

CHALLENGE IN DIAGNOSIS OF ECZEMA HERPETICUM IN RURAL AREA IN EAST NUSA TENGGARA: A CASE REPORT**Nur Aida Oktasari, Adisty Ridha Damasuri, Indah Sari, Anita Tanuwijaya**

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Abstract

Eczema herpeticum is an infection caused mostly by the herpes simplex virus which arises from an impaired skin barrier that may have a life-threatening bacterial complication. This case report unfolds the clinical reasoning behind diagnosing and treating eczema herpeticum in a rural area in East Nusa Tenggara, Indonesia, that has limited healthcare facilities in favor of recovery without any sequelae. We describe a 5-month-old girl who has dry skin with acute extensive itchy vesicles and papulopustular with crusts starting from the face down to the neck, back, and extremities that worsened even after receiving antibiotics yet showed improvement after receiving acyclovir.

Keywords: *Eczema herpeticum, rural area, East Nusa Tenggara, case report***INTRODUCTION**

Eczema herpeticum, also known as Kaposi varicelliform eruption or pustulosis acuta varioliformis, is a sudden extensive vesiculopustular eruption usually caused by Herpes Simplex Virus (HSV) which arises from pre-existing skin disease, such as atopic dermatitis (Liaw, Huang, Hsueh, & Chiang, 2012; Traidl, Roesner, Zeitvogel, & Werfel, 2021). It has been stated that around 3% of atopic dermatitis patients are predicted to develop eczema herpeticum during their lifetime and 90% of them are caused by HSV-1 (Beck et al., 2009; Damour, Garcia, Seneschal, L  v  que, & Bodet, 2020; Leung, 2013; Sanga, Darius, Rangga, & Naga, 2018). The diagnosis and treatment of eczema herpeticum should be concluded rapidly as untreated eczema herpeticum may lead to a life-threatening infection (Liaw et al., 2012; Satria, Chen, Soebono, Radiono, & Danarti, 2019; Sharif & McMullen, 2018).

Sikka Regency is one of the rural areas in East Nusa Tenggara Province, Indonesia, which still has many health welfare obstacles such as limited healthcare facilities and the existence of slums area which may contribute to the higher morbidity rate in rural areas compared to the urban area from the year 2020 to 2022 (Statistik, 2019) This report presents a challenging case of diagnosing eczema herpeticum in a rural area in East Nusa Tenggara.

Case Report

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Challenge in Diagnosis of Eczema Herpeticum in Rural Area in East Nusa Tenggara: a Case Report

A 5-month-old girl was brought to Primary Health Care Service (PHCS) Kewapante in Sikka Regency, East Nusa Tenggara, with vesicles on the face, neck, and left extremities for 3 days. The vesicles started as a single clear blister on the face and spread down to the neck and left extremities, but there wasn't any vesicle found on the body. This was the first time for the baby to experience vesicles as she was a healthy full-term newborn, despite the 2000-gram birth weight. The vesicles were itchy as the baby scratched them until the vesicles turned into pustules that were broken into round erythematous collarette crusts. This patient also had intermittent nocturnal dry cough along with the vesicle eruption. There was no complaint of runny nose, fever, gastrointestinal tract, or micturition problems nevertheless. At that time, this patient only breastfed and never had other kinds of foods or drinks, including fortification milk. On the other hand, this patient, who lived in a water shortage area, bathed twice a day with baby soap and water from a rainwater tank which rarely cleaned. Moreover, she always had dry skin, which was similar to her friends who had the same complaint but never sought any medical advice. However, a history of atopy in the patient or her family was denied. Thus far, her mother gave initial treatment such as baby oil and powder to the lesions, yet no improvement was seen.

On this examination, this patient didn't have a fever as it was verified with a temperature of 37.0° C. However, there were multiple discrete round herpetiform vesicles some of which were in the pustules and collarette crusts form on the face, a collarette crust on the left palm, and a vesicle on the left sole (**Figure 1-3**). Additionally, there were no other physical abnormalities found on the examination. Hence, there were no laboratory studies ordered at that moment. This patient was examined by a general practitioner who consulted a dermatologist who was available only at a hospital in Maumere, the capital of East Nusa Tenggara, via telemedicine. The dermatologist diagnosed the patient with bullous impetigo which had a good prognosis, accompanied by varicella and atopic dermatitis as the differential diagnosis. Therefore, the dermatologist prescribed an amoxicillin drop of 0.7 ml 3 times/day for a week, a chloramphenicol ointment 3 times/day for a week, and pulverized drugs consisting of 0.6 mg of CTM, 3 mg of ambroxol, 5 mg of vitamin C, and 1/10 tablet of vitamin B complex, which taken 3 times/day for a week. The patient was also advised to maintain hygiene, avoid excessive sweating, keep the nails short, not use any unprescribed oil or powder, avoid scratching, and schedule an appointment for the following week.

On the second appointment at PHCS Kewapante, which was delayed a week after the initial schedule, the patient's complaint was the reappearing of vesicles together with pustules and collarette crusts after taking the drugs even though previously showed a temporary mild improvement. The vesicles spread to the back and right arm in addition to more severe vesicles on the face, which were accompanied by erythematous patches. The application of baby oil and powder to the lesions was continued even though it was not recommended. The nocturnal dry cough remained, and further elaboration showed that the patient was living with heavy smokers. There were no other complaints.

On this checkup, there were more vesicles and papulopustular with many yellowish crusts on erythematous bases on the face that extended to the scalp, multiple papulovesicular alongside erythematous patches on the back, and multiple discrete vesicles with halo erythematous on the

right arm (**Figure 4-6**). The worsening condition of the patient made the consideration to figure out the predisposing factor in this case. The fact that the patient had dry skin which was prone to infection and her condition might be influenced by her environment, had led to the suspicion of skin barrier impairment, such as atopic dermatitis. These facts were strengthened by the location of the primary lesion on the face and the pruritus sensation in the patient. Furthermore, the fact that the patient was a passive smoker might be suspected as the trigger of allergy sensitization despite the history of atopy in the patient and her family was previously denied. Unfortunately, there were no laboratory studies ordered in this case since the inability to perform the Tzanck test and the unavailable of viral and allergy detectors at the PHCS. Consequently, the dermatologist, via telemedicine, changed the working diagnosis to eczema herpeticum with suspected atopic dermatitis involvement based on the clinical judgment, which still had a good prognosis, accompanied by bullous impetigo as the differential diagnosis. This condition was treated with 120 mg of oral acyclovir 4 times/day for five days as the antiviral, a betamethasone ointment twice a day for dry lesions, an open compress with NaCl 0.9% twice a day for crusted skin, and continuing pulverized drugs. Additionally, the patient was advised to schedule an appointment for the next 5 days.

On the third appointment at PHCS Kewapante, the patient showed improvement and there was no reappearing of papulovesicular lesions despite the multiple crusts on erythematous bases on the face and back of the body (**Figure 7-8**). There were no other complaints or physical abnormalities. Thus, the dermatologist, via telemedicine, prescribed the same medicines as the second appointment with an amoxicillin drop of 0.7 ml 3 times/day for a week and advised to schedule an appointment for the next week. Regardless of how the patient didn't fulfill the next appointment, she had fully recovered without any sequelae when we met her a year later (**Figure 9**).



Figure 1. Multiple discrete round herpetiform vesicles some of which were in the pustules and collarette crusts form on the face



Figure 2. A collarette crust on the left palm

Figure 3. A vesicle on the left sole



Figure 4. Vesicles and papulopustular with many yellowish crusts on erythematous bases on the face that extended to the scalp



Figure 5. Multiple papulovesicular alongside erythematous patches on the back



Figure 6. Multiple crusting on erythematous bases on the face



Figure 7. Multiple crusting on erythematous bases on the back



Figure 8. Fully recovered without any sequelae

Discussion

Eczema herpeticum (EH) is an infection caused by herpes simplex virus (HSV) mostly HSV-1 that causes sores around the face and inside the mouth, which also appear on other body parts. The EH affects people especially infants under 5 years and young children who have severe inflammatory skin disease - in this case, it is focused on atopic dermatitis which has barrier dysfunction. EH presents small, dome-shaped, multiple papule vesicles on an erythematous base that leave punched-out ulcers if they rupture. These vesicles lead to erosions after 2-7 days. The manifestations are also followed by systemic symptoms such as fever, malaise, and lymphadenopathies. Predilections of EH are focused on the face, neck, chest, and extremities (1).

Two main underlying conditions may provoke HSV infection into EH such as skin barrier impairment and immune system disorders. Conditions that could affect the skin barrier in infants such as Darier's disease, epidermolysis bullosa simplex, pemphigus foliaceus, Hailey-Hailey disease, pityriasis rubra pilaris, staphylococcal scalded skin syndrome, ichthyosis, atopic dermatitis, irritant contact dermatitis, burns, or trauma (Traidl et al., 2021). In our case, the patient had a first episode of sudden onset of itchy vesicles and papulopustular with crusts starting from the face down to the neck, back, and extremities at the age of 5 months old without any burn or trauma involved. Thus, atopic dermatitis and irritant contact dermatitis are left for possibilities.

Atopic dermatitis (AD) is one of the most common skin inflammatory diseases that is related to the incidence of EH. AD is characterized by barrier dysfunction such as Filaggrin mutation which plays a major role in developing AD as it maintains skin hydration, skin pH, protease activity, desquamation, and lipid synthesis while also keeping the barrier permeability for defense against pathogens could facilitate the entry of microorganisms including HSV through the first keratinized layers of the skin and binding to its receptors at the target cells. Another defect of skin proteins such as claudin, nectin, and the cadherin-catenin complex could loosen the skin's adhesive ability and provide an entrance for viral or bacterial infection. Whenever there's an entrance of a pathogen to the skin, the immune system in AD through IL-1 β , IL-25, IL-33, macrophage-derived chemokine (MDC), thymus and activation-regulated chemokine (TARC), and thymic stromal lymphopoietin (TLSP) could activate dendritic cells or directly activate macrophages to trigger T helper (Th) 2, IL-4, IL-5, IL-13, IL-31, and IL-33 driven inflammation

which could also suppress the filaggrin and decrease the production of interferon- γ (IFN- γ), which has the function to activating dendritic cells, macrophages, Th cells, and natural killer cells that play role in antiviral defenses, impaired keratinocytes differentiation and provoke itching. Additionally, there are altered antimicrobial peptides production in AD such as cathelicidin LL-37, human β -defensins (hBD), psoriasin (S100A7), and ribonuclease 7 (RNase 7), which can directly kill bacteria or virus (Damour et al., 2020; Kim, Kim, & Leung, 2019; Traidl et al., 2021). Therefore, the existence of AD could indeed exacerbate HSV infection into EH.

The establishment of AD diagnosis is through the fulfillment of Hanifin-Rajka diagnosis criteria. This criteria includes at least 3 of the major criteria such as pruritus, typical morphology and distribution, chronic or chronically relapsing dermatitis, and personal or family history of atopy. Along with at least 3 of the minor criteria such as xerosis, ichthyosis/ palmar hyperlinearity/ keratosis pilaris, immediate (type 1) skin-test reactivity, raised serum IgE, early age of onset, a tendency towards cutaneous infection, a tendency toward non-specific hand or foot dermatitis, nipple eczema, cheilitis, recurrent conjunctivitis, Dennie-Morgan infraorbital fold, keratoconus, anterior subscapular cataracts, orbital darkening, facial pallor or erythema, pityriasis alba, anterior neck folds, itch when sweating, intolerance to wood and lipid solvent, perifollicular accentuation, food intolerance, course influenced by environmental or emotional factors, and white dermographism as delayed blanch (Joji, 2002). Some minor criteria matched our case such as xerosis skin as the patient had dry skin, a tendency toward cutaneous infection as the patient showed clustered vesiculopustular with yellow crusts, and a course influenced by environmental factors as the patient used a rarely cleaned rainwater tank for bathing. However, there are some doubts regarding the major criteria, as in our case only two things matched the major criteria such as pruritus as the patient had itchy skin and typical morphology and distribution as the patient's primary lesion is on the face, but this was the first skin disorder for the patient and she and her family had no known of atopy history. However, further history-taking revealed that the patient was living among heavy smokers which could trigger allergy sensitization in the patient as a passive smoker is strongly associated with food allergy sensitization, susceptibility to developing eczema, allergic rhinitis, and asthma (Wang et al., 2023). Therefore, profound history-taking and follow-up sessions should be done to make sure of any atopy condition. After all, if there's any suspicion toward AD diagnosis in a patient, the definitive diagnosis of AD should be established as if there's an infection in an AD patient that has clusters of vesicles and/or punched-out erosions or 1-3 mm depressed ulcers and keep worsening even after being treated with antibiotics and topical steroids, rapid diagnosis and prompt management of EH should be put into consideration (Sun et al., 2019).

Some infected individuals who have AD could be grown up with a history of eczema herpeticum (ADEH+) and without EH (ADEH-). ADEH can happen as a primary infection or reactivation from latent viruses. Sometimes we must explore more specifically the patient whether they have a herpes infection history because 20% of EH patients reported recurrent herpes infections in their medical history. In addition, other factors such as atopy history, food allergens

history, and house dust are noted in ADEH+ patients (2). Besides that – the literature says the other factor that is susceptible to appearing EH is Th2 predominance (Beck et al., 2009).

ADEH+ may be susceptible to multiple factors including EH is often diagnosed based on patient history (AD) and the characteristic skin lesions. It takes viral swabs from the base of blisters which are analyzed through polymerase chain reaction (PCR) as the gold standard to differentiate EH from other similar presentations such as impetigo or hand-mouth food disease (HFMD). Misdiagnosis can lead to severe complications like bacteremia or even death (Vera-Kellet & Hasbún, 2020) (Nix et al., 2011).

However, eczema herpeticum can be clinically diagnosed when the morphology of the skin pattern is present, with Tzank smear, direct fluorescent antibody (DFA) testing, and viral cultures can confirm HSV infection. Neither help nor clinical presentation might be atypical, a skin biopsy is indicated and the results of laboratory tests are lymphopenia and an increased erythrocyte sedimentation rate.

The most common organisms that cause complications of EH in bacterial superinfection are *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, and *molluscum contagiosum virus* (Traidl et al., 2021) (Luca, Lara-Corrales, & Pope, 2012). When the cutaneous HSV infection disseminates systemic infection can occur with fever, malaise, and multiple organ involvement, which can lead to septic shock, meningitis, and encephalitis (Luca et al., 2012). HFMD patients presenting papulovesicular, are more febrile and suffer oral stomatitis, it is almost the same characterized as EH, but in terms of causes it is different, one side is because of Coxsackie Virus (A6), and the other side is HSV (Chen et al., 2023). Other factors are some patients who suffer HFMD are more often known as 1-year-old, and it is truly differentiated from EH (Chatproedprai et al., 2015). Moreover, complete blood count (CBC) and the Tzanck test have a role that can rapidly confirm an HSV infection and also can confirm the diagnosis of EH and rule out some other diseases. In this case, the patient did not have blood drawn because of not needed yet in the Primary Health Care Service (PHCS). CBC can distinguish the disease in general whether bacterial or viral etiology and the study said that the patients who suffer EH have lymphopenia

Another possibility for the underlying skin disease in our case besides AD, is irritant contact dermatitis (ICD). The patient was given baby oil and powder on the active skin lesion by her mother despite being advised not to. Irritants could damage epidermal cells, the keratinocytes, which allow increased permeability to irritants and further inflammation. However, in our case, both AD and ICD conditions could play a role in the development of EH as individuals with AD are thought to have a higher risk for the development of ICD (Patel & Nixon, 2022) (Gittler, Krueger, & Guttman-Yassky, 2013).

Treatment for EH should begin with oral antiviral such as acyclovir or valacyclovir. These medications could minimize the risk of complications and prevent progression to severe conditions. In this case – the recommended dosage of oral acyclovir is 30-60 mg/kg/d divided into three doses per day in children and for the most severe cases - we should consider some conditions that are related to an individual's immune system like HIV, prolonged diabetes, undernutrition,

and using corticosteroids or other immunosuppressant medications), these conditions should be addressed with hospitalized and intravenous administration of antiviral therapy (Liaw et al., 2012) (Luca et al., 2012). Another concern in our case is the use of topical corticosteroids for EH as they were previously thought to disseminate HSV and worsen the disease. However, a prior study showed that the use of topical corticosteroids didn't affect the hospital length of stay, unlike systemic corticosteroids which increase the hospital length of stay by 18% (Aronson, Shah, Mohamad, & Yan, 2013).

The onset of eczema herpeticum and viral infection during atopic dermatitis may be significantly impacted by dysbiosis of the skin microbiome. Dysbiosis of the skin microbiome has been linked to atopic dermatitis and corresponds with the severity of the condition (Bjerre, Bandier, Skov, Engstrand, & Johansen, 2017). The diverse range of bacteria that make up the skin microbiota varies depending on the environment, and individual, and ecological characteristics of each body site (Grice et al., 2009). More than 60% of bacteria linked with the skin belong to three genera: *Corynebacterium* (Actinobacteria), *Propionibacterium* (Actinobacteria), and *Staphylococcus* (Firmicutes) (Scharschmidt & Fischbach, 2013). Due to their role in regulating skin immunity, AMP synthesis, neutrophil recruitment, and defense against pathogens, commensal bacteria including *Staphylococcus epidermidis* and *Propionibacterium spp.* are crucial for normal skin (Yamazaki, Nakamura, & Núñez, 2017). The genus *Staphylococcus* accounted for around 90% of bacteria in the antecubital and popliteal creases of patients with atopic dermatitis during untreated flares, compared to only 16% of bacteria in healthy patients, 31% in treated flares, and 20% post flare (Kong et al., 2012).

As evidence of the critical role commensal microbiota plays in viral infections, it has been demonstrated that a dysbiosis of microbiota caused a more severe HSV-2 infection (Oh et al., 2016). Patients with atopic dermatitis have an imbalanced lesional skin microbiota due to significant colonization of *S. aureus*, which produces toxins such as α -toxin. Together with each other, these changes promote the invasion, reactivation, and replication of HSV leading to the development of eczema herpeticum.

Furthermore, because *S. aureus* produces a large number of virulence factors and may be linked to an increased risk of viral infections, it is the cause of severe skin infections in people with atopic dermatitis (Oh et al., 2016). Phenol-soluble modulins (PSMs), another virulence factor generated by *S. aureus*, with the capacity to perforate cell membranes (Yamazaki et al., 2017). Similarly, PSM α can trigger the production of inflammatory cytokines and induce the death of keratinocytes (Syed, Reed, Clark, Boles, & Kahlenberg, 2015). Given their involvement in α -toxin-induced eczema herpeticum and atopic dermatitis, PSMs may contribute to viral infection in eczema herpeticum (Damour et al., 2020)

Sikka Regency is one of the rural areas in East Nusa Tenggara, Indonesia, that has a health issue in sanitation. Around 51% of houses in Sikka regency are considered uninhabitable with only 1.5% of them having access to uncontaminated water (9,33). In our case, the appearance of yellowish crusts on a patient with sanitation issues directs our concern in determining whether the lesions resulted from primary or secondary bacterial infection instead. Further, follow-up from the

inadequate antibiotic response and skin appearance drives our sight to secondary bacterial infection with a primary viral infection on eczematous skin.

Other health issues that come to mind are hampered health access and lack of competent health workers (Statistik, 2019). PHCS Kewapante for example, has blood smear equipment for a malarial test but is unable to perform the Tzanck test because it lacks an experienced worker to successfully unroof the vesicle and scrape its base to be examined under the microscope. A thorough history-taking about sanitation aids the diagnosis process in our case despite the lack of data from medical diagnostic tools in rural areas.

Conclusion

The diagnosis of eczema herpeticum in rural areas could be done by history taking and clinical appearance. Immediate treatment with acyclovir results in complete recovery and prevents complications from bacterial infection. A sudden extensive vesiculopustular eruption that doesn't respond to antibiotics should be considered as eczema herpeticum with skin barrier impairment for one of the differential diagnoses.

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