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Hypertension as Comorbidity in Pemphigus Vulgaris Patients: A Case Series

Bobby Febrianto^{1*}, Lian Kamilah¹, Fanny Fauziyyah Heryadi¹, Azhar Arrosyid¹, Nurrachmat Muliarto¹

¹Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi General Hospital, Surakarta, Indonesia

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*Corresponding author:

Bobby Febrianto

E-mail address:

bobbyf100289@gmail.com

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ABSTRACT

Background: Pemphigus Vulgaris (PV) is a chronic autoimmune bullous disease characterized by flaccid blisters on the skin and mucous membrane. This study aimed to report a serial case of PV followed by hypertension as comorbidity. **Case presentation:** Four patients, 2 males, and 2 females were hospitalized due to PV. All of these patients also suffer from hypertension, but only 2 patients take antihypertension. Drugs relatively, histopathology features of all patients revealed a cleft above the basal epidermal layer with a tombstone appearance. Pemphigus vulgaris can be accompanied by hypertension as comorbidity, but its pathogenesis is unclear. A low level of programmed cell death 1 (PD1) in PV patients promotes downregulating protective factors, including T regulator (Treg) cells. In addition, decreasing the PD1 level may cause apoptosis and inflammation process in the vascular endothelial, which may lead to hypertension. **Conclusion:** Pemphigus vulgaris is significantly associated with hypertension.

1. Introduction

Pemphigus Vulgaris (PV) is a blistering autoimmune disease involving skin and mucosal membrane histologically. It is characterized by blisters above the basal layer due to circulation immunoglobulin directed against the cell surface of keratinocytes.¹ The annual incidence of PV range between 0.76 cases per million in Finland and 32.0 cases per million in the United States. PV tends to be lower in males than females, with the ratio ranging from 1:1.33 to 1:2.25.²

Recent epidemiologic studies have identified that PV patients have a high prevalence of cardiovascular

diseases such as hypertension. A meta-analysis study by Kwa and Silverberg showed a significant association between PV and hypertension. Razzaque et al. also reported that hypertension was the most common comorbidity in patients with PV.^{3,4}

Several mechanisms have been proposed for the association between PV and hypertension. Increased tissue and/or serum level of interleukin (IL) 17 and IL22 in PV patients are thought to play a role in increasing the risk of hypertension risk. In addition, PV can be triggered by antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors or beta blockers, although its mechanism remains

unclear.⁵ This study aimed to report serial cases of PV followed by hypertension as a comorbidity in order to improve the knowledge as well as appropriate management of the related disease.

2. Case Presentation

Patient 1

A 48-year-old female presented to the emergency department of Dr. Moewardi General Hospital with blisters all over her body 2 months prior to her visit. First, it appeared on both hands and legs as vesicles. The blisters were all over her body then she was hospitalized for 7 days. At discharge, she received cefadroxil, prednisone, ranitidine, and levorphanol

(antalgic). Unfortunately, one day later mucosal ulcer appeared, followed by several blisters on her body. Then she was referred to Dr. Moewardi General Hospital. She reported having hypertension and took amlodipine daily. Based on Dermatological examination showed flaccid blisters accompanied by erosion with haemorrhagic crust on her trunk and extremities. There were multiple superficial ulcers in her oral cavity. The histopathological findings obtained a cleft above the epidermal basal layer with a tombstone appearance. She was diagnosed with PV and then received systemic therapy for 18 days of hospitalization.



Figure 1. Multiple flaccid blisters on her face and truncal.

Patient 2

A 55-year-old male was admitted to our hospital with blisters on his trunk, legs, and lips. The vesicle appeared on the scalp and then gradually spread to his face, lips, and back. He visited a medication dermatologist and was diagnosed with PV, then received oral methylprednisolone and topical therapy for 10 days. He also had hypertension and routine took the antihypertensive drug. Because there was no

improvement, he was then referred to Dr. Moewardi General Hospital for further management. Dermatological examination obtained multiple flaccid blisters with erosion on his trunk as well as extremities and multiple erosions covered by haemorrhagic crust on his lips. Histopathological features showed intraepidermal cleft above basal layer along inflammatory cells infiltration. He was diagnosed with PV and then hospitalized for 7 days.



Figure 2. Flaccid blisters on his trunk and multiple erosions on the lips.

Patient 3

A 45-year-old female presented to the dermatology and venereology outpatient clinic of Dr. Moewardi General Hospital due to blisters all over her body. First, it appeared on her chest and then gradually spread to her body, including the mucous membrane. She could not eat because of oral ulcers, then went to a dermatologist and was diagnosed with PV. She received oral methylprednisolone, cyclosporine, and topical agent for 4 months. Two days prior to

admission, blisters appeared on her body and extremities then she was referred to the hospital. Her dermatologist, her previous illness history, revealed that she has been on antihypertensive therapy. Dermatological examination blisters with erosion and haemorrhagic crust on the lips, trunk, and extremities. The histology findings showed acantholysis on the basal layer with tombstone appearance and inflammatory cell infiltration. She was diagnosed with PV and hospitalized for 12 days.



Figure 3. Multiple flaccid blisters with erosion.

Patient 4

A 60-year-old male presented to our hospital with blisters all over his body. The blister appeared on his face, trunk, and extremities 2 weeks prior to admission, which then worsened. These blisters have easily been recurrent in the past 5 years. Thus, he often takes methylprednisolone. He had hypertension but did not take antihypertensive drugs regularly.

Dermatological examination obtained multiple flaccid blisters accompanied by erosion, bleeding, and thick crust in some areas. Histopathological features showed acantholysis on the basal layer with a tombstone appearance. Then he was diagnosed with PV. During hospitalization, his condition worsened due to hypoalbumin and severe pain. Then he passed away on day 30 of hospitalization.



Figure 4. Haemorrhagic flaccid blisters with erosion.

3. Discussion

Pemphigus Vulgaris (PV) is the most common form of the autoimmune bullous disease characterized by a flaccid blister on the skin and mucous membrane. The incidence of PV is variable worldwide, ranging from 0.05 to 27 cases per million per year. This disease can occur at any age, but it is usually seen between the fourth and sixth decades of life. Pemphigus vulgaris seems to affect males and females equally though some studies reported a slight female preponderance.⁶ The clinical features of PV are flaccid blisters filled with clear fluid either on normal or erythematous skin. The

most common predilection sites are the scalp, face, neck, upper chest, and back.¹

About 50-70% of PV patients have mucosal lesions and appear as ill-defined irregularly shaped buccal or palatal erosions. Other mucosal surfaces may be involved, including the conjunctiva, nasopharynx, larynx, oesophagus, urethra, vulva, and cervix.⁷ In our cases, PV affects males and females equally, with a mean age of 52 years old. Dermatological examination of all patients showed flaccid blister accompanied by erosion and crust, while the skin lesions are mostly

found on the trunk and extremity with oral involvement.

Histopathological features of PV are characterized by suprabasal epidermal cells separated from the basal cells to form clefts and blisters. The basal cells remain attached to the basement membrane zone but separate from one another and stand like a “tombstone appearance” on the floor of the blister. Blister cavities contain mixed inflammatory infiltrate that may include eosinophil.⁸ most of the histopathological findings in our cases are epidermal cleft on the basal layer with a tombstone appearance, and some of them had inflammatory cells in the blister.

Pemphigus vulgaris can be followed by several comorbidities, including hypertension. A retrospective study by Askin et al. reported that hypertension was the most common comorbidity in the PV population was hypertension in 39 patients.⁹ Another study by Hsu et al. showed that hypertension was significantly associated with PV (OR=2.15;95%CI=1.25-3.71).¹⁰ The certain correlation between PV and hypertension remains unclear, but Zeid et al. suggested that serum levels of programmed cell death protein 1 (PD1) were significantly lower in PV patients than in healthy controls ($p<0.001$).¹¹ Programmed cell death protein 1 (PD1), also known as CD279, is a major inhibitory receptor that is preferentially expressed on the surfaces of T and B cells.¹² The interaction between PD1 and its ligands impairs T-cell survival and blocks T-cell responses such as proliferation, cytokine secretion, and cytotoxic ability. It enhances forkhead box p3 (Foxp3) expression and regulates the differentiation of induced T regulator (Treg) cells so that it has a protective function.^{13,14} In vivo study of pemphigus mouse model revealed that PD1 cell expression was positively correlated with anti-desmoglein (Dsg)3 antibody levels and can predict the disease activity.¹⁵

In hypertension, structural changes of vascular tissues may lead to decreased microvascular density, which represents apoptosis. Bu et al. study. Found that PD1 has an important role in downregulating proatherogenic T-cell response in the vascular

endothelial.¹⁶ Administering of a blocking anti-PD1 antibody increases lesional inflammation in a hypertensive mouse model, which is characterized by the upregulation of lesional T cells.¹⁷ Inhibition of PD1 will decrease lesional CD4+ and CD8+ levels in the blood vessels, which triggers the inflammation process by increasing several cytokines.¹⁸ Hence, further study is needed to determine the relation of PV with hypertension to achieve optimum management as well as prevent worsening of the disease.

4. Conclusion

Pemphigus vulgaris is the most common form of autoimmune bullous disease, which is significantly associated with hypertension. The certain mechanism of hypertension and PV remains unclear, but a recent study suggested that the inflammation process in PV causes hypertension. In addition, further investigation is needed to achieve the optimum outcome and better management of PV patients with hypertension.

5. References

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