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Glucocorticoid-induced hyperglycemia (GIH) in pemphigus vulgaris patient at Bangli District General Hospital: A case report

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ABSTRACT

Background: Pemphigus vulgaris (PV) is an autoimmune disease characterized by mucocutaneous blistering and erosion. This is rare, but greatly affects the patient's life quality and often cause complication of disease and therapy. Hyperglycemia is a complication due to steroid use called glucocorticoid-induced hyperglycemia (GIH). This case report describes hyperglycemia in PV treatment, which later can be a consideration of PV management.

Case: A 44-year-old male patient complained of painful lesions on almost the whole body with a form of bullae, erosion, crusting, brittle, the Nikolsky sign (+), and Asboe-Hansen sign (+). The patient was diagnosed with PV. After he had supportive therapy and high-doses of methylprednisolone, his blood sugar is increased. Patients diagnosed by hyperglycemia state due to steroid use, then given insulin as therapy. The patient diagnosed with PV based on

history taking and physical examination, but the histopathologic examination wasn't done due to lack of modality at the hospital. The steroid was given as an immunosuppressive. Be the main therapy for PV, steroids lead hyperglycemia due to disruption of glucose metabolism, thereby increasing insulin resistance in tissues. The diagnosis of hyperglycemia due to steroid use is made in a patient with a normal sugar level before PV therapy. It occurred within the first 1-2 days of therapy. In these patients, diagnosis confirmed by increasing pre-prandial, 2 h post-prandial, and any-time glucose level, after two days methylprednisolone administration. Collaboration with internal medicine colleagues is needed.

Conclusion: PV treatment with steroids can induce hyperglycemia, which is dangerous. The understanding mechanism is needed to make early detection and provide therapy properly.

Keywords: Pemphigus vulgaris, autoimmune disease, glucocorticoid-induced hyperglycemia

Cite this Article: Setyawati, N.K., Sari, A.A.I.A.N., Mahariski, P.A. 2019. Glucocorticoid-induced hyperglycemia (GIH) in pemphigus vulgaris patient at Bangli District General Hospital: A case report. *Bali Dermatology and Venereology Journal* 2(2): 28-33. DOI: [10.15562/bdv.v2i2.19](https://doi.org/10.15562/bdv.v2i2.19)

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Received: 2019-08-10
Accepted: 2019-10-30
Published: 2019-12-01

INTRODUCTION

Pemphigus Vulgaris (PV) is a chronic autoimmune disease characterized by pain in bullae and mucocutaneous erosion.¹ Lesions usually occur in the oral first until they are often misdiagnosed with aphthous stomatitis. This disease is rare but greatly affects the patient's quality of life because of pain and prolonged treatment. PV can also be life-threatening to have mortality around 5-15% if left untreated. Mortality is usually associated with skin infection or pneumonia as a result of structural damage. Management with high doses of steroids can also cause complications.² The presence of systemic corticosteroids and other immunosuppressive agents as therapy provides a clear improvement in PV prognosis, but morbidity and mortality can occur significantly as a result of the therapeutic complications. Hyperglycemia is a complication of PV therapy, which can occur due to high doses of steroids or called glucocorticoid-induced hyperglycemia (GIH).¹

Glucocorticoids are a class of corticosteroids that are widely used in various conditions.

Although widely given as an anti-inflammatory and immunosuppressive therapy, steroids also have several side effects. Hyperglycemia is one of the most frequent and representative complications. Steroids are also said to be the most common type of drug that caused hyperglycemia.³ This article reports patients with PV who were given high doses of steroids and then had a hyperglycemic effect. This report provides a description of the complications of hyperglycemia in PV treatment, which can later be taken into consideration when treating PV patients.

CASE DESCRIPTION

A 44-year-old man came to the Emergency Department of Bangli District General Hospital with complaints of blisters from almost the entire body for about 2 weeks before the examination. Initially, ulcers develop on the lip mucosa and oral cavity. Then the first blister wound appeared on the back about 1.5 cm x 1.5 cm. The blisters similar burn wound, some bulge to form bullae, some are flat. Furthermore, blisters widen and spread

throughout the back, chest, abdomen, neck, to the head. The patient complained of pain in the blisters that were peeling off. History of allergies, taking previous medicine, and systemic diseases such as diabetes mellitus are denied by the patient.

Based on the physical examination, it was found that the general condition looked severe pain, compos mentis awareness, blood pressure 130/80 mmHg, pulse rate 96 times/minute regular, breathing 18 times/minutes, temperature 36.5°C. In dermatological status found abnormalities in the skin in the almost whole body, erythema, macules, bullae, multiple, and extensive erosion, some of which have the yellowish crust, generalized distribution, irregular shape, nummular, and firm boundaries. There are also several hyperpigmented lesions, which are thought due to healed blisters (Figure 1). Examination of the typical signs of PV was done, normal skin which is located between two bullae pressed and shifted, causing the normal skin peel off, this condition indicates a positive Nikolsky sign. Furthermore, the pressure is applied



Figure 1. Patient's initial condition



Figure 2. Patient's lesion on treatment

to the bullae, and there is an expansion of blisters on adjacent normal skin, signifying the positive Asboe-Hansen sign.

At the first laboratory examination in the Emergency Room, random blood glucose results were 119 mg/dl, creatinine 0.72 mg/dl, urea 12 mg/d, the electrolyte levels, and liver function within normal limits. There was no histopathological examination in this patient due to low resources in the hospital. The patient referred to Dermatology and Venerology Department and diagnosed with pemphigus vulgaris. Therapy of IVFD NaCl 0.9% 20 drops per minute, methylprednisolone 62.5 mg in the morning, and 62.5 mg in the daytime intravenously, cefotaxime 1 gram every 8 hours. Lesions treated with NaCl 0.9% compress three times a day for 20 minutes in wet lesions, topical desoximetasone 0.25% + 2% chloramphenicol twice daily to dry lesions, and triamcinolone acetonide ointment twice daily on the lip mucosa lesions.

Two days after therapy administration, laboratory tests were repeated, and fasting blood sugar increasing significantly to 199 mg/dl. On day four treatment, we evaluated the fasting blood glucose of 205 mg/dL and blood glucose 2-hours postprandial of 278 mg/dl. Patients diagnosed with hyperglycemia state et causa suspect glucocorticoid induce hyperglycemia with a differential diagnosis of stress hyperglycemia and type 2 diabetes mellitus, given NaCl 0.9% loading therapy with 200 ml to 500 ml followed by 20 drops per minute. Evaluation of HbA1c was suggested. The fifth day of hospitalization resulted in fasting blood glucose of 207 mg/dl, the 2-hours postprandial blood sugar of 265 mg/dl, and an HbA1c level of 3.8%. The patient received additional insulin therapy 8 subcutaneous units every 8 hours. Day 7 of treatment, the result of fasting blood glucose was 115 mg/dl, random blood glucose was 125 mg/dl.

The management of PV and hyperglycemia in the patients was carried out simultaneously. A gradual reduction in the dose of methylprednisolone in patients. The initial dose is given 62.5 mg in the morning and 62.5 mg in the afternoon intravenously for five days. After the lesion showed improvement and there were no new blisters, the dose of methylprednisolone was reduced to 62.5 mg morning, 31.25 mg on the daytime, and added 8 mg orally every 12 hours, given for five days. In re-evaluation, the lesions improved, the dose was reduced to 62.5 mg morning, 31.25 mg afternoon, and oral medication 8 mg for 24 hours for 5 days (Figure 2). Side effect or other adverse event was not found during treatment. Furthermore, the dose is reduced again until the patient can use oral doses and do outpatient treatment. After one week of



Figure 3. Lesion improved and the patient outpatient treated



Figure 4. Two weeks follow up shown hyperpigmentation lesion was found without new blister

treatment, the improvement was noticeable (**Figure 3**). Two weeks follow up followed with outpatient medication shown improvement and without the appearance of new lesion (**Figure 4**).

DISCUSSION

This case report describes patients with pemphigus vulgaris who were diagnosed and received high-dose methylprednisolone therapy, experiencing complications of hyperglycemia.

Pemphigus is a term in the autoimmune disease group with blisters on the skin and mucosa, histologically characterized by intraepidermal blistering due to acantholysis (separation of epidermal cells from one another).⁴ One of the most common types of pemphigus is pemphigus vulgaris (PV). The incidence is associated with loss of cohesion of epidermal cells and the presence of IgG antibodies to determine antigens on the surface of the differentiating keratinocytes. The antibody target is desmoglein 1 and 3 on the cell surface.¹ The average onset of patients with PV starts at nearing 40 years. Pemphigus is said to be rare in children, except in endemic areas.⁴ In this

case, it was found that the patient was 44 years old, male, with complaints of blistering, had bullae, and fragile skin since approximately 2 weeks before the examination. History of allergies, taking previous medications, systemic diseases such as diabetes mellitus, were denied by patients. This complaint shows symptoms that arise in patients with vesiculobullous dermatosis disorders, one of which is pemphigus.

Clinically the mucous membrane most commonly affected in PV patients is the mucosa in the oral cavity and the lips. Very rarely found blisters that are still intact, usually will be seen erosion. Erosion of the oral mucosa causes pain, which makes it difficult for patients to eat and drink.⁴ In this patient, the lesion begins with an ulcer at the lip mucosa. These complaints are increasing day by day, and the erosion becomes quite extensive. Patients are said to have difficulty eating and drinking and lead to low intake.

Primary skin lesions in PV are soft or brittle blisters, which can affect the entire surface of the skin, but rarely on the palms and feet. Usually, blisters appear on normal skin but later can develop into reddish skin. Because PV skin lesions are fragile blisters, the lesions that often found are erosions due to blisters that are damaged or peeled. The erosion is usually quite extensive and tends to expand to the side.^{4,6} There are Nikolsky and Asboe-Hansen signs that are positive because of the process of thrombosis. Nikolsky sign in patients can be identified by pressing and sliding the skin between two bullae or in the most peripheral active lesions, and the skin will peel off. Asboe-Hansen sign is said to be positive if there is an expansion of blisters or bullae on normal skin adjacent to the lesion when pressed over the bullae.^{4,6} Erosion lesions can also be induced on normal skin that is located far from the active lesion due to pressure or mechanical shear force.⁴ In this patient, the same clinical results were described in theory. Skin lesions appear on the patient's first time on the back, measuring about 1.5cm x 1.5cm, which is increasingly expanding and increasing in number. A few days after blisters appear in the form of bullae to erosion at locations such as the stomach, chest, neck, face, and scalp. Lesions obtained in patients are dominated by erosion caused by brittle blisters. The erosion is what causes pain in this patient. Itching does not exist. In this patient, a physical examination is also performed to look for the characteristic sign of pemphigus vulgaris, and the presence of positive Nikolsky and Asboe-hansen sign was obtained.

Pemphigus vulgaris is generally a loose bulla, fragile so it breaks easily. This is exactly what distinguishes pemphigus vulgaris from

other vesiculobullous diseases such as bullous pemphigoid, pemphigus foliaceus, or dermatitis herpetiformis. Fragile and broken bullae will become erosional.⁴ In this patient, there are also erythema macular lesions, bullae, multiple and extensive erosions, generalized distribution, irregular shape, nummular, firm boundaries. Another lesion is hyperpigmentation, which is thought to be due to a healing blister that has healed. Clinically it is in accordance with existing theories. Patients with PV rarely feel itchiness, but rather complain of pain due to peeling blister lesions.^{3,4}

Gold standard examination in PV patients is a histopathological examination taken by skin biopsy of new lesions to determine the location of blisters. Generally found suprabasal blisters with acantholysis. Above the basal cell layer, epidermal cells lose contact between cells and form blisters.^{4,6} However, in this patient, the gold standard examination was not performed because of incomplete modalities in the hospital.

Several other investigations were carried out to look for the causative factors, on the first-day blood glucose results obtained at 119 mg/dl. Blood sugar is still within normal limits, other laboratory tests on the first day are also within normal limits. Patients are given supportive care according to complaints, and the main therapy in the form of steroids is methylprednisolone at a dose of 62.5 mg in the morning and 62.5 mg in the afternoon. Doses of steroids are given quite high at the beginning and lowered slowly while the patient's lesions do not increase. This therapy is in accordance with the management of PV patients, where the main medication is a steroid because it is immunosuppressive. The steroid that is often used is methylprednisolone or dexamethasone.³ With the presence of extensive blister lesions, and it is also important to administer antibiotics to prevent secondary infections and intravenous fluids from preventing dehydration.

Based on consensus, one steroid that can be given is methylprednisolone at a dose of 1.5 mg/kg/day for 2 to 3 weeks. But before the administration of other adjuvant immunosuppressive therapies, the steroid dose is given was very high (>2 mg/kg/day). When the lesion is controlled, a slow dose must be taken until it reaches the minimum dose.^{3,4} In this case, the initial dose of methylprednisolone is given intravenously high enough. Then based on evaluating the improved lesion, the dose is reduced until it can be given orally.

Systemic administration of corticosteroids and other immunosuppressive agents provides an improvement in the prognosis of PV. However, it must be considered a significant cause of mortality

due to complications from therapy. Hyperglycemia is one of the major complications, which is caused by the disruption of glucose metabolism by corticosteroids thus increasing insulin resistance in tissues, increasing glucose production in the liver and disrupting the use of glucose in muscles and adipose cells.^{1,7-9} Steroids provide a substrate for the metabolism of oxidative stress that increases lipolysis, proteolysis, and glucose production in the liver. The mechanism of the cause of glucose intolerance after steroid therapy is said to be similar to the mechanism in type 2 diabetes mellitus, which depends on the dose and type of steroid given.^{7,8} GIH is mostly detected in postprandial sugar tests.^{3,8,9}

This case report provides a case due to high doses of corticosteroid therapy in PV patients. Complications can lead to hyperglycemia or even diabetes mellitus if they are not properly treated. In this patient, after being known to have normal blood sugar levels, there was no history of diabetes mellitus in the patient or family. A diagnosis of GIH can be made in patients who have normal glucose before starting steroid therapy. The diagnosis is based on the American Association of Diabetes: fasting blood sugar level ≥ 126 mg/dl, random blood sugar level ≥ 200 mg/dl, HbA1c $>6.5\%$, or blood sugar 2-hours postprandial >200 mg/dl. In patients who are hospitalized, a blood sugar examination must be carried out before starting steroid therapy. It is said in almost 94% of cases of hyperglycemia occur within the first 1-2 days of steroid therapy in the hospital.^{3,7,8} In this patient, the diagnosis was made based on the results of the patient's random blood sugar examination before being given steroid therapy. After two days of administration of high-dose methylprednisolone, fasting blood glucose increased to 199 mg/dl. On day 4 of hospitalization, 205 mg/dl of fasting blood glucose and blood sugar 2-hours postprandial of 278 mg/dl were obtained. The fifth day of hospitalization fasting blood glucose was 207 mg/dl, 2-hour postprandial blood sugar was 265 mg/dl, and HbA1c levels of 3.8%. Based on these results, patients can be diagnosed with GIH. Although the HbA1c results of patients are normal. Based on studies, the HbA1c results can be replaced with the results of blood sugar levels 2-hours postprandial >200 mg/dl.³

Patients with fasting blood glucose <200 mg/dl, without a history of diabetes and receiving low-dose steroid therapy, the management can be focused on exercise, dietary therapy, and oral anti-diabetes. Insulin therapy is given to patients with persistent hyperglycemia with sugar levels of ≥ 200 mg/dl. In general, hyperglycemia associated with insulin resistance, which arises after the start of

therapy with steroids, requires high doses of insulin in the early stages of therapy. Corticosteroid then lowered gradually when blood sugar has begun to be controlled. Based on weight and the use of steroid doses, the use of the initial dose is 0.4-0.5 U/kg, and then the dose is adjusted depending on the patient's response. A scheme in steroid hyperglycemia described in Figure 5.^{3,10} In accordance with the theory, with the results of sugar levels, this patient received insulin 8 units subcutaneous every 8 hours. The following day, the patient's fasting blood glucose results were 115 mg/dL, and random blood glucose was 125 mg/dL.

The limitation of this case report is that there is no gold standard examination, which is histopathology in blister lesions or other tests such as direct immunofluorescence. The diagnosis was made only by physical examination due to limited resources. In addition, the absence of combination steroid therapy with other adjuvant immunosuppressive also has a significant effect on increasing blood sugar levels. This is due to the lack of supporting modalities and variations of adjuvant immunosuppressive therapy in the Bangli District General Hospital. However, this case report can be used as a reference to diagnose and provide

treatment in cases of hyperglycemia due to steroid use in patients with pemphigus vulgaris in hospitals with limited resources.

CONCLUSION

Steroid use is known to be quite extensive in several medical conditions. Pemphigus vulgaris is a disease that uses steroids as the main treatment. Although its success is quite high, steroids can induce hyperglycemia, which is also dangerous. A good understanding of the mechanisms involved is necessary to detect early and provide appropriate therapy. Appropriate guidelines regarding the diagnosis and treatment of GIH are needed to prevent complications associated with hyperglycemia due to steroid administration.

ETHICS IN PUBLICATION

Clinical finding documentation and publication was approved by the patient (signed informed consent).

AUTHORS CONTRIBUTION

All authors have contributed from patients examination, treatment, follow up medication, reference finding, manuscript preparation, and publication.

CONFLICT OF INTEREST

None

FUNDING

None

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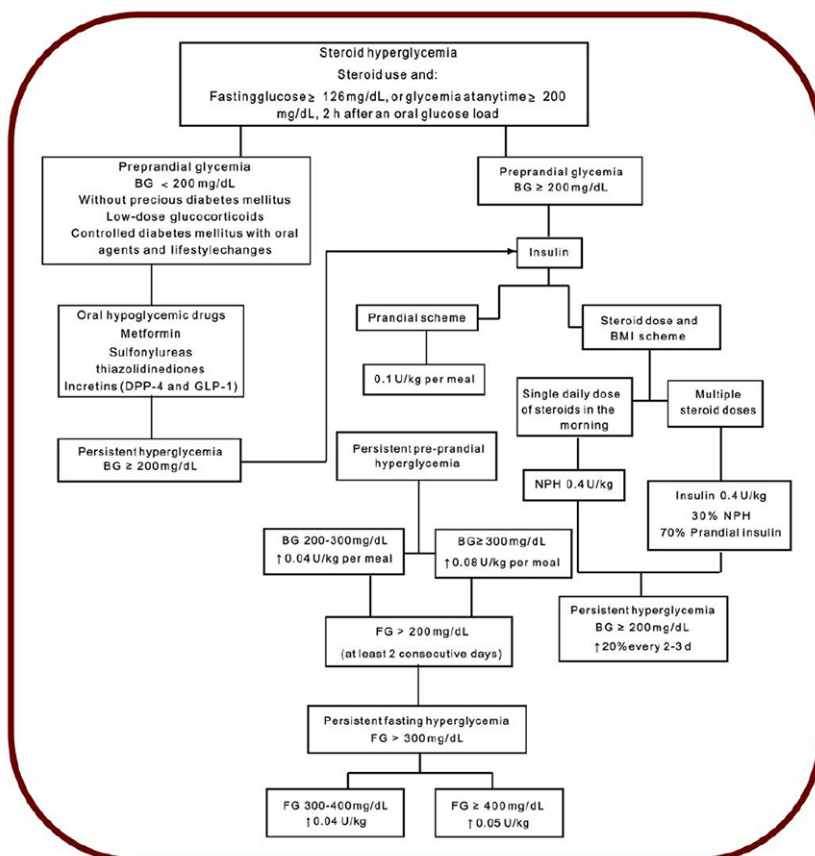


Figure 5. Glucocorticoid-Induced Hyperglycemia algorithm therapy³

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