A successful treatment of a rare case of dermatitis herpetiformis

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Abstract. Dermatitis herpetiformis (DH) is a rare autoimmune bullous disease characterized by intensely pruritic, chronic, and recurrent vesicles on extensor surfaces such as the elbows, knees, and buttocks. There is a genotype relationship with HLA-DR3, HLA DQw2, discovered about 80-90% of cases. Immunofluorescence is the gold standard for diagnosis, but serologic testing can help if immunofluorescence result is negative. On histopathological examination, at the tips of papillary dermis, a collection of neutrophils are found and granular immunoglobulins A. Dermatitis herpetiformis associated with gluten intolerance (celiac disease), although the mechanism is not fully understood. Patients with gluten free diet will reduce of this disease both in the skin and intestinal tract, thereby reducing risk of lymphoma progression. Dapsone is the main therapy, but it require monitoring side effects.

1. Introduction
Dermatitis herpetiformis (DH) is characterized by severe itching, common chronic papulovesicle eruption, distributed on the extensor surface, symmetrically. This disease is different from other subepidermal blistering eruptions from gastrointestinal criteria, histological, and immunologic [1]. Cormane described clinical characteristics of deposition immunoglobulin A at dermoepidermal junction. Although asymptomatic, patients also experience gastrointestinal disorders, specifically gluten sensitive enteropathy (GSE). The relationship between DH and GSE is further associated with IgA deposits in the skin [1,2]. Dermatitis herpetiformis and GSE have similar HLA haplotypes (DQ2 and DQ8), so the gluten free diet is one of the management of this disease [3].

The prevalence of dermatitis herpetiformis is most common in Northern European descendants. Male ratios are higher than women, 1.5: 1 to 2: 1 [4]. Dermatitis herpetiformis can occur at any age, but mostly in young adults, between 15 and 40 years [5]. Dermatitis herpetiformis prevalence varies across countries. In Germany 1:100,000 new cases/year; Ireland 58.8:100,000; Sweden 20-39:100,000 and Scotland 11: 100,000 [6]. Even though DH is a common disease in Caucasian populations, but rare in Asians [7]. In General Hospital Moh. Hoesin Palembang, DH is one of the rare cases. From January 2014 until December 2017 we only have one patient diagnosed with DH.

Diagnosis of DH is made by clinical, histologic, serological tests ([IgA anti-tissue transglutaminase antibodies (anti-TTG), IgA anti-epidermal TG (eTG) and IgA endomycial autoantibodies] and immunopathological [direct immunofluorescence (DIF)]. The histologic examination found neutrophil accumulation in the papillary dermis. Direct immunofluorescence is a gold standard tests for diagnosis, granular IgA deposits throughout the basement membrane zone, especially at papillary tips [3].
Management of DH based on non-pharmacological and pharmacological treatment. Non-pharmacological therapy includes a gluten free diet, while pharmacological therapy is dapsone [1,3]. This case report aimed to report a man, 42 years, diagnosed with DH, successfully treated with dapsone and gluten free diet (GFD).

2. Case Report
A 42-year-old man came to the dermatology and venereology outpatient clinic with complaints of multiple blisters of the skin, that accumulated on the faces, abdomen, back, legs, 2 weeks before admission. Two weeks before consult, patient complained that apperance of urticaria like plaque, erythematous vesicles and bullae on the regio facialis, truncus anterior et posterior, brachii et antebrachii bilateral, anterior femoris, crus et dorsum pedis bilateral with multiple, lenticular and discrete (figure 1). Additional complaints are itching and burning sensation. He did not complain fever, diarrhoea or steatorrhea. The patient went to the general practitioner, gets an ointment and tablet, but patient forgets the name of the drug. Complaint not reduced. The patient then given 2 herbal drink taken for 3 days, vesicles and bullae did not improve so patient went to a dermatologist and was referred to Mohammad Husein Hospital in Palembang and admitted. On physical examination, the dermatologic status: regio facialis, truncus anterior et posterior, extremitas superior et inferior dextra et sinistra: macula-patch, hyerpigmented, multiple, milier-numuler, discrete partial confluent. Vesicles-bullae, multiple, milier-lenticular, diskret; erosion-excoriated, multiple, irreguler, discrete, partly covered with blackish crust, thick and easily removed. Cutaneous sign: Nikolsky and Asboe hansen were negative. The result of laboratory tests were within normal limits. Histopathologic examinations showed inflammatory cells of neutrophils, neutrophil fragment, varying numbers of eosinophils and junctional separation. Immunofluorescence (IF) examination founds to be granular IgA deposits (figure 2). Systemic treatment of these patient are IVFD: RL xx gtt/min, dapsone tablet 100 mg/day, cetirizine tablet 1x10 mg/day. Topical therapy: acid salicylic solutio 1 0/00, 2x30 min/day compressed on erosion and excoriation. The patient was also started on GFD. He was referred to a nutritionist and was advised to avoid the following gluten. In the eight week of therapy, the skin lesions were completely resolved with residual hypo- and hyperpigmented macules and patches (figure 3). Finally, the patient was diagnosed to have dermatitis herpetiformis.

3. Discussions
Dermatitis herpetiformis was first known in 1884 by Louis Duhring. Initially dermatitis herpetiformis has the same clinical category as pemphigoid and pemphigus, then is grouped into vesicobullous disease. In 1888, Brocq diagnosed it as "polymorphic pruritic dermatitis". Therefore, the synonym of DH is Duhring-Brocq's disease [1,6].

Although minimal, DH patients will experience gastrointestinal disorders when patients consume gluten. Some literature states that gluten plays an important role in the pathogenesis of DH. Gluten is found in rye, barley and wheat. The mechanism by which IgA Tgase antiepidermal is bound to the skin of DH patients is not fully understood. An old hypothesis states that immune complexes circulating containing IgA contribute to the formation of IgA deposits in the skin of DH patients. The latest discovery of antiepidermis IgA Tgase antibodies suggests that the epidermal IgA Tgase immune complex can form on the skin of DH patients. However, only a small proportion of DH patients were found to have IgA and deposit the colonization of Tgase epidermal tissue with a perivascular pattern. Although IgA deposits in the skin play an essential role in pathophysiology of bullae formation, it is not certain. This hypothesis still requires further research [1].

Dermatitis herpetiformis primary lesions are urticaria like plaque, erythematous papules, mostly found vesicles. Large bullae rarely found. Lesions will produce hyperpigmentation and hypopigmentation. In some areas the herpetiformis group appears, but there are also non-grouped lesions. Other clinical manifestations are burning and severe itching. In these patients, vesicles erythematous and bullae on the anterior and posterior trunk had found. Symmetrical lesion distribution in elbows, shoulder, buttock and knees area [1,5].

In addition to clinical manifestations, DH diagnosis criteria are obtained by granular IgA deposits in the skin of patients. These IgA deposits are unaffected on the treatment with drugs, but can decrease or disappear with a long-term GFD. IgA deposits are not evenly distributed throughout the skin and can be detected more easily on normal skin adjacent to active lesions. IgA deposits are also present in
bullous pemphigoid patients, Henoch-Schonlein purpura, scarring pemphigoid, although there are differences in the pattern of spread with DH. Some studies mention IgA subclasses in DH. IgA1 is an IgA subclasses that is often found in DH [1,8].

Figure 1. Multiple tense vesicles and bullae with area of erosions with crusts symmetrically seen on the A. Entire face, B. Truncus anterior, C. Truncus posterior, D. Extremities superior, E. Extremities inferior, F. vesicles of truncus posterior.

Figure 2. A. Granular deposition of IgA at the tips of the dermal papillae, B. Skin biopsy, Subepidermal blister, C. Neutrophils contained in the blister cavity.

Figure 3. Skin lesions after eight weeks of dapsone. Complete resolution of lesions with residual hyper-and hypopigmented macules and patches. A. Face, B. Truncus Anterior, C. Truncus posterior.

On histologic examination for early DH lesions, there are neutrophils in papillary dermal, neutrophilic fragments, some eosinophils, fibrin and separate papillary from epidermis. In these patient, neutrophil infiltrate in the dermal papillary with a cleft formation between the dermal-epidermal junction had found [9].

One hundred percent of DH patients are sensitive to gluten, but only small percentage have symptoms of colic or malabsorption of intestinal at a ratio of 1: 5. There is evidence to suggest that with GFD, DH lesions on the skin and intestinal disorders will improve, although improvement may not be seen in the first 1 to 2 years. Barley, wheat and rye and all kinds of products must be removed, but pure oats, rice and corn can still be consumed. This is evident in patients who have better progression lesions after a GFD, although not in the recent time [10].

Additional therapy is needed to quickly control the disease. Management is successful in patients receiving diaminodiphenyl sulfone (dapsone), the initial dose given is between 100 and 200 mg/day. The repair response will occur 3 hours or several days after the initial treatment and the new lesion no
longer erupt after 1 to 2 days of the initial treatment. Dapsone has no side effects on intestinal, so it is important for a GFD. Dapsone is important in the field of dermatology as an anti-inflammatory and inhibits neutrophil retrieval through chemotaxis and also suppresses neutrophils mediated tissue injury. Dapsone is given if G6PD tests has been examined because the side effects of dapsone can cause severe hemolysis. It is related to the oxidant effects of stress on aging red blood cells in susceptible individuals, so patients should check their complete blood count after getting initial treatment for dapsone. In these patients, G6PD values showed normal results, thus given dapsone tablet 100 mg/day. Cetirizine is provided to reduce the symptoms of itching at a dose of 10 mg/day. Combined treatment with nutritionist for a GFD is needed [10]. In this patient, symptoms are reduced in 5 days after initial treatment and complete resolution of lesions with residual hyper-and hypopigmented macules and patches in 8 weeks.

4. Conclusions
Dermatitis herpetiformis is a rare autoimmune disease with specific immunopathological alterations at the skin level. In fact, DH is considered a specific manifestation of gluten-sensitive enteropathy. It presents on extensor surfaces with intensely pruritic papulovesicles, with excoriations and crusting and a corresponding neutrophilic infiltration of dermal papillae and granular IgA deposits on direct immunofluorescence. Generally, DH has a good prognosis with combined initial therapy of GFD and dapsone. An interprofessional team involving a dermatologist and dietician is ideal.

5. References
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