (central gene in the Arachnoid Acid Pathway) encoding COX-2 is up-regulated in T1R patients. In addition, the TNFAIP6 gene encodes TNF-stimulated gene 6 (TSG6), whose function as an inducer of COX-2 expression in macrophages is also upregulated in early-onset T1R.[16]

## DISCUSSION

Management of leprosy reactions is still a challenge because it is a chronic disease and often recurs. If not managed properly, there is a risk of nerve damage which in turn causes disability. Various pathways have been identified to underlie this reaction, one of which is the pathway that requires COX-2 involvement. In this review, it was found that increased COX-2 expression was associated with leprosy reactions, especially T1R. So it has the potential to be a therapeutic target.

The cyclooxygenase enzyme is a substance that plays a role in catalyzing the conversion of cell membrane arachidonic acid to prostaglandins and leukotrienes. There are two types of COX that are often known, namely COX-1 and COX-2. The COX-1 enzyme is found in almost all tissues and is produced during inflammation. While COX-2 is induced only in response to inflammatory stimuli.[15,17] Therefore, targeting COX-2 selectively in the management of leprosy reaction may be safe without affecting constitutive body homeostasis.

Given that leprosy reactions can occur before, during, or after treatment,[2] identification of COX-2 is also important in patients who are not on treatment as a basis for prevention. The study found that lepromatous leprosy patients had a strong COX-2 expression, while healthy controls were weakly expressed.[18] Based on the Ridley-Jopling classification, BB, BL, and LL tend to show higher COX-2 expression. Thus, these types may provide a better advantage with the administration of COX-2 inhibitors.[14-15] COX-2 acts through an increase of prostaglandins.[14] This also explains that T1R is rare in type LL because in this type COX-2 macrophages are higher. COX-2 reduces T cell activity through intermediate mediators such as prostaglandin E-2 (PGE-2) and interleukin 10 (IL-10). These intermediate mediators down-regulate CD4 helper T cells and then decrease cell-mediated immunity.[14,19-20] Other pro-inflammatory mediators such as leukotriene B4 (LTB4), prostaglandin D2 (PGD2) and lipoxin A4 (LXA4) also contributed in this reaction. Those all of their production need COX-2.[12] Given that, the administration of COX-2 inhibitors has the potential to prevent or reduce leprosy reactions.

Prostaglandin E-2 produced through COX-2 is also associated with increased VEGF.[21] The VEGF-1 is a growth factor that centrally mediates vascular permeability and dilatation as seen in T1R.[17] Research on cancer reveals that COX-2 inhibitor concomitant with VEGF inhibitor improves the outcome compared to anti-VEGF alone.[22] But our review found that one study reveals VEGF is overexpressed in T1R[13] meanwhile another study found nondifference of VEGF in T1R compared to non-T1R.[15] Therefore, the role of COX-2 in T1R through this VEGF pathway is controversial.

Genetically, T1R patients carry different genes, especially in the arachidonic acid metabolism pathway. This pathway is important in the inflammatory process. This review found that the PTGS2 gene encodes COX-2 and the TNFAIP6 gene encodes TNF-stimulated gene 6 (TSG6), whose function in COX-2 induction is upregulated.[16] The results of this study are supported by the study of Mindrescu et al. which found that COX-2 expression was increased by the induction of TSG-6 protein in macrophage cells.[23] These findings provide preferential administration of COX-2 inhibitors in patients with this genetic predisposition to prevent leprosy reactions.

Based on this review, COX-2 has the potential to become a target of therapy, but all studies found in this review only focused on analyzing its pathways. Unfortunately, no interventional study using COX-2 inhibitors was found, either pre-clinic or clinical experimental. That means a further preclinical and clinical study using COX-2 inhibitor is needed to confirm and weigh the safety and cost-effectiveness of the drug as a prevention or treatment of leprosy reaction.

In addition, COX-2 has become a widely targeted treatment for several diseases such as osteoarthritis, rheumatoid arthritis, antipyretics, and analgesics. Several COX-2 inhibitors are known, including non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin. But in general, this drug acts as an anti-inflammatory and analgesic. However, it should be noted that this drug also has side effects such as gastrointestinal bleeding and ulceration, impaired renal function, and inhibition of platelet aggregation.[24-27]

## CONCLUSION

Pre-clinically, COX-2 is a potential target in managing leprosy reactions. The COX-2 expression increases in macrophage cells of nerves and vessels. The COX-2 expression is more significant in T1R compared to T2R. Genetically, gene-encoding COX-2 production tends to increase in T1R.

## CONFLICT OF INTEREST

Authors declare there is no conflict of interest regarding this publication.

## AUTHOR CONTRIBUTIONS

Author LMMR contributes to systematic review concept and proofread of the manuscript. Author LGMPS contributes in manuscript construction, literature research, and translation.

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