Journal of Pakistan Association of Dermatologists. 2024;**34(4)**:1098-1103.

Case Report

Chemical-induced vitiligo in a rubber gloves factory worker

Oky Fauzul Zakina[1], Windy Keumala Budianti[2,3], Astri Mulyantini[1,3], Dewi S Soemarko[1]

[1] Occupational Medicine Division, Department of Community Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
[2] Allergy and Immunology Division, Department of Dermatology and Venereology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
[3] Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.

Abstract Chemical-induced vitiligo or chemical leukoderma, is an acquired skin depigmentation due to repeated exposure to specific chemical compounds in subjects with genetic susceptibility to vitiligo. Male patient with vitiligo who worked in a rubber gloves factory came to dermatology clinic. We analyze the relationship between his disease and his work. A 31-year-old man presented with a history of white plaque on the forehead, nose, right cheek bone and palpebra and behind both ears in the last 18 months. He reported no itchiness, redness, or pain. He works as a rubber gloves factory worker whose job is to carry and pour raw rubber gloves material such as potassium hydroxide and powdered premixed latex into the boiler for 3 years. The patient's diagnosis of vitiligo was chemical-induced or aroused from occupational exposure, possibly the premixed latex. Further investigation is needed to find the composition of premixed latex to establish chemical-induced vitiligo as the occupational diagnosis.

Key words
Chemical induced vitiligo; Chemical leukoderma; Rubber gloves; Latex.

Introduction

Vitiligo is an obtained pigmentary skin disorder due to the absence or altered function of melanocytes in epidermis.[1] Symmetrical white spots on the body become vitiligo most common symptom and more prominent in dark-skinned population. Characterized by well-demarcated chalk white or depigmented macules and patches, oval, round, or linear-shaped, with convex borders, range from few millimeters to centimeters and enlarge centrifugally in size, vitiligo is obvious and aesthetically bothers the patient.[2] This is the most common cause of depigmentation, affects all races equally, and could appear at any age approximately 0.1% to 2% worldwide with the peak incidence in the second and third decade.[3]

Chemical leukoderma or chemical-induced vitiligo represents exactly like vitiligo with the history of repeated exposure to specific chemical compounds in subjects with genetic susceptibility to vitiligo.[4] It was first reported by Oliver *et al.* in 1939 who studied workers using rubber gloves soaked in acid, namely monobenzyl ether of hydroquinone (MBEH) in a leather manufacturing company. Monobenzyl ether of hydroquinone is a phenolic compound used as offending agent in the rubber industry.[5] Further studies revealed paraphenylenediamine (PPD) and benzyl alcohol[6] used in hair colors and free paratertiary butylphenol (PTBP)[7] as adhesive in 'bindi', decorative color used on the

Manuscript: Received: October 01, 2023
Revision: October 14, 2023/ January 17, 2024
Accepted: March 25, 2024
Address for correspondence
Dr. Oky Fauzul Zakina
Faculty of Medicine, University of Indonesia,
Jakarta, Indonesia.
Ph: +6281394100964
Email: okyfzakina@gmail.com

forehead by Indian females can also cause leukoderma.

In 2006, European Union risk assessment reported 4-Tertiary Butyl Phenol (4-TBP), a bleaching agent and plasticizers mainly found in the production of epoxy resins and curing agents and in polycarbonate resins, can serve as an alternative substrate for tyrosinase and has inhibitory effect on melanin synthesis, causing depigmentation of the skin.[8] This case report aims to investigate whether the patient's work and job demand is associated with his disease.

Case report

A 31-year-old man complained about white spots on the face that emerged on March 2022. The white spots were first appeared on the nose, right forehead, and right cheek, measured around 2-3 centimeters. The sense of itching, pain, and numbness were all denied. Other systemic complaints such as fever, headache, cough, runny nose, nausea, vomiting, and diarrhea were also denied. A week later the patient felt the spots had increased, appearing on the right eyelid, left cheek, and behind the right and left ears. The patient consulted the complaint to the City Hospital and was diagnosed with non-segmented vitiligo. The patient was referred to the National Hospital for further therapy.

The patient does not have any history of skin depigmentation, nor his family. Patient said he is embarrassed with his condition and stopped hanging out with his friends because some of them thought the disease is contagious. Now the patient is undergoing the 52nd phototherapy, with no complaints after treatment and showed in present. The patient said there is no new spots. Currently, the patient routinely applies topical corticosteroid and sunscreen as recommended.

The patient lives alone in a rented house, it is located near the factory he works at with 0.5 meter the width of the road, poor sanitation. The house had concrete walls and cement floors, enough ventilation with no signs of dampness or fungi. He has no specific hobbies associated with the complaint. The patient did not drink alcohol. However, he smokes 10 cigarettes per day since he was 15.

The patient has been working in rubber gloves factory for 3 years. It is a local, middle-class factory with 80 employees. He goes to the factory by walking for 12 minutes. He works 6 days a week for 8 hours with 1-hour rest. His job demand is to carry and pour raw rubber gloves material into the mixer. He starts his day at 08.00 a.m. by taking a trolley to the warehouse to pick raw rubber gloves materials, namely potassium hydroxide (KOH) and premixed latex, both in powder formed. Each bag weighs 25 kilograms and he usually took 100-125 kilograms per trip. He pours KOH into a mixer filled with water. He then goes to another boiler to pour premixed latex to create jellies, ready to be molded into rubber gloves. He works alone in his workstation. He only wears ordinary clothes and shoes (not standard PPE) and cloth gloves. Patients did not use goggles, helmets, boots, safety vest and there is no morning briefing before doing work. The patient admitted there were work induction when he was first entered. The induction contained information for the patient to work as instructed, according to the order, but was not educated regarding the active ingredients, the dangers of excessive doses, or the importance of using a proper PPE. The patient had agreed and inform consent has been signed before the author raise this case.

Several potential hazards in patient's workplace were identified; there were UV rays, particulate dusts, and hot temperature (33-35^{o}C) as potential physical hazards. The potential chemical hazards are lead, carbon monoxide (CO) and nitric oxide (NO) from vehicle emission, and KOH, latex

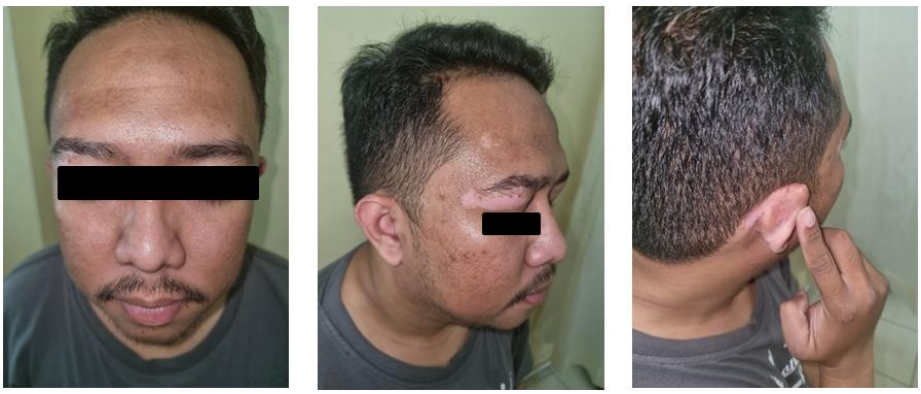

Figure 1 Physical examination findings. Depigmented, hypopigmented, erythematous, multiple, lenticular-nummular, and circumscriptive macules located at right ears and right upper eyelid.

premixed from the patient's workflow. Potential ergonomic hazards consisted of extended, flexed and deviation of, both hands and wrists with >4.5 kg of grip, fully extended elbows from pushing the trolley; raised arms and shrugged shoulders with weights >4.5kg carrying bags of KOH and premixed latex into the boiler; and flexed neck with flexed and twisted back from the overall workflow. The potential psychosocial hazards are monotonous work and the quantitative burden the patient felt since the factory forced him to load 300 kg of raw materials per day.

Current physical examination revealed patient has grade I hypertension (138/90 mmHg), and grade II obesity (IMT 32.3 kg/m^2). The skin examination reported depigmented, hypopigmented, erythematous, multiple, lenticular-nummular, and circumscriptive macules located at right ears and right upper eyelid **(Figure 1)**. These findings were consistent with the diagnosis of vitiligo. Additional diagnosis such as The Survey Diagnostic Stress (SDS) revealed he has moderate stress in quantitative and qualitative workload, while the New Brief Job Stress Questionnaire (NBJSQ) revealed moderate stress in job demand, and Patient's Health Questionnaire-9 (PHQ-9) reported mild depression.

Discussion

Occupational disease is defined as malady that either due to or exacerbated by exposure at work. Diagnosing occupational disease requires specific methods:

1. Establishing the clinical diagnosis.
2. Determining the occupational exposures.
3. Determining the relation between occupational exposures and the clinical diagnosis.
4. Determining dose-response exposure; whether it is intense enough to cause the clinical diagnosis.
5. Establishing individual factors suspected as the cause or a risk factor of the diagnosis.
6. Scouting for other factors outside the workplace.
7. Establishing occupational diagnosis; whether it is work-related, work-aggravated or non-occupational disease.

The patient had white spots that were first appeared on the nose, right forehead, and right cheek, measured around 2-3 centimeters, and no additional complaints. Specific characteristic of the lesions found are depigmented, hypopigmented, erythematous, multiple, lenticular-nummular, and circumscriptive macules. Vitiligo as clinical diagnosis is established considering the patient's medical history, physical, and histopathological examination. He was treated with phototherapy and the spots were slowly reduced,

strengthening vitiligo as the clinical diagnosis.

Patient's job demand, workflow, and workplace environment are taken via interview to identify occupational exposure. Thoroughly analyzing the environment and details of the patient's work, we found the patient encountered the following possible risks such as physical hazards (hot temperature, UV rays and particulate dusts), chemical hazards (lead, CO, NO, KOH, and premixed latex), ergonomic hazards (push and carry weights, pouring 25 kg weights, repetitive movements), and psychosocial hazards (physical exhaustion, monotonous work, and quantitative workload). We suspected the vitiligo could be chemical induced, mainly from the latex premixed. Further investigation must be conducted in the factory to reveal the composition of the latex premixed.

Gathered information undergo analyzing process. Using evidence-based medicine (EBM) is we look for possible connection between occupational exposure and clinical diagnosis. Studies has found clear evidence regarding specific chemicals can induce hypopigmentation of the skin. We identified possible melanin synthetase inhibitor which are 4-TBP or MBEH in latex premixed. There is a high chance of either 4-TBP or MBEH contained in premixed latex. Mono benzyl ether of hydroquinone is known for its usage in "acid cured" rubber gloves. While 4-Tertiary Butyl Phenol is used as plasticizers and bleaching agents. We know that rubber gloves are made from rubber or latex, with the main color of white, making it possible to add 4-TBP or MBEH in its premixed. It acts as competitive inhibitor at low 4-TBP concentrations for tyrosinase, the rate-limiting enzyme involved in melanogenesis. Reactive Oxygen Species (ROS) was formed due to conversion of 4-TBP into semiquinone, causing cytotoxic responses. Chemical leukoderma relies on the degree of melanocytes' pigmentation and the concentration of 4-TBP; the higher the concentration, the worse the clinical presentation. Exposure to 4-TBP also sensitize melanocyte to apoptosis, due to enhanced A2b receptor for adenosine.[9] However, this still cannot explain the relation, since vitiligo is an autoimmune disease with genetic, epigenetic, and environmental components that are characterized by the absence of melanocytes from the epidermis, could it be disrupted by inhibitors or malfunction from melanocytes syntheses. Cited from Mosher and Fitzpatrick, chemical leukoderma constitutes of an acquired vitiligo-like depigmentation induced by frequent, possibly continuous exposure to specific chemical compounds, regardless of their sensitizing potential. Subjects having genetic susceptibility specific to vitiligo are the ones affected, since exposure to these compounds become toxic for their melanocytes.[10]

Melanin synthesis pathway is disrupted by phenolic and cathecolic derivates as the competitive inhibitor for tyrosinase, keeping the melanocyte immature and cannot be used. Substance attached are oxidized by tyrosinase or tyrosinase-related protein, converting to more reactive o-quinones, and generating ROS, causing oxidative stress and melanocytes to apoptosis.[9,11] This process is accelerated by the excess of H_2O_2.[12] Kroll *et al.*[9] first documented that phenolic compounds could cause melanocyte death indirectly by stimulating inflammatory cascade in dendritic cells. This was observed when phenolic compounds simultaneously cultured with melanocytes. Cellular stress response becomes greater affixing 4-TBP to melanocytes, causing tumor necrosis factor-related apoptosis-inducing ligands (TRAIL) death receptor expression by the secretion of the heat shock protein namely proinflammatory protein-activated dendritic cells (HSP70), killing the melanocytes. Systemic autoimmunity was observed spread by activated, sensitized dendritic cell (DC) effector functions via lymph node **(Figure 2)**.

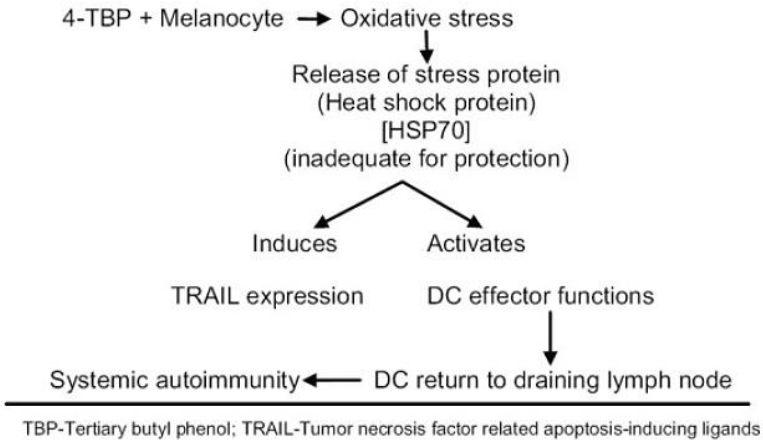

Figure 2 Patho-mechanism of chemical vitiligo.[9]

Psychological stress must be considered as autoimmune disease cannot be entirely ascribed to hereditary and genetic propositions. Epidemiological studies have indicated that stress may both herald the autoimmune diseases advancement and increase the symptoms. Based on patient's stress questionnaire, we found no suspicion toward stress as contributing factors to his disease.

The dose-response relationship was seek through the duration of exposure gathered from patient's interview along with the patency of derivate according to EBM. The patient had handled premixed latex for 3 years for 8 hours a day, 6 days a week. He needed to push, carry, and pour 150 kg or 6 bags of latex premixed per day. The patient did not use proper PPE so, we can say he is directly exposed to the compounds. It can be concluded that the occupational exposure's intensity was enough to cause or exacerbate the clinical diagnosis of vitiligo and making it chemical-induced vitiligo.

Determining individual factors for vitiligo is not easy since this is an autoimmune disease. Susceptibility to vitiligo has been found to be correlated with more than 30 genes, such as NLRP1, IFIH1, CASP7, TICAM1 that control innate immunity, and CTLA4, CD80, HLA, GZMB, FOXP3 as gene modulators of adaptive immunity. Epidemiological studies strengthened the genetic susceptibility as 28.3% cases are exist of chemical leukoderma with preexisting familial vitiligo, whereas it was seen only in 4.8% cases without one.[4] Therefore, gene investigation must be taken as additional examination since skin biopsy cannot differentiate the diagnosis of vitiligo and chemical leukoderma. For the patient himself, there is no patient's familial history of vitiligo.

Personal factors identified as risk factors for vitiligo are stress, bad sunburn and frequently exposed to sun, exposure to strong chemicals. Skin trauma, whether it is deep cut of act of frequent rubbing, scratching, or putting pressure are more likely the sites of vitiligo to occur. We found no other factors outside chemical exposure from the workplace that can contribute to patient's diagnosis.

After analyzing from the available evidence, history taking, and rigorous examination of the patient, it is suspected that the patient's diagnosis of vitiligo was chemical induced, possibly from the premixed latex.

Conclusion

Comprehensive and thorough examination is essential to diagnose occupational disease.

Analyzing the clinical findings, various potential workplace hazards, personal factors, and other external factors must be taken into account to understand how they intertwined to each other, creating evidence backed-up occupational diagnosis. In this case, there is a possibility that vitiligo in the patient is chemical-induced. The patient's job at the rubber gloves factory makes him vulnerable by the exposure to premixed latex which contains either 4-TBP or MBEH. This could be the main contributing factor to cause vitiligo. Further investigation is needed to find the composition of premixed latex to understand the exact dose-response relationship and establish chemical-induced vitiligo as the occupational diagnosis.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship None.

Conflict of interest Authors declared no conflict of interest.

Author's contribution

OFZ, WKB: Identification, diagnosis and management of the case, manuscript writing and critical review, final approval of the version to be published.

AM, DSS: Management of the case, critical review, final approval of the version to be published.

References

1. Mazzei Weiss ME. Vitiligo: to biopsy or not to biopsy? *Cutis*. 2020;**105(4)**:189-90.
2. Eleftheriadou V. Reliability and validity of the Vitiligo Signs of Activity Score. *Br J Dermatol*. 2020;**183(5)**:801-2.
3. Bergqvist C, Ezzedine K. Vitiligo: A Review. *Dermatology*. 2020;**236(6)**:571-92.
4. Ghosh S, Mukhopadhyay S. Chemical leucoderma: a clinico-aetiological study of 864 cases in the perspective of a developing country. *Br J Dermatol*. 2009;**160(1)**:40-7.
5. Oliver EA, Schwartz L, Warren LH. Occupational leukoderma. *J Am Med Assoc*. 1939;**113(10)**:927.
6. Taylor JS, Maibach HI, Fisher AA, Bergfeld WF. Contact leukoderma associated with the use of hair colors. *Cutis*. 1993;**52(5)**:273-80.
7. Pandy RK, Kumar AS. Contact Leukoderma Due to 'Bindi' and Footwear. *Dermatology*. 1985;**170(5)**:260-2.
8. Meier S, Andersen TC, Lind-Larsen K, Svardal A, Holmsen H. Effects of alkylphenols on glycerophospholipids and cholesterol in liver and brain from female Atlantic cod (Gadus morhua). *Comp Biochem Physiol C Toxicol Pharmacol*. 2007;**145(3)**:420-30.
9. Kroll TM, Bommiasamy H, Boissy RE, Hernandez C, Nickoloff BJ, Mestril R, *et al*. 4-Tertiary Butyl Phenol Exposure Sensitizes Human Melanocytes to Dendritic Cell-Mediated Killing: Relevance to Vitiligo. *J Invest Dermatol*. 2005;**124(4)**:798-806.
10. Mosher D, Fitizpatrick T. Chemical leukoderma. In: Sober A, Fitzpatrick T, editors. Yearbook of Dermatology. Bonston: Mosby; 1994. p. 3-13.
11. Miyamoto L, Taylor J. Chemical leukoderma. In: Hann S, Nordlund J, editors. A Comprehensive Monograph on Basic and Clinical Science. London: Blackwell Science; 2000. p. 269-80.
12. Glassman SJ. Vitiligo, reactive oxygen species and T-cells. *Clin Sci (Lond)*. 2011;**120(3)**:99-120.