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Case Report

Bullous pemphigoid associated with Covid-19 vaccine in child: A case report

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Abstract Bullous pemphigoid (BP) is a vesiculobullous autoimmune disease mediated by autoantibodies against the hemidesmosomal proteins BP180 and BP 230. This disease is rare in children. Several COVID-19 vaccinations have been linked to bullous pemphigoid. The diagnosis of bullous pemphigoid is based on anamnesis, physical examination, histopathological and DIF examinations. This study reports an 11-year-old boy with the chief complaint of swelling and fluid-filled blisters all over his body accompanied by pain after receiving the Sinovac-Coronavac COVID-19 vaccination. Examination of the dermatological status of the oris et genitalis region showed multiple erosions on an erythematous base. In the generalized region, multiple tense vesicles and bullae were seen scattered discretely, some confluent, some bullae ruptured to form erosions and crusts. Histopathological examination showed a subepidermal fissure, inflammatory cells, eosinophil cells and extravasation. DIF examination showed IgG deposits in the epidermis of the blister roof and formed a serrated pattern on the roof of the dermis and C3 deposits were found in the upper dermis which were consistent with bullous pemphigoid. The patient was given a combination therapy with injection of methylprednisolone, erythromycin and mycophenolate mofetil with good results until the 2nd month of evaluation.

Key words
Bullous pemphigoid; COVID-19, Sinovac-Coronavac.

Introduction

Bullous pemphigoid (BP) is an autoimmune disease characterized with pruritus, tense bullous commonly with urticaria plaque base. This disease is mediated by autoantibody resisting hemidesmosomal proteins BP180 and BP 230 triggering inflammatory cascade activation and bullous formation.[1] This disease is commonly found in children.[2] The incidence of BP in children culminates at 4-month and 8-year ages, on average.[3] Vaccination is the main factor triggering BP in children that can appear several hours or days following the vaccination injection.[4] Some vaccinations have reportedly trigger BP incidence in children including diphtheria, pertussis, tetanus (DPT), pneumococcus, poliovirus, hepatitis B recombinant, *mumps, measles and rubella* (MMR), and some corona virus disease of 2019 (COVID-19) vaccines such as COMIRNATY Pfizer-BioNTech, Moderna mRNA-1273, ChAdOx1/nCoV-19-AstraZeneca/Vaxzevria.[5,6]

BP diagnosis is established in children through some findings such as under-18 year age, the presence of vesicle or tense bullous in physical examination, and supepidermal bullae followed with eosinophilia in histological examination (test) and linear deposition *immunoglobulin* (Ig)G or *complement* (C) 3 basalis membranes in *Direct Immunofluorescence* (DIF) examination or the presence of anti-basalis membrane autoantibody in Indirect Immunofluorescence(IIF) examination.[7]

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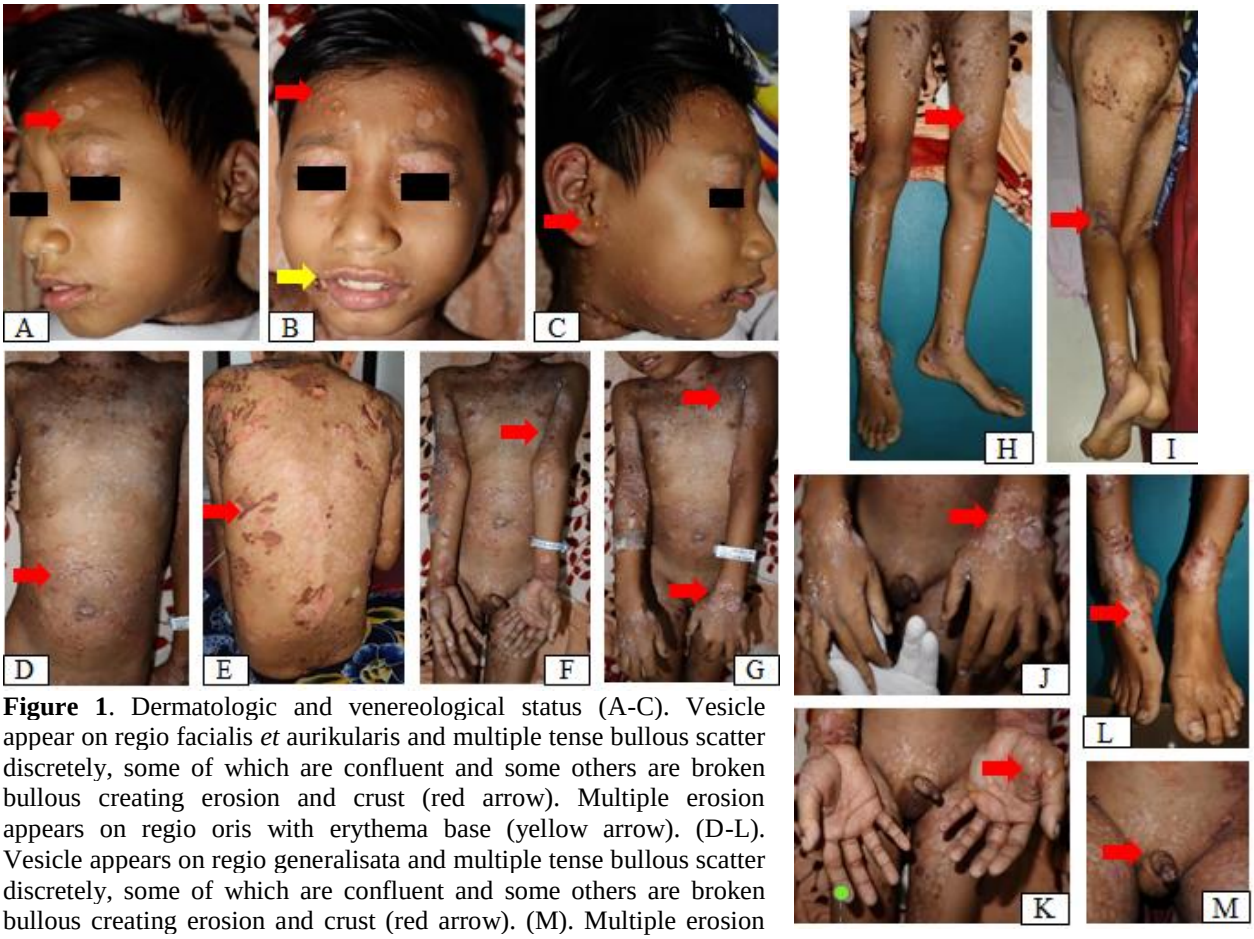

Figure 1. Dermatologic and venereological status (A-C). Vesicle appear on regio facialis *et* aurikularis and multiple tense bullous scatter discretely, some of which are confluent and some others are broken bullous creating erosion and crust (red arrow). Multiple erosion appears on regio oris with erythema base (yellow arrow). (D-L). Vesicle appears on regio generalisata and multiple tense bullous scatter discretely, some of which are confluent and some others are broken bullous creating erosion and crust (red arrow). (M). Multiple erosion appears on region genitalis with erythema base (red arrow).

This paper writing aims to establish diagnosis and to find out the appropriate therapy in BP cases related to Covid-19 vaccination in children to accelerate the clinical improvement in the patient.

Case report

An 11-year child came with large pus-filled swellings and blisters on entire body followed with itchy rash and pain. A month before coming to the hospital, the patient received Sinovac-Coronavac COVID-19 vaccination. Four days following the vaccination, itchy rash appeared and then developed into blister filled with pus on neck and breast areas. Sprue appeared and blister filled with pus also appeared on genital organ. The patients were treated in another hospital for 1 (one) week before and received methylprednisolone therapy at dose of 24 mf/day but the symptoms did not improve. The history of similar disease, food allergy, drug allergy, and autoimmune disease is denied. The history of family with similar disease is also denied.

The physical examination on general condition found that the patient seem to be sick moderately, with compos mentis consciousness, and pain score of 5-6. The examination on vital signs found normal result and good nutrition status. Laboratory examination found Hb, hematocrit, thrombocyte, erythrocyte, random blood glucose, SGOT, SGPT, albumin, urea, calcium in normal range with the decrease of creatine by 0.4 mg/dl (N= 0.6-1.1 mg/dl) and calcium by 3.5 mmol/l (N= 3.6-6.1 mmol/l).

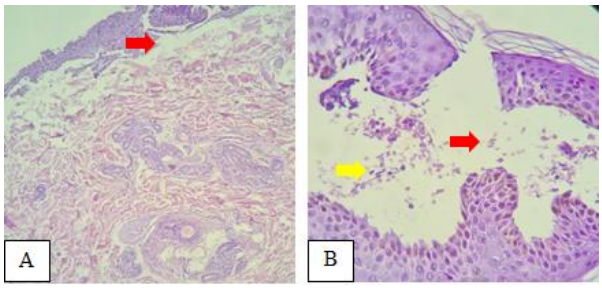

Figure 2 Histopathological representation (A). Subepidermal fissure representation appear on epidermis (red arrow) (100X). (B). Subepidermal fissure representation appear on epidermis (red arrow), inflammatory cells and eosinophil cells and erythrocyte extravasation (yellow arrow) (400X).

The examination of dermatologic and venereological status shows multiple erosion on regio oris *et* genitalis with erythema base. Vesicle appears on regio generalisata and multiple tense bullous scatter discretely, some of which are confluent and some others are broken bullous creating erosion and crust.

Skin biopsy examination using hematoxyclin and Eosin (H&E) colorant was conducted on the lesion on back region and obtain the representation of subepidermal fissure, inflammatory cells, and eosinophil and extravasation cells **(Figure 2)**. The *direct immunofluorescence* (DIF) examination found IgG deposition in the roof-part epidermis of blister creating serrated pattern on the dermis roof and found C3 deposit on upper dermis **(Figure 3)**.

Considering the result of anamnesis, physical examination and supporting examination, the patient was diagnosed with BP. We gave the patient Na 0.9% infuse therapy at dose 20 drop/minute, methylprednisolon injection 31.25 mg/24 hour tapering off, erythromycin 3x300 mg per oral, cetrizine 1x10 mg per oral paracetamol 3x250 mg per oral if pain, Kenalog in orabase ® (triamcinolone) applied to mouth area twice a day in the morning and evening. The 5th-day treatment still found new bullous; thus, mycophenolate mofetil 2x250 mg per oral therapy was added. Lesion medication was done per 24 hour with NaCl 0.9% compress for 10-15 minutes, and then mupirocin 2% ointment was applied twice a day to the erosion area. Inpatient therapy was administered for 8 days and followed with outpatient therapy. Evaluation was conducted for 2 (two) months and the lesion improved.

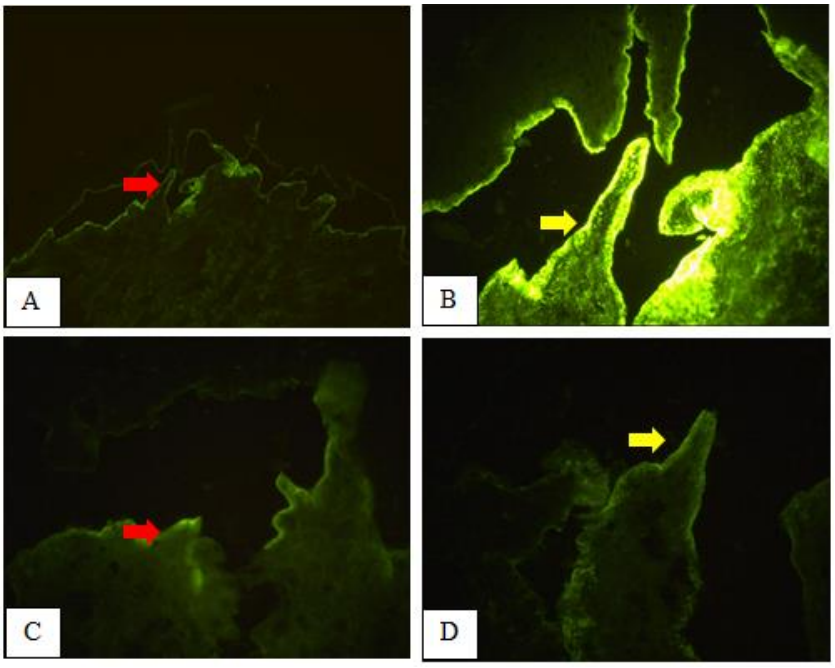

Figure 3 *Direct immunofluorescence*. (A). IgG deposit appears on roof part epidermis of bullous and creates *serrated pattern* on dermis roof (red arrow) (40X) (B). IgG deposit appears on roof part epidermis of blister and creates *serrated pattern* on dermis roof (yellow arrow) (400X). (C). Deposit C3 appears on upper dermis (red arrow) (40X) (D). Deposit C3 appears on upper dermis (yellow arrow) (400X).

Discussion

Bullous pemphigoid is subepidermal immunobullous disease characterized with clinical manifestation of BP in children, with acral and genital involvement often occurring in infantile.[8] The COVID-19 vaccination-related Bullous pemphigoid is putatively regulated by a specific pathogenic process in individual having predisposition genetically. This vaccination will cause cytokine interleukin (IL)-12 and IL-23 and the presence of new antigen triggering the T-cell-dependent immune response that then leading to the production of autoreactive B cell. B cell then produces IgG and IgE autoantibodies (autoAbs). BP autoantibodies, particularly IgG autoantibody fights against 2 hemidesmosomal proteins directly: BP180 and BP230 antigens constituting the component of *dermo-epidermal junction*. Autoantibody bond triggers the activation of complement, the release of inflammatory cells and proteolytic enzyme.[10]

Supporting examination that can be done to help establish BP diagnosis is histopathology with Hematoxyciline and Eosin (HE) dyeing and DIF examination. Histopathological representation that can be found on epidermis includes subepidermal fissure with superficial and eosinophil perivascular inflammation infiltrate. Spongiois and eosinophil infiltrates are also found on superficial papilla dermis without vesiculation constituting the characteristic of urticaria lesion representation. The histopathological representation in this patient includes subepidermal fissure, inflammatory cells, eosinophil cells and extravasation and thereby confirms BP diagnosis. DIF examination is used to detect directly the autoantibody in the tissue constituting gold standard to evaluate autoimmune bullous disease. IgG and C3 deposits with linear homogenous pattern can be found in baseline membrane zone in DIF examination on BP patient.[11] In this patient, the DIF examination found IgG deposit on roof part epidermis of bullous creating *serrated pattern* on the dermis roof and C3 deposit on upper dermis, thereby confirming BP diagnosis.

Systemic corticosteroid is the best early therapy for BP in children. Corticosteroid can be administered to children at dose equivalent to prednisone 1-2 mg/kg/day.[12] Methylprednisolone can inhibit the production of *reactive oxygen species* (ROS), *neutrophil elastease* (NE) and *matrix metalloproteinase*(MMP)-9, IL-8 and IL-17. Methylprednisolone inhibits the release of *B-cell-activating-factor* (BAFF) responsible for triggering the proliferation of and maintaining the autoreactive B cell. Methylprednisolone suppresses the production of IL-5 by Th2 cell and inhibit the production of various inflammatory cytokine by mast cell.[13] In this case, methylprednisolon injection at dose 31.25mg/24 hour is administered to the patient during inpatient therapy (8 days), and then methylprednisolon tapering off with dose 24 mg/day for 2 weeks and continued with dose 16 mg/day in outpatient therapy.

Erythromycin and mycophenolate mofetil can be administered as the therapy combined with corticosteroid in refractory case. Erythromycin is macrolid-class antibiotic with anti-inflammatory effect. Erythromycin can inhibit the production of proinflammatory cytokine such as IL-1, IL-6, IL-8 and *tumor necrosis factor alpha* (TNF-α) through suppressing transcription factor *nuclear factor kappa B*(NFκB) or *activator protein-1*.[19] This drug can be administered to children at dose of 50 mg/kg/day.[14]

Mycophenolate mofetil is mycophenolate acid prodrug. This drug inhibits the proliferation of T and B cells effectively, induces T cell apoptosis and blockades the production of antibody by B

cell. Mycophenolate mofetil is an alternative therapy with minimum side effect on the refractory BP. This drug is administered at dose of 20-30 mg/kg/day.[2] In this case, methylprednisolone 31.25 mg/24 hour tapering off is combined with erythromycin 3 x 300 mg per oral because in the administration of corticosteroid previously, lesion improvement was not found. In the 5th day therapy, mycophenolate mofetil is added with 2 x 250 mg per oral because new bullous remained to appear. Lesion improvement is obtained following the administration of three combinations for 3 days and then, the treatment was continued in outpatient polyclinic.

Cetrizine is 2nd generation antihistamine working quickly and having ability as selective antagonist of peripheral H1 histamine receptor. Cetrizine can inhibit H1 histamine receptor in immune cells, have anti-inflammatory activity, reduce inflammatory cell infiltration, and reduce neutrophil and eosinophil migration.[16] In BP histamine is released by mast cell. Mast cell also plays an important role in inflammation process involved in bullous formation.[17] Therefore, cetrizine can be used as a therapy in BP. In this case, cetrizine was administered to the patient at dose of 10 mg/day.

Mupirocin is a crotonic acid-derived drug. This drug is a secondary metabolite produced in bacterial dormancy phase and can inhibit protein synthesis through *bacterial isoleucyl-tRNA synthetase* bond. Mupirocin is often used to fight against positive gram bacteria such as staphylococcus and is used rarely to fight against negative gram bacteria.[18] The research conducted by Belheouane *et al*. in 2022 reported that a change occurs in the composition of skin microbiota in BP patients in which *Staphylococcus aureus* is found to be primary skin microbiota.[19] Therefore, mupirocin can be administered to BP patient to fight against the bacteria to prevent further infection from occurring. In this case, mupirocin 2% ointment was applied twice (2 times) a day to the erosion area.

Triamcinolone is a glucocorticoid with anti-inflammatory and immunosuppressant activities through inhibiting phospholipase enzyme A2 in phosholipid cellular membrane. The anti-inflammatory mechanism of triamcinolone is to inhibit NF-κB.[20] The administration of triamcinolone can prevent new lesion from being created due to inflammation process. In this case, topical triamcinolone was applied twice a day to the patient on mouth area.

Conclusion

Bullous pemphigoid can occur in children, despite rare incidence. The establishment of BP diagnosis should be based on histopathological and DIF examinations. The primary therapy management used to this disease is systemic corticosteroid administered in tapering dose. Another treatment can be given to relieve the symptoms and to resist infection. Earlier diagnosis establishment is important to provide appropriate therapy in order to accelerate clinical improvement in the patient.

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