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Successful Treatment of Pemphigus Vulgaris in Children Using Methylprednisolone Pulsed Treatment

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Abstract— Pemphigus vulgaris (PV) is a disease which clinical manifestation of mucosal and skin surface blisters classified as autoimmune disease. Intermittent adhesion damage to the epidermis due to IgG autoantibodies complements and sometimes against Desmoglein-1 and Desmoglein-3 can cause acantholysis. PV is mostly found in Jewish, Mediterranean descent, and Asians. PV is most commonly appeared in elderly between 40 and 70 years old. Methylprednisolone pulsed-dose is known as an effective therapy for PV in adult. This case shows successful methylprednisolone pulsed-dose therapy in childhood PV.

Keywords - Pemphigus vulgaris, childhood pemphigus vulgaris, autoimmune, methylprednisolone, pulsed-dose

I. Introduction

Pemphigus is characterized by histological smear which shows epidermal blisters due to acantholysis of epidermal cells adhesion and immunopathological examination shows immunoglobulin G (IgG) autoantibodies directed against the cell surface of keratinocytes. This condition leads to the appearance of blister on the skin and mucous surface.[1] It is considered as an autoimmune condition.[2] Based on its pathophysiology, pemphigus is divided into 4 major types: vulgaris, foliaceus, paraneoplastic, and IgA pemphigus. Pemphigus shows very fluid presentation and patient's symptoms varies overtime. They present with chronic evolution, with periods of remission and exacerbation and impairment in quality of life.[3]

Epidemiological data shows pemphigus is a rare disease which occur 0.076 to 5 within 100.000 person per year. Pemphigus is more common in Jews and people with Mediterranean descent.[1] People within 40 – 60 years of age are mainly affected by this condition. Children only accounted 3.7% of PV cases. PV in children aged less than 12 years is called childhood PV and juvenile PV aged between 12 – 18 years.[4] Children with predisposition of PV may be triggered by environmental factors, medications and acantholytic substances. Sex ratio between women and men is 1.33 to 2.25.[5]

Antigens involved in PV are Desmogleins-1 and Desmoglein-3 (Dsg-1 and Dsg-3). Dsg-1 is found in superficial part of epidermis while Dsg-3 is deep inside epidermis. Inhibition of these proteins by autoantibodies resulted in loss of cell adhesion, resulted in blister formation. In PV, patients with only Dsg-3 autoantibodies present with dominant mucosal lesions and patients with both autoantibodies have similar amount of mucocutaneus lesion.[6]

Patient with pemphigus vulgaris generally come with multiple skin blisters which described as reddish, painful, itchy, and fragile. Predominant primary skin lesions are vesicles, bullae, and erosion (fresh or crusted) on erythematous skin. Extension to the vermillion border of the lips may results in hemorrhagic crust, making it similar to Steven-Johnson syndrome. Skin lesions may start from anywhere in the body surface with exception of palm and soles. Generalized distribution lesion is

seen in 79% patients. Characteristic Nikolsky sign usually presents, essential in differentiating pemphigus and other blistering skin disease. Erosion may present secondary to ruptured blisters. Vegetating lesion, excessive papillomatosis and crusting, may appear during healing course on intertriginous area in the scalp or on the face. Lesions on scalp may progress to alopecia. Oropharyngeal involvement usually occurs before skin lesions. Onset between oral and skin lesions varies from 2 to 22 weeks with average of 12 weeks. Endoscopic evaluation revealed 55-85% PV patients had lesions on ear, nose, nasal mucosa, pharynx, or larynx, resulted in feeding difficulty caused by excruciating pain. This needs thorough nutrient control and requiring hospitalization.
PV is potentially life-threatening without proper treatment. Loss of epidermal barrier on extensive part of the skin may leads to loss of body fluids and malnutrition. Patient with pemphigus is in risk of developing secondary condition such as dehydration and secondary systemic infection. Monitoring of hypovolemic and/or septic shock should be considered on observation on patients with pemphigus. Pemphigus vulgaris is less common in children, making the diagnosis delayed and sometimes is misdiagnosed with impetigo, staphylococcal ecthyma, or herpes simplex.[7] Delayed of diagnosis or misdiagnosis often leads to delay of treatment, increasing the morbidity to the patient.

II. Case Report

2.1 History Taking

A 4-year-8-month-old girl was referred to Dr. Soetomo General Academic Teaching Hospital on June 25th 2019 with the diagnosis of Steven Johnson Syndrome/Toxic Epidermal Necrolysis (SJS-TEN). The patient's chief complaint was the appearance of blisters on head, forehead, chest, stomach, back, and hands for the last 1.5 months. At first, blisters appeared on head and spread to the forehead, chest, back, and palms. Approximately one week ago, the blisters spread to the genital area. The blisters erupted easily and bleed afterwards. Patient's family gave her self-medication Amoxicillin and Paracetamol syrup. After the blisters spread, patient came to an alternative medicine practice and was given a mixture of unknown liquid and leaves to be placed onto the open wounds. After the blisters covered almost the entire body, the patient came to H. Slamet Martodirdjo General Hospital Pamekasan and was referred to Dr. Soetomo General Academic Teaching Hospital. The history of medication from the previous hospital was Gentamycin injection 2 x 40 mg and Dexamethasone injection 1x ¼ ampule. The patient was the 3rd child, born spontaneously, full-term, 2800 gram in weight and 45 cm in length with no complication during prenatal, natal and post-natal period. The patient was breastfed until 11 months old. Basic immunization was complete and there was no developmental delay. The patient and the family members had no history of allergy. The patient was never hospitalized before.

2.2 Physical Examination

The patient weighed 12.5 kg, heighted 96 cm, with Ideal Body Weight (IBW) 68%. Based on WHO child growth standard, the patient was underweight and stunted. Weight-to-height showed mild malnutrition. At the emergency room, the vital sign was normal, BP: 120/97 mmHg, HR: 141 bpm, RR: 20 bpm, Temperature 36.7 °C, and oxygen saturation 98%. From physical examination, on head and neck, there were no signs of anemia, cyanosis, icterus or dyspnea. From chest examination, there were no abnormalities of heart and lung. From abdominal examination, liver and spleen were not palpable. No lymph nodes enlargement was found on cervical, axillar, and inguinal region.
Cutaneous examination showed multiple erythematous macules, not well-demarcated, pleomorphic, covered with yellowish crusts on the patient's head. In the facial region, multiple erythematous macules were found, not well-demarcated, pleomorphic, covered with black crusts and thick squama, and some appeared to be actively bleeding. At the thoracic region, multiple erythematous macules were found, not well-demarcated, and pleomorphic. Some of the skin showed hypopigmented

macules that covered with black crusts. Erosion and pus were presented on the head, facial, and thoracic region. The skin manifestation is shown in the pictures below.

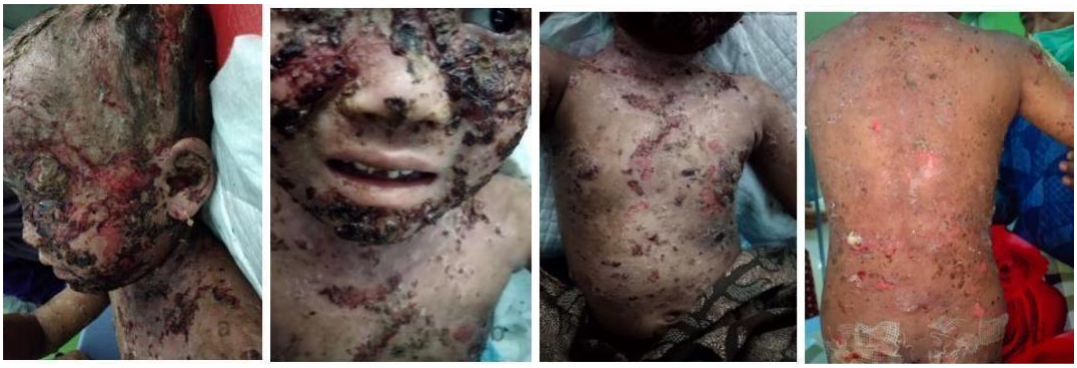

Figure 1 Patient's condition as of June, 25th 2019. A and B showed multiple erythematous macules (multiple stages of development) and yellowish crust on facial region. C and D showed multiple erythematous macules (multiple stages of development) covered by black crust on the trunk region

2.3 Laboratory Examination

Laboratory examination showed normal result, except increased white blood cell, increased plasma glucose, and hypernatremia. Urine analysis also showed leukocyte in the urine. To confirm the diagnosis, skin biopsy was performed. The sample was taken at the transitional edge of the blister and inflamed skin. Microscopic evaluation with hematoxylin and eosin (H&E) staining showed suprabasal blister containing several cells of thrombolysis. The dermal layer appeared to have slight infiltration of lymphocyte cells. Direct immunofluorescence showed IgG deposit on the surface of the epidermis with a slight basal predominance, as seen in Figure 2.

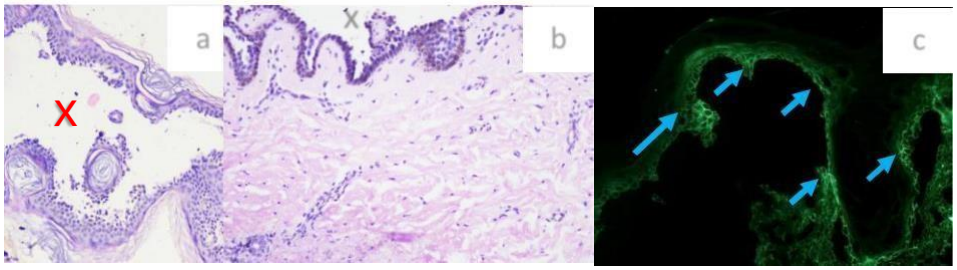

Figure 2 Skin biopsy (A) with magnification 100x and (B) magnification 400X. Sign (x) was intraepidermal blisters. (C) direct immunofluorescence showed green which indicated the deposit of IgG in epidermis.

2.4 Diagnosis and Therapy

From the history taking, physical examination, and supporting examinations, the diagnosis of pemphigus vulgaris was confirmed. The initial assessment of the patient was pemphigus vulgaris, secondary infection, hypernatremia, underweight, and stunted. Patient received Methylprednisolone 3x4 mg oral, Gentamycin injection 3x12 mg, Cetirizine syrup 1x2.5 mg, Sodium fusidate cream 2% twice a day, and NaCl 0.9% for wound flushing. The patient was also consulted to the Division of Pediatric Nutrition and was given infusion of Kaen 3B 600 cc in 3 hours and then D5½ NS 100 cc in

24 hours. The therapeutic monitoring included complaint, new blister, vital sign, urine output, electrolyte serum, and fluid balance.

On the next day, patient complained about pain and new blister on the left hand. There was no fever, the urine output was minimal. The therapy was the same as the previous day. The Division of Pediatric Nutrition considered that the patient needed parenteral nutrition and close monitoring of growth chart. The diet was adjusted based on Recommended Dietary Allowance (RDA) and additional formula (Nutrini formula) 5x100cc was added. On the third day, new blisters appeared on the fingers and leg. Pus culture was also performed. During hospitalization, patient received Nutrini 5x100 cc, Methylprednisolone 4mg/8hour, Cetirizine 2.5 mg/24-hour, Gentamycin injection 12mg/8hour, Sodium fusidate cream, and NaCl for wound washing. The patient was consulted to the Division of Ophthalmology for ocular lagophthalmos on both eyes and was given eyedrop and chloramphenicol eye ointment.

From laboratory result on June 28th 2019, there was an increase of creatinine serum and the patient was assessed with acute kidney injury. The Division of Pediatric Infection consider to substitute the antibiotic Gentamycin to Erythromycin syrup 4x3/4 tea spoon. The patient was consulted to The Division of Pediatric Nephrology and was advised to perform sediment urine test and restriction of water input, which was 500 cc of D51/2 NS for 24 hours. The patient underwent compensated metabolic acidosis (Blood gas analysis: pH 7.38 and HCO3 18.3). Immediate treatment to balance out blood acidity was carried out using Sodium Bicarbonate 8,4% 7 mEq in Dextrose 5% 200 ml for 6 hours, followed with Sodium Bicarbonate 8,4% 7 mEq in Dextrose 5% 200 ml for 18 hours and later continued with 1 tablet of Sodium Bicarbonate orally daily. The Division of Pediatric Nephrology also recommended fluid monitoring.

The result of pus culture showed *Proteus mirabilis*, sensitive to Amikacin, Aztreonam, Amoxiclav, Piperacillin, Piperacillin Tazobactam, Cephazolin, Ceftazidime, Cefotaxime-Sulbactam, Cefotaxime, Meropenem; resistant to Gentamicin, Ampicillin, Cotrimoxazole, Tetracycline, Chloramphenicol, Ciprofloxacin, Levofloxacin, Moxifloxacin. In the early first to second week of therapy, there was no significant clinical improvement. Blisters still appeared and easily ruptured on femoral region, back, and shoulder. Some of blisters ruptured and others became dry.

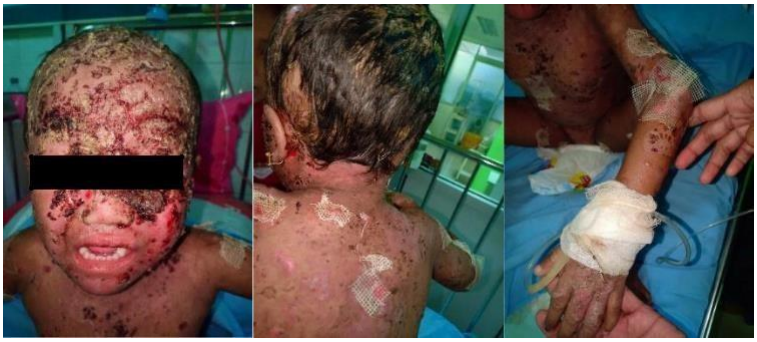

Figure 3 Patient condition during the 1st and 2nd week of hospitalization.

The patient was given Mupirocin topical for dry wound and additional treatment of Dapsone 25mg/24 hour. The Division of Pediatric Tropical Disease considered to stop Erythromycin and changed to Ampicillin 300mg/6hour intravenously for antibiotic treatment, and then Amikacin 225 mg intravenously. On the 16th day of treatment, we received the 2nd (performed on the 11th day) pus culture to check for any improvement or any additional skin infection. Pus culture showed MRSA bacteria present; sensitive to Amikacin, Quinupristin–Dalfopristin, and Chloramphenicol; resistant to Tobramycin, Gentamycin, Ampicillin, Amoxicillin – Clavulanate, Penicillin G, Oxacillin, Tetracycline, Cotrimoxazole, Erythromycin, and Clindamycin. On the 3rd week of hospitalization, patient still complained of new blisters that erupted in the body. Some old blisters ruptured and some

erosions on the skin appeared. Dose of Methylprednisolone was increased into 6mg-6mg-4mg on July 18th. The patient complained of new blisters on the hand and leg. In July 23th, the patient received Methylprednisolone pulse 30 mg/kg in three days, from July 23rd to 25th. During Methylprednisolone pulse, vital sign was evaluated in 15 minutes and 1 hour and blood glucose was also monitored before and after treatment. Patient was in a stable condition based on vital sign and glucose monitoring. After Methylprednisolone pulse, there was a significant clinical improvement.

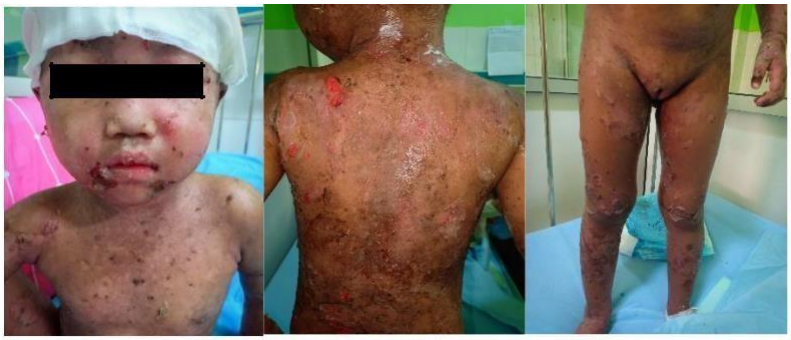

Figure 4 Patient condition as of July 15th 2019.

Early assessment, additional laboratory work, and results from both pus culture and skin biopsy made the final assessment of Pemphigus vulgaris, secondary infection, acute kidney injury stage injury, lagophthalmos on both eyes, stunted, and underweight.

Table 1 Observation of patient skin condition (vesicle, bullae, and crusta) throughout patient stay in Dr. Soetomo General Academic Teaching Hospital.

	Day 1	**Day 3**	**Day 5**	**Day 9**	**Day 11**	**Day 13**	**Day 15**	**Day 23**	**Day 25**	**Day 28**	**Day 33**
Subjective/ Objective	**25/6**	**27/6**	**29/6**	**3/6**	**5/7**	**8/7**	**10/7**	**18/7**	**20/7**	**23/7**	**28/7**
Vesicle	+	+	+	+	+	+	+	-	-	-	-
Bullae	-	-	+	+	+	+	+	+	+	-	-
Crusta	+	+	+	+	+	+	+	+	+	+	+

Table 2 Patient therapy list throughout patient stay in Dr. Soetomo General Academic Teaching Hospital

Therapy	**Day 1**	**Day 3**	**Day 5**	**Day 9**	**Day 11**	**Day 13**	**Day 15**	**Day 23**	**Day 25**	**Day 28**	**Day 33**
	25/6	**27/6**	**29/6**	**3/6**	**5/7**	**8/7**	**10/7**	**18/7**	**20/7**	**23/7**	**28/7**
IVFD KaEN 3B 600 ml/3 hr	+	+	+	-	-	-	-	-	-	-	-
IVFD D5% 0.455% NS 1000 ml/24 hr	+	+	+	-	-	-	-	-	-	-	-

Topical Fucidic acid 2% cream	+	+	+	-	-	-	+	-	-	-	-
Normal saline wash	+	+	+	+	+	+	+	+	+	+	
Methylprednisolone inj. 3 x 4 mg	+	+	+	+	+	+	+	-	-	-	-
Methylprednisolone 6mg-6mg-4mg oral	-	-	-	-	-	-	-	+	+	-	+
Methylprednisolone 30mg/KgBB pulse	-	-	-	-	-	-	-	-	-	+	-
Gentamycin inj. 3 x 12 mg	+	+	+	-	-	-	-	-	-	-	-
Ampicillin inj. 4 x 300 mg	-	-	-	-	+	+	-	-	-	-	-

The patient was discharged at July 29th. Patient came to the outpatient clinic and was given prescription of Methylprednisolone 14 mg oral for 4 days, 12mg oral for the next 4 days, and Atopiclair. The follow up examination is shown below:

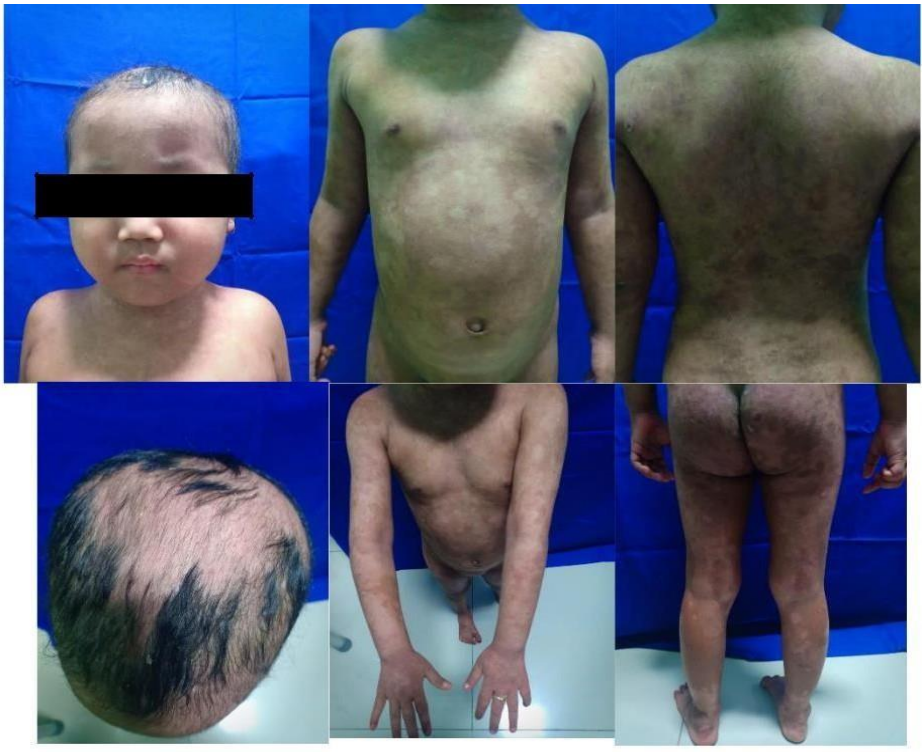

Figure 4 Patient condition on August 13rd, 2019 (follow up examination).

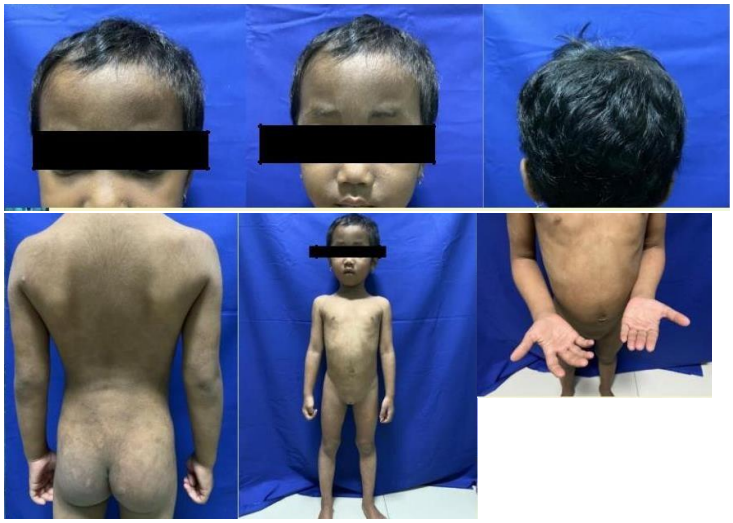

Figure 5 Patient condition on September 3rd, 2019 (follow up examination).

III. Discussion

Pemphigus vulgaris is the most common type of pemphigus.8,9 Pemphigus vulgaris is rare in children, but common in elderly between the age of 40 to 60.8 Pemphigus in children less than 12 years old is known as childhood PV, and PV in children 12 – 18 years old are called as juvenile PV.10 Epidemiological study showed that pemphigus in children reach 3.7% from all cases of pemphigus vulgaris. Clinical features of pemphigus vulgaris is consisted of flaccid cutaneous vesicles and bullae, typically spread throughout body surface with exception of palmoplantar surface.11,12 Large erosions are common presentation which occurred after the blisters ruptured. Nikolsky sign is usually present. Nikolsky sign is indicative of active acantholysis, which is moderately sensitive but highly specific for pemphigus.

Pemphigus demands a diagnosis based on clinical manifestation and specific laboratory work up, such as skin biopsy. Histopathological examination yielded 100% positive results and also help in differentiating subtypes between pemphigus. Characteristic histopathologic finding in PV is a suprabasal blister with acantholysis. Direct immunofluorescence microscopy of perilesional biopsy specimens is the most reliable and sensitive diagnostic test for all type of pemphigus.

PV lesions may be fatal if not treated effectively. Severe blistering of the skin and mucous membranes may lead to fluid loss, protein loss, dehydration, malnutrition, and sepsis. The goal of pemphigus therapy is to control the disease, heal the bullous skin and mucous and minimize functional impairment. Most therapies aim to improve symptoms through the reduction of serum autoantibodies, either directly or through generalized immune suppression. In early phase, pemphigus therapy is to prevent a formation of new blisters.11,13 Corticosteroid is the first line therapy due to its effect as immunosuppressant and rapid effect. Some recommend topical and intralesional corticosteroids as adjunctive therapy or even monotherapy in localized mild disease. The guidelines by EDF and European Academy of Dermatology and Venereology recommend initial prednisolone dose at 0.5 mg–1.5 mg/kg/day, and a higher prednisolone dose (up to 2 mg/kg) could be administered. Japanese guidelines recommend short-term high-dose intravenous methylprednisolone in refractory cases. If doses of prednisolone above 100 mg/d are required, pulse treatment with either oral or intravenous (IV) steroids may be considered.8,13 As soon as the disease is controlled, tapering of corticosteroid should be started. Slow tapering of 2-to-4-week interval is recommended. Corticosteroid treatment for pemphigus treatment is widely used but prolonged used

of corticosteroid may have a side effect such as weight gain, acne, growth retardation, osteoporosis and hormonal disturbance closely monitored.13 Lately, recent study showed that intravenous high-dose steroid pulse therapy is an effective method for the control of pemphigus vulgaris, in hope that pulse will give enough and minimize adverse effect.14 Clinical improvement usually happens in 2 to 3 weeks from the beginning of the treatment.15

Broad spectrum of antibiotic can be given to prevent secondary infection such as tetracycline and erythromycin. Topical use of antibacterial creams, such as benzyl peroxide and saline compress can be used for soothing effect and edema control. Systemic antibiotic is indicated only in definite clinical or laboratory evidence of secondary infection, not as a prophylaxis. It is preferable that antibiotic choice is based on culture sensitivity.10,12,16

Supportive measures such as wound management & dressings, analgesic mouthwash in case of mucosa involvement, adequate analgesia, and dietary supplements in case of erosions in the oral cavity.10,12,16 Maintaining healthy diet, regular evaluation of secondary infections and giving long-term low-dose steroid maintenance therapy and controlling its side effects are important to be done.10

IV. Conclusion

- Pemphigus is characterized by histological smear which shows epidermal blisters due to acantholysis of epidermal cells adhesion. This condition leads to the appearance of blister on the skin and mucous surface.
- Children only accounted 3.7% of PV cases. PV in children aged less than 12 years is called childhood PV.
- Methylprednisolone pulsed-dose was known as an effective therapy for PV in adult.
- This case report shows significant clinical improvement of childhood PV treated with pulsed-dose methylprednisolone.

Acknowledgement
We sincerely thank the patient who participated in the present study. We report no competing interest.

List of Abbreviations

PV	: Pemphigus Vulgaris
IgG	: Immunoglobulin G
IgA	: Immunoglobulin A
Dsg-1	: Desmoglein-1
Dsg-3	: Desmoglein-3
SJS/TEN	: Steven Johnson Syndrome/Toxic Epidermal Necrolysis
WHO	: World Health Organization
BP	: Blood Pressure
HR	: Heart Rate
RR	: Respiration Rate
H&E	: Hematoxylin & Eosin
RDA	: Recommended Dietary Allowance
IBW	: Ideal Body Weight
EDF	: European Dermatology Forum

Figure Legends

Figure 1. Patient's condition as of June, 25th 2019.
Figure 6. Skin biopsy with magnification 100x and magnification 400X.
Figure 3. Patient condition during the 1st and 2nd week of hospitalization.
Figure 4. Patient condition as of July 15th 2019.

Figure 7. Patient condition on August 13rd, 2019 (follow up examination).

Figure 8. Patient condition on September 3rd, 2019 (follow up examination).

Table 3. Observation of patient skin condition (vesicle, bullae, and crusta) throughout patient stay in Dr. Soetomo General Academic Teaching Hospital.

Table 4 Patient therapy list throughout patient stay in Dr. Soetomo General Academic Teaching Hospital.

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