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Rare occurrence of shiitake dermatitis in Indonesia: A case report

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Abstract. *Adji A, Tan S, Warouw M, Liong GK, Walid FR, Christopher PM. 2024. Rare occurrence of shiitake dermatitis in Indonesia: A case report. Biodiversitas 25: 4790-4795*. The present study identified shiitake dermatitis as a unique dermatological manifestation of undercooked shiitake mushrooms. However, this discovery has not yet been reported in Indonesia. Shiitake mushrooms contain lentinan, a natural polysaccharide β-D-glucan polymer. Lentinan is considered a pathogen-associated molecular pattern that may trigger both innate and adaptive immunological responses by binding on pattern recognition receptors on immune cells. The binding of lentinan to its receptors activates many signaling pathways, eliciting an enhanced innate immune response, which may manifest as shiitake dermatitis. A 48-year-old Caucasian man of German nationality presented with a 3-day history of an extensive, minimally pruritic skin eruption of linear groups of erythematous papules in a flagellate pattern on both sides of the abdomen and mainly on his back. The patient denied any previous history of scratching, exposure to new/routine medications, supplements, topical products, animals, plants, recent travel, or outdoor activities. Additionally, constitutional symptoms were denied. Based on the clinical results and the exclusion of differential diagnoses, a diagnosis of shiitake dermatitis was established. The patient was prescribed symptomatic treatment consisting of oral and topical corticosteroids and an oral antihistamine, which yielded a significant improvement in response. This is the first case of shiitake dermatitis to be reported in Indonesia.

Keywords: Flagellate dermatitis, lentinan, *Lentinula edodes*, Shiitake mushroom, toxicoderma

INTRODUCTION

Various global cultures recognize and utilize mushrooms as highly nutritious medicinal food items. Nutrient-rich varieties harvested from ancient forests to meticulously cultivated species that grace modern markets, mushrooms are integral to diet and health. In Asian countries, they are extensively used for their medicinal and dietary properties, and numerous studies have explored their benefits (Ponnusamy et al. 2022). Among the myriad varieties, such as enoki, oyster, and maitake, the shiitake mushroom (*Lentinula edodes* (Berk.) Pegler) stands not only for its culinary versatility (e.g., as part of seasonings, sauces, drinks, and candy) but also for its medicinal properties, i.e., anticarcinogenic, antihypertensive, and serum cholesterol reduction properties (Boels et al. 2014; Lee and Dalley 2021; Ponnusamy et al. 2022). Over the past 20 years, its production has significantly increased from 2.68 to 10.8 million tons (Li et al. 2019). Its cultivation significantly contributes to the world's mushroom industry, making it the second most consumed mushroom globally (Shrestha et al. 2024). Dried extracts of *L. edodes* are composed of 58-60% carbohydrates, 20-23% proteins, 9-10% fiber, 4-5% ash, and 3-4% lipids. Additionally, *L. edodes* contains amino acids, polysaccharides (lentinan, β-D-glucans), minerals, vitamins, choline, adenine, and hexose (Ponnusamy et al. 2022).

Several studies have linked food components, e.g., polysaccharides, to improving intestinal damage recovery through their structural characteristics, molecular weight, and bioactivities among patients with inflammatory bowel disease (Wang et al. 2021; Manski et al. 2023). Administration of polysaccharides may alleviate oxidative stress by downregulating the production of oxygen free radicals (Wang et al. 2021). However, food components have also been associated with worsening dermatological conditions, e.g., gluten and dermatitis herpetiformis (Reunala et al. 2018). Additionally, the aforementioned beneficial effects may only be partially observed in uncooked or undercooked shiitake mushrooms, which can also cause a unique dermatological condition known as shiitake dermatitis.

Shiitake dermatitis, also known as flagellate dermatitis, was first described in Japan by Nakamura (1977). This condition was identified in 23 cases of linear, erythematous dermatosis resembling whip marks that occurred after ingesting poorly cooked shiitake mushrooms (Nakamura 1992). The presentation of this whip mark rash is uncommon with only an estimated 100 reported incidents since its first reported observation (Lee and Dalley 2021). Shiitake dermatitis is more common in East Asian countries, such as China and Japan, where it is mainly grown and consumed. However, owing to its widespread consumption, it may also be found worldwide. The pathophysiology of shiitake dermatitis is not entirely

understood; however, it is believed to be a toxic rather than an allergic reaction (de Mendonça et al. 2015). Presumably, this dermatological response is primarily attributed to lentinan, a thermolabile polysaccharide present in shiitake mushrooms, known for its immunomodulatory properties, which triggers an inflammatory response induced by scratching the skin (de Mendonça et al. 2015; Nguyen et al. 2017).

Cutaneous eruption of flagellate dermatitis is described as erythematous, hyperpigmented, linear papules with an onset of 2 h to 5 days (median: 24 h) following the ingestion of mushrooms (Boels et al. 2014; Gofman et al. 2024). The initial rash, which can last up to 3 weeks and includes petechiae, plaques, vesicles, and morbilliform or pustular lesions, is frequently preceded by pruritus. Although rare, systemic symptoms including diarrhea and fever may accompany this cutaneous manifestation. A clinical diagnosis of suspected shiitake dermatitis is made (Pakran et al. 2017). The flagellate pattern of a rash can be associated with chemotherapy (e.g., bleomycin, peplomycin, docetaxel, and bendamustine), rheumatological disorders (e.g., dermatomyositis or Adult-Onset Still's disease (AOSD)), toxins (*Cnidarian* stings, *Paederus*, and other insects), and other pruritic dermatoses and must be differentiated by the history of the disease course and constitutional symptoms (Bhushan et al. 2014).

This is the first case of shiitake dermatitis in a male patient reported in Indonesia. The case reported a 48-year-old man who presented with generalized erythematous linear skin lesions after ingesting shiitake mushrooms. Recognizing this condition is crucial owing to increasing consumption of shiitake mushrooms in occidental countries and to remember to take a detailed dietary history. Proper cooking is essential to denature lentinan and prevent its adverse effects. This report also presents theories from various sources to enhance the understanding of shiitake dermatitis.

MATERIALS AND METHODS

A consultation was initiated for an investigation at the Dermatology and Venereology Outpatient Department of Siloam Hospital in Lippo Village, Indonesia. In April 2024, a detailed history taking, systematically captured photographs, and visual observations was conducted to explore the issue. Analysis of the historical descriptions was performed and synthesized them into a coherent narrative to present the current findings and support the hypotheses.

Clinical sign

A 48-year-old previously healthy Caucasian man of German nationality consulted the Dermatology and Venereology Outpatient Department of Siloam Hospital, Lippo Village, Indonesia, presenting with a 3-day history of an extensive, minimally pruritic skin eruption. The patient claimed that he had not scratched the rash. He denied exposure to new/routine medications/supplements or topical products (e.g., cream or ointment), animals, or plants. Recent travel histories and outdoor activities were also denied. He complained of no other constitutional symptoms, such as fever, muscle weakness, or lymphadenopathy. However, the patient admitted that he and his wife had consumed a large amount of undercooked shiitake mushrooms 4 days before the symptoms appeared. His wife, of Japanese-Chinese descent, did not complain of any rash.

The patient demonstrated compos mentis status during the physical examination, with vital signs within normal limits. The dermatological examination revealed no abnormalities except for the patient's trunk, which displayed linear groups of erythematous papules in a flagellate pattern on both sides of the abdomen and primarily on the back (Figure 1). There was no mucosal involvement or dermatographic findings. The patient admitted that he had not scratched the reddish lines on the skin of his stomach or back. The patient also denied involuntary scratching at night or during sleep. Gottron papules, Gottron sign, and violaceous erythema of the eyelids, upper chest, back, elbows, knees, and lateral hips were negative.

Patient therapy

Considering the patient's typical history and physical examination findings, laboratory examinations and biopsies were not performed, and the patient was diagnosed with Shiitake Dermatitis. The rash ameliorated after 4 days and resolved entirely after 5 days of oral antihistamines (desloratadine 5 mg daily) and corticosteroids (methylprednisolone 24 mg daily for 3 days, tapering off to a daily dose of 12 mg on days 4-6). The patient had his rash resolved entirely on the 14th day of follow-up.

Figure 1. Linear erythematous papules arranged in a flagellate pattern on the left and right sides of the abdomen

RESULTS AND DISCUSSION

Shiitake mushrooms are one of the most widely produced edible mushrooms. Initially grown and consumed in East Asia, it has become increasingly popular in various medicines and culinary preparations in other regions (Ponnusamy et al. 2022). A systematic review of case reports and case series about shiitake dermatitis in 2017 included 50 patients (male-to-female ratio, 3.17:1) with a mean age of 44.58 years (Nguyen et al. 2017). The consumption of raw or undercooked mushrooms can lead to shiitake dermatitis, which was first described by Nakamura in 1977 (Nakamura 1992). In the case described here, the patient admitted to consuming a large amount of undercooked shiitake mushrooms, which led to the observed cutaneous phenomenon.

Shiitake dermatitis, also known as shiitake flagellate dermatitis or toxicoderma, is a rare skin condition that typically manifest 2 h to 5 days after ingesting raw or undercooked shiitake mushrooms. This phenomenon is characterized by pruritic linear or crisscrossed erythematous wheals, petechiae, grouped papules, and plaques (Netchiporouk et al. 2015; Nguyen et al. 2017; Liu et al. 2019). The eruption exhibits a pattern similar to that of whips or flagellation marks, and the pustular type has also been reported. The most commonly affected areas of the body are the trunk and extremities, with the occasional appearance of a rash in the head and neck region (Rodrigues and Pandya 2018; Liu et al. 2019). This condition is almost exclusively limited to the skin, and no manifestations in mucous membranes or other organs have been reported (Liu et al. 2019). A systematic review reported systemic signs and symptoms, such as fever, diarrhea, mouth ulcers, and dysphagia, in a small number of cases. However, it is unclear whether this is associated with shiitake dermatitis or other co-occurring conditions (Nguyen et al. 2017). To date, no life-threatening systemic reactions have been reported (Czarnecka et al. 2014). Other reported adverse reactions to shiitake mushrooms, include allergic contact dermatitis, phototoxicity, contact urticaria, allergic asthma, and isolated cases of chronic hypersensitivity pneumonitis induced by shiitake spores (Díaz-Corpas et al. 2011).

The Koebner phenomenon underlies the distinctive linear pattern of rashes (Nguyen et al. 2017; Liu et al. 2019; Maruthappu and Hader 2021). This was indicated by the appearance of a rash after trauma due to scratching. Scratching increases vascular permeability, and elevated serum lentinan levels can lead to greater lentinan deposition, and a more pronounced inflammatory response (Nguyen et al. 2017). According to the literature, 4 days after consuming shiitake mushrooms, grouped erythematous papular lesions appeared predominantly on the patient's truck, with no systemic symptoms. Although the literature correlates the rash to scratching, our patient experienced minimal pruritus and denied scratching the reddish streaks on his abdomen and back.

Therefore, the pathophysiology of shiitake dermatitis needs to be better understood. A dose-dependent toxic mechanism may explain why some patients develop this condition after consuming large amounts of mushrooms (Nguyen et al. 2017; Ponnusamy et al. 2022). The main component of shiitake mushrooms that reportedly elicits this reaction is lentinan. Lentinan, a natural polysaccharide β-D-glucan polymer, exists in conjugate form and forms structural fibrils with other matrix components, such as lipids and proteins within the cell wall (Fajri et al. 2013; Chakraborty et al. 2023). The inner cell wall comprises a branching structure covalently associated with a lentinan core, containing 3-4% interchain chitin (Chakraborty et al. 2023). Structural transition of lentinan from triple to single helical or coiled structures has also been reported at temperatures above 130ºC. This is further supported by the absence of a cutaneous response to shiitake mushrooms cooked at approximately 150ºC (de Mendonça et al. 2015; Nguyen et al. 2017; Lindequist 2024).

Glucan compounds such as lentinan are Pathogen-Associated Molecular Patterns (PAMPs) that target Pattern Recognition Receptors (PRRs). Lentinan acts like a wake-up call to the body's defense system making it more vigilant, effective, and active (Zhou et al. 2024). They can trigger both innate and adaptive immunological responses by binding to receptors on the surfaces of monocytes, monocytes/macrophages, neutrophils, natural killer cells, dendritic cells, as well as T and B cells, including dectin-1, Complement Receptor 3 (CR3), lactosylceramide, and other receptors (biological response modifiers). Dectin-1, a crucial fungal polysaccharide receptor, is a type-II transmembrane receptor belonging to the C-type lectin family receptor, binding specifically to (1→3) β-D-glucans with branched side chains. Dectin-1 has diverse biological functions, including activation of macrophages, dendritic cells, and neutrophils; phagocytosis; and cytokine production. Dectin-1 collaborates with Toll-like receptors in a signaling pathway to induce immunological responses through the augmented synthesis of cytokines, including Tumor Necrosis Factor (TNF)-α and interleukin (IL)-2. CR3 is another mushroom β-glucan receptor widely expressed by neutrophils, monocytes, natural killer cells, dendritic cells, and macrophages. CR3 is a dimer comprising two domain CD11b and CD18. CD11b is a lectin domain with a high affinity for β-glucan (Chakraborty et al. 2021).

The binding of lentinan to its receptors can trigger numerous signaling pathways, *e.g.*, the Syk, PI3K/protein kinase B (Akt), mitogen-activated protein kinase, and nuclear factor of activated T cells, resulting in enhanced innate immune responses (phagocytosis, reactive oxygen species production, IL-1, IL-2, IL-12, IL-6, IL-10, and TNF-α), which subsequently lead to vasodilatation, red blood cell extravasation, oxidative burst reaction, further cytokine release, reinforcement of phagocytosis, and an overall Th1-mediated inflammatory response (Roszcyk et al. 2022; Sudy and Urbina 2023; Lindequist 2024). However, because not everyone who consumes raw or poorly cooked shiitake mushrooms develop shiitake dermatitis, some researchers have postulated a delayed hypersensitivity process. In this process, individuals with specific genetic variations may be more prone to sensitization (Nguyen et al. 2017). In this case, the patient's

wife, who also consumed the mushrooms but denied any development of a cutaneous eruption, suggests a possible genetic predisposition.

Supporting diagnostic tests are usually not necessary. An oral provocation test was not performed for the patients' convenience. Laboratory tests indicate a mild elevation in leukocytes, C-reactive protein, and IgE levels (Eubanks et al. 2023; Sudy and Urbina 2023). Histopathological examination reveals nonspecific inflammatory findings, such as elongated epidermal rete ridges, spongiosis, lymphocytic and eosinophilic infiltrates, degenerative keratinocytes in the epidermis, edema in the stratum papillare/dermis, and perivascular lymphocytic infiltrates (Boels et al. 2014; Czarnecka et al. 2014; Browning et al. 2021; Sudy and Urbina 2023). Allergy tests such as patch or skin-prick tests show inconsistent results (Sudy and Urbina 2023). No supporting laboratory or biopsy tests were performed because of the clear causal relationship with the patient's history.

A new phenomenon concerning the etiology of shiitake dermatitis has emerged. The presence of this phenomenon is conditional upon the method of mushroom cultivation log-grown, where spores are directly inoculated onto wood logs, vs substrate-grown, where spores are disseminated onto sawdust. It was observed that there were minimal instances of shiitake dermatitis in China, where mushrooms are substrate-grown, whereas the majority of cases have occurred in Japan, where the mushrooms are log-grown. Moreover, there were nearly no documented incidents in Japan following the government's transition to substrate-grown mushrooms (Lee and Dalley 2021).

In the differential diagnosis of flagellate dermatitis, chemotherapy-induced causes should be considered, particularly bleomycin (a fungal extract from *Streptomyces verticillus*) and its derivatives. Bleomycin is a cytotoxic glycopeptide known for its adverse effects primarily on the skin and respiratory system, presumably owing to the absence of the inactivating enzyme hydrolase in these tissues. Chemotherapy-induced flagellate dermatitis typically presents as diffuse, pruritic, flagellate, erythematous plaques on the trunk and extremities (scratch dermatitis) from a few hours to 6 months after drug administration. However, this diagnosis was excluded based on the patient's medication history (Bhushan et al. 2014; Erkek et al. 2019).

Dermatomyositis is an idiopathic inflammatory myopathy characterized by linear lesions such as centripetal flagellate erythema, zebra-like striped erythema, and linear streaks. Traditionally, cutaneous findings have been categorized into pathognomonic (Gottron papules, Gottron sign, and heliotrope rash), characteristic (nail fold changes [i.e., periungual erythema and telangiectasias, dystrophic cuticles, and hemorrhagic nail fold infarcts], Shawl sign, V sign, Holster sign, and scalp involvement), compatible (poikiloderma and periorbital edema and facial swelling), less common (vesiculobullous, necrotic, or ulcerative lesions, cutaneous vasculitis, and calcinosis cutis), rare (mechanic's hands, flagellate erythema, Deck chair sign, follicular hyperkeratosis, panniculitis, mucinosis, erythroderma, and oral mucosal changes), and nonspecific (Raynaud phenomenon). Patients may present with one or a combination of dermatomyositis-related skin changes. Lesions are often pruritic or burning and are usually photosensitive (Bhushan et al. 2014; Lewis and Fiorentino 2019; DeWane et al. 2020). Additionally, dermatomyositis may also be accompanied by systemic manifestations in various organ systems, including the pulmonary system (interstitial lung disease, pulmonary hypertension or serositis), cardiac system (cardiovascular risk factors, subclinical diastolic dysfunction, myocarditis, myocardial fibrosis, arrhythmias, and congestive heart failure), gastrointestinal system (dysphagia, gastric and small intestinal motility issues, and rarely, vasculopathy leading to gastrointestinal infarction or perforation), and vascular system (cutaneous vasculopathy may lead to ulcerations) (Lewis and Fiorentino 2019; DeWane et al. 2020).

Similarly, Adult-Onset Still's Disease (AOSD), an autoinflammatory disorder, is occasionally associated with flagellate erythema. AOSD is characterized by arthralgia, dermatitis, organomegaly (hepatomegaly and/or splenomegaly), fever, and lymphadenopathy. Other concomitant symptoms of AOSD, such as pharyngitis, odynophagia, myalgia, pleuritis, or abdominal pain, may occur and vary from person to person. The typical cutaneous manifestation of AOSD is a nonpruritic macular or maculopapular evanescent salmon-colored confluent eruption on the proximal limbs and trunk. However, atypical AOSD with pruritic urticarial eruptions, flagellate morphology, and hyperpigmented plaques has been documented (Bhushan et al. 2014; Tomaras et al. 2021; Vora et al. 2023). In this investigation, dermatomyositis and AOSD were considered unlikely owing to the negative systemic symptoms of fever, arthralgia, muscle weakness, Gottron papules, or Gottron sign, and the absence of violaceous erythema of the eyelids, upper chest, back, elbows, knees, and lateral hips. A drug reaction was ruled out, as our patient had not started any new medication prior to the formation of lesions.

Other toxin-induced etiologies, such as *Cnidarian* stings and exposure to *Paederus* spp. and other insects, are also possible causes of flagellate dermatitis. Cnidarians (Portuguese man-of-war and jellyfish) contain nematocysts in their tentacles and release their contents through osmotic processes when injected into their prey. *Anthozoa* (anemones and corals), *Hydrozoa* (Portuguese man-of-war and hydroids), *Scyphozoa* (true jellyfish), and *Cubozoa* (box jellyfish) are the most common causes of human envenomation. Contact with jellyfish tentacles causes an intense, burning pain. Within minutes, a zigzag, whip-like pattern of raised red wheals, 2-3 mm wide, appears on the skin. The sting of *Chironex fleckeri* (Southcott, 1956) jellyfish is particularly distinctive, with lesions forming a frosted, cross-hatched, or ladder-like pattern. Microscopic diagnoses can also be made using blade scrapings or tape stripping from the sting site. While cutaneous symptoms account for approximately 80% of cases, some instances may also present with systemic symptoms, *e.g.*, tachycardia, vomiting, dyspnea, and malaise (Janniger et al. 2019; Curatolo et al. 2024). Another toxin-induced

etiological agent is pederin, a vesicant found in rove beetles of the genus *Paederus* within the family Staphylinidae. This toxin causes skin lesions when the beetles are crushed against human skin. Within 12-24 h, a blister appears at the location of the wheal, which could be a linear case of whiplash dermatitis (Bhushan et al. 2014). However, toxin-induced stings or lesions caused by insects were excluded because of the absence of contact or travel history.

Shiitake dermatitis is self-limiting. Without treatment, lesions resolve spontaneously within 1-4 weeks (Eubanks et al. 2023; Sudy and Urbina 2023). Symptomatic management consists of corticosteroids, usually of medium potency (class 4-5), such as 0.1% triamcinolone acetonide ointment twice daily, and oral antihistamines, depending on severity (Ma and Liu 2022). However, individual responses may vary, and close monitoring is necessary to assess treatment efficacy and manage any adverse events (Talour et al. 2011). Corticosteroids exert their biological effects by binding to glucocorticoid receptors. The glucocorticoid receptor complex then translocates into the cell nucleus in association with a transcription gene, which functions through inhibition (transrepression) or stimulation (transactivation). This transcription yields ribonucleic acid and protein synthesis to inhibit transcription factors controlling pro-inflammatory mediator synthesis, among which macrophages, eosinophils, lymphocytes, mast cells, and dendritic cells are affected. Corticosteroids inhibit phospholipase A2, thereby reducing the production of various inflammatory mediators. Additionally, gene inhibition plays a role in the reduction of cyclooxygenase 2 expression, nitric oxide synthesis, and pro-inflammatory cytokines (Mehta et al. 2016; Suardamana and Setiawan 2023).

In addition to corticosteroids, antihistamines aid in decreasing the production of pro-inflammatory cytokines (constituting a decrease in arachidonic acid metabolites, superoxide radical release, granule products, and cytokine release), the expression of cell-adhesion molecules, and chemotaxis of eosinophils and other immune cells. Antihistamines may also decrease the release of mediators from mast cells and basophils by inhibiting the calcium ion channels (Tharp 2019). The combination of corticosteroids and antihistamines is expected to counteract the immune response and activate signaling pathways towards lentinan-the proposed cause of shiitake dermatitis. Considering the extent of the lesion, the patient was administered oral antihistamines and corticosteroids. Desloratadine 5 mg daily and methylprednisolone 24 mg daily for 3 days were prescribed, and methylprednisolone was tapered off to a daily dose of 12 mg on days 4-6. On the 14th day of follow-up, the rash showed significant improvement, with a complete cessation of symptoms in response to the treatment.

In conclusion, shiitake dermatitis is a distinct clinical feature rarely reported in Indonesia despite its high consumption load. This could be attributed to a lack of clinical suspicion or distinct histopathological features. The differential diagnosis of flagellate dermatitis includes a variety of conditions, including drug reactions, adverse drug reactions, autoinflammatory diseases, and toxin-induced skin reactions. In this case, the diagnosis of shiitake dermatitis was based on the clinical features. Several differential diagnoses should be considered through thorough history taking and awareness before a diagnosis is established. Shiitake dermatitis is not a life-threatening condition, and therapy is straightforward; therefore, prompt identification is necessary to avoid redundant procedures and ease patients. Thoroughly cooking shiitake mushrooms prior to ingestion usually prevents recurrence.

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