Bullous Systemic Lupus Erythematosus Mimicking Bullous Pemphigoid: A Case Report

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Abstract

Introduction: Bullous systemic lupus erythematosus (BSLE) is an infrequent but distinct presentation of systemic lupus erythematosus (SLE) in less than 5% of lupus cases. It is characterized by vesicobullous skin eruption in SLE that can develop either before or after SLE diagnosis has been established. Distinguish between BSLE with other autoimmune blistering diseases such as bullous pemphigoid (BP), dermatitis herpetiformis, linear IgA, etc., is very important to prevent misdiagnosis. The physician must be able to combine clinical, histological and immunofluorescence finding for the diagnosis approach. We report a case of blistering skin eruption in SLE patient. **Case Report:** A 19-year-old female patient complained of tense blistering on her lip, face and wrists since one month ago. She was diagnosed with SLE two weeks ago. The dermatological state showed bullae and vesicle on erythematous/ normal base, erosions, excoriation and blackish red crust on the lip, face, armpit, neck, abdomen and wrists. Histopathological examination of the lesion showed sub-epidermal bullae containing PMN leukocytes consist of abundant neutrophils, only occasional eosinophils and the presence of keratotic plugs. Direct immunofluorescence (DIF) of the skin showed linear deposition of IgG, IgA, IgM and C1q at the dermo-epidermal junction. This patient exhibited similar features to both BSLE and BP with tensed clear blisters and subepidermal cleft. BSLE differ from BP by abundant neutrophils found on histopathological examination, whereas BP has abundant eosinophils. **Conclusion:** Immunofluorescence examination shows linear IgG in BP, whereas linear or granular IgG in BSLE. Establishing the correct diagnosis is important to prevent misdiagnosis and mistreatment.

Keywords – Bullous Systemic Lupus Erythematosus, Systemic Lupus Erythematosus, Bullous Pemphigoid, Histopathology, Direct immunofluorescence.

Abstrak

Pendahuluan: *Bullous Systemic Lupus Erythematosus (BSLE) sangat jarang tetapi memiliki gambaran khas dari systemic lupus erythematosus (SLE) yang terjadi pada kurang dari 5% kasus lupus. Ini ditandai dengan erupsi kulit vesikobulosa pada SLE yang dapat muncul baik sebelum atau setelah diagnosis SLE ditegakkan. Membedakan BSLE dengan penyakit lepuh autoimun lainnya seperti pemfigoid bulosa (BP), dermatitis herpetiformis, IgA linier dll sangat penting untuk mencegah kesalahan diagnosis. Dokter harus dapat menggabungkan temuan klinis, histologis dan imunofluoresensi untuk penegakkan diagnosis. Kami melaporkan suatu kasus erupsi kulit melepuh pada pasien SLE.* ***Laporan Kasus:*** *Seorang pasien wanita berusia 19 tahun mengeluhkan gelembung yang tegang di bibir, wajah, dan pergelangan tangannya sejak 1 bulan lalu. Pasien didiagnosis sebagai SLE sejak 2 minggu lalu. Status dermatologikus ditemukan bula dan vesikel pada dasar yang eritem/ normal, erosi, eksoriasi, dan krusta merah kehitaman pada bibir, wajah, ketiak, leher, perut, dan pergelangan tangan. Pemeriksaan histopatologis menunjukkan bula sub-epidermal dengan adanya leukosit PMN terdiri dari neutrofil yang banyak, eosinofil yang jarang dan adanya keratotik plug. Imunofluoresensi langsung pada biopsi kulit menunjukkan deposisi linear IgG, IgA, IgM dan C1q di dermo-epidermal junction. Pasien ini menunjukkan fitur yang mirip antara BSLE dengan BP dengan gelembung yang tegang dan memiliki celah pada subepidermal. BSLE berbeda dari BP pada pemeriksaan histopatologis, dimana neutrofil lebih banyak ditemukan pada pemeriksaan histopatologis BSLE, sedangkan BP memiliki eosinofil yang lebih banyak.* ***Kesimpulan:*** *Pemeriksaan imunofluoresensi menunjukkan IgG linear pada BP dan IgG linear atau granular pada BSLE. Menegakkan diagnosis yang benar merupakan hal penting untuk mencegah kesalahan diagnosis dan terapi.*

Kata kunci - Sistemik Lupus Erythematosus Bulosa, Systemic Lupus Erythematosus, Pemfigoid Bulosa, Histopatologi, Direct immunofluorescence.

I. Introduction

Bullous systemic lupus erythematosus (BSLE) is a sub-epidermal vascular disease caused by autoantibodies in patients with systemic lupus erythematosus. Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease with an unknown aetiology with various clinical manifestations. The skin is responsible for more than 85% of SLE cases and is one of the organs involved in lupus erythematosus. Bullae and vesicles in BSLE can appear on erythema or normal and non-scarred skin. Skin lesions occur in areas exposed to sunlight and flexure areas.[1] Bullous type systemic lupus erythematosus is rare; less than 5% of SLE cases occur. The mean incidence of BSLE was estimated to be 0.22 per million in three French regions. Lupus erythematosus usually happens in adult female young (decades 2 and 3), while the ratio of male and female is 1: 9.[2–4]

The causes and mechanisms of pathogenesis of bullous systemic lupus erythematosus are not completely understood. The pathogenesis of bullous type systemic lupus erythematosus is interrelated with the pathogenesis of systemic lupus erythematosus. SLE is a disorder in which interactions between factors host (gene susceptibility, hormonal) and environmental factors (ultraviolet radiation, viruses, drugs) cause loss of cell tolerance and induce autoimmunity. It is followed by activation of the immune system and results in immunological damage that could lead to clinical manifestation. BSLE could act as an initial manifestation of lupus erythematosus.[2,4]

Diagnosis of systemic lupus erythematosus is based on American Rheumatism Association criteria if 4 of the 11 symptoms are fulfilled: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder and antinuclear antibody. Systemic lupus erythematosus often involves other organ systems, especially the kidneys.[1–3] Clinical symptoms of BSLE patients include vesicles or tense bullae filled with serous or hemorrhagic fluid, spreading rapidly throughout the body, regarding areas exposed to sunlight, the neck, body, or areas not exposed to the sun and can affect the mucosa.[1]

On BSLE negative indirect immunofluorescence examinations, positive direct immunofluorescence was found to be deposition linear or granular IgG and/or IgM and IgA frequently in the basement membrane zone (dermo-epidermal junction).[1,4] C3 can also be found but rare. Histopathological examination of BSLE found sub-epidermal bullae in the presence of neutrophil infiltrates in the upper dermis with microabscess formation on papillary. [1,5] Differential diagnoses of this disease are dermatitis herpetiformis and bullous pemphigoid, which are clinically similar but different in histopathology and immunofluorescence examinations.[2,3]

Bullous pemphigoid (BP) is an acquired, acute or chronic, inflammatory, subepidermal, immunobullous disease. It is caused by autoantibody-mediated disruption of adhesion between basal keratocytes and the basement membrane. It occurs most frequently in older adults patients older than 60 years of age. In Singapore, the incidence was determined to be 7.6 per million per year, with a mean age of onset 77 years old and the male-to-female ratio of 1:2.[6–8]

The classic form of bullous pemphigoid is characterized by large, tense blisters on normal skin or an erythematous or urticarial base. These lesions most commonly found on flexural surfaces, the lower abdomen, and the thighs, although they could occur anywhere. The bullae are typically filled with serous fluid but could be hemorrhagic. One symptom, however, is found in all of the

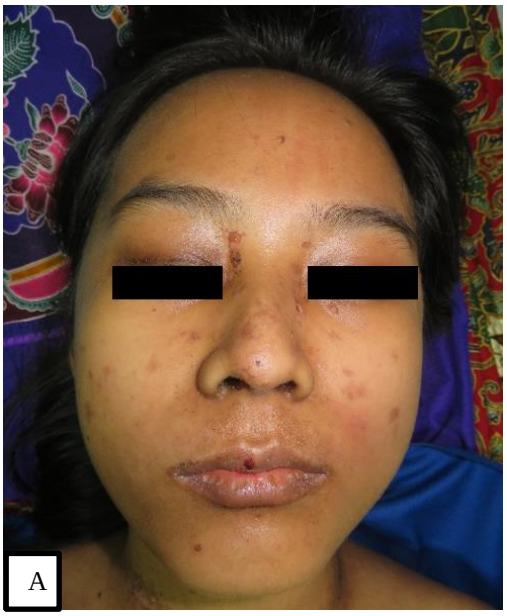
clinical presentations: moderate to intractable pruritus but may be minimal in some patients.[5,7]

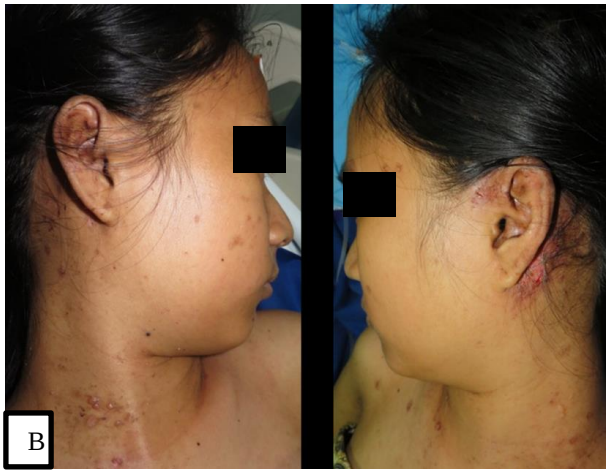
Treatment of BSLE could be given dapsone (25-50 mg/day); if no response to dapsone could be given prednisone (1 mg/Kg), high-dose corticosteroids aim to control visceral manifestations.[2] Azathioprine 100 mg / day, cyclophosphamide 100 mg / day, chloroquine (4 mg / kg), or mycophenolate mofetil (2.5-3 mg / kg) could be given in this patient.[1,2] It could be given as a combination of azathioprine with prednisone if there is no response to dapsone.[1,5]

II. Case Report

A 19-year-old female patient presenting with the chief complaint of multiple blisters filled with clear fluid appeared on the lips, armpit, neck and wrists that she sometimes felt itchy since one week ago. Initially, one month ago, there appeared a tense blister filled with clear fluid on the lip. There was a history of fever since two weeks ago, and she went to an internist. The patient was diagnosed with systemic lupus erythematosus. The patient took medication paracetamol 3x 500 mg, hydroxychloroquine sulphate 200 mg and methylprednisolone 12 mg per days. But two days ago, the patient went to Painan hospital because of fatigue, and she was diagnosed with SLE then referred to Dr. M. Djamil Padang Hospital. A history of hair loss and joint pain existed. The patient was diagnosed with SLE two weeks ago. History of facial redness after exposure to sunlight, seizures and hallucination, scars on the face, scalp and ears was denied.

On physical examination, we found pale conjunctivae. Dermatological examination showed bullae and vesicle on erythematous/ normal based, erosions, excoriation and blackish red crust on the face, neck, abdomen and wrist (fig. 1). From hematology examination result was moderate anemia (8.7 g/dl), hypoalbuminemia (2,1 g/dl), proteinuria (+++), increase ureum (116 mg/dl) and creatinine (1,5 mg/dl). Histopathological examination of the lesion showed sub-epidermal bullae containing PMN leukocytes consist of abundant neutrophils, only occasional eosinophils and the presence of keratotic plugs (fig. 2). Direct immunofluorescence (DIF) of the skin showed linear deposition of IgG, IgA, IgM and C1q at the dermo-epidermal junction.





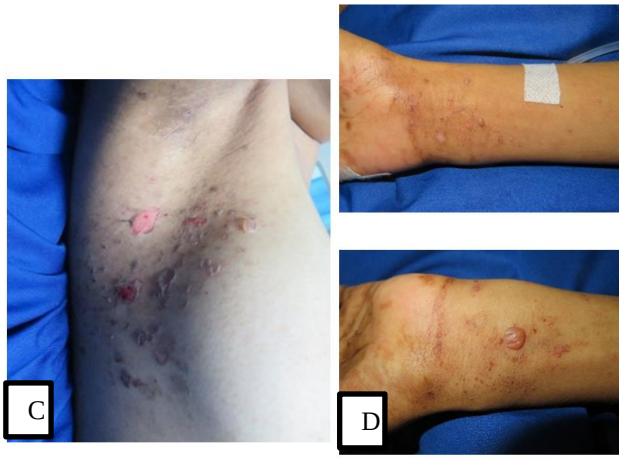


FIG. 1. A, B, C & D: DERMATOLOGICAL EXAMINATION SHOWED BULLAE AND VESICLE ON ERYTHEMATOUS/NORMAL BASED, EROSIONS, EXCORIATION AND BLACKISH RED CRUST ON FACE, NECK, ABDOMEN AND WRIST.

Diagnosis of bullous systemic lupus erythematosus based on Camisa and Sharma criteria: (1) a diagnosis of SLE based on four or more of the American Rheumatism Association's criteria; (2) vesicles and bullae arising upon but not limited to sun-exposed skin; (3) histopathology compatible with dermatitis herpetiformis and leukocytoclastic vasculitis in the superficial and mid dermis; (4) negative indirect immunofluorescence for circulating BMZ antibodies; (5) DIF of lesional and nonlesional skin always reveals linear or granular IgG and/ IgM and often IgA at the BMZ. ARA criteria found: presence of arthritis, haematological disorders, renal disorders (3+ proteinuria), oral ulcer; (2) vesicles and bullae arising upon but not limited to sun-exposed skin in this patient.

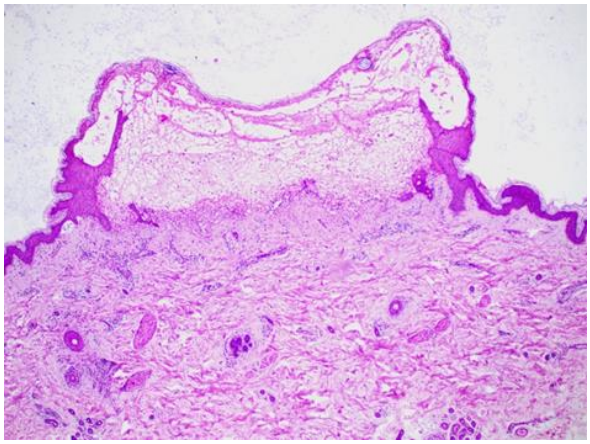


FIG. 2. HISTOPATHOLOGICAL EXAMINATION SHOWED SUB-EPIDERMAL BULLAE CONTAINING PMN LEUKOCYTES CONSIST OF ABUNDANT NEUTROPHILS, ONLY OCCASIONAL EOSINOPHILS AND THE PRESENCE OF KERATOTIC PLUGS.

III. Discussion

Bullous systemic lupus erythematosus (BSLE) is a sub-epidermal vascular disease caused by autoantibodies in systemic lupus erythematosus patients. Bullous lesions on the skin are rarely found in systemic lupus erythematosus patients (<5%). SLE usually occur in adult women young (decades 2 and 3). Miziara et al. reported BSLE events in 3 regions in France, around 0.22 cases per one million.[1,2,4,9] Bullous with SLE has never been reported in the Dermatology-Venereology Department of Dr. M. Djamil Padang Hospital until now.

Camisa and Sharma (Neples, 1983) state the criteria for diagnosing bullous type SLE: (1) diagnosis of SLE based on the American Rheumatism Association (ARA), (2) widespread and non-scars vesicobullous eruption, (3) sub-epidermal bullae with dermal inflammation characterized by papillary neutrophilic microabscess as in the case of dermatitis herpetiformis, (4) negative indirect immunofluorescence in the basement membrane zone, (5) direct immunofluorescence in lesions and non-lesions always showing linear or granular IgG and/or IgM and IgA in the basement

membrane zone.[9–11]

BSLE can occur as an initial manifestation of lupus erythematosus.[2,4] In this case, a 19-year-old female patient with bullous systemic lupus erythematosus in which from the history the main complaint appeared red patches with bullous that are not itchy on the lip, armpit, neck and wrists since one month ago and history of hair loss and joint pain since one month ago. The patient was diagnosed with SLE two weeks ago. The dermatological state showed bullae and vesicle on erythematous/normal base, erosions, excoriation and blackish red crust on the lip, face, armpit, neck, abdomen and wrists. Nikolsky sign was negative.

From the haematological examination, we found the impression of moderate anaemia, an increase in creatinine ureum levels and proteinuria. Patients are clinically diagnosed differentially with bullous pemphigoid where BSLE is found in tense-bullae filled with clear or hemorrhagic fluid at the base of diffuse erythema or urtica skin and absence of mucosal involvement, similar to bullous pemphigoid, but in bullous pemphigoid usually often in older age.[11,12]

On BSLE, positive direct immunofluorescence was found to be deposition linear or granular IgG and/or IgM and IgA frequently in the membrane zone basement.[1,4] C3 can also be seen, but rarely. Histopathological examination of BSLE found sub-epidermal bullae in the presence of neutrophil infiltrates in the upper dermis with microabscess formation on papillary.[1,7]

On bullous pemphigoid, histopathological examination showed sub-epidermal bullae with inflammatory eosinophil- predominant infiltrate, also containing lymphocytes and neutrophils. Whereas in BSLE, sub-epidermal bullae with neutrophil infiltrate will be found to form microabscess on the papillary dermis.[10] Immunofluorescence examination, the direct immunofluorescence bullous pemphigoid found their C3 and IgG antibodies to the basement membrane zone, indirect immunofluorescence was found in the presence of the basement membrane zone IgG in serum.[11,13]

Differences with BP, a biopsy of the vesicle is diagnostic with histology revealing a subepidermal blister and a superficial dermal infiltration consisting of prominent eosinophils. However, neutrophil and mononuclear cells are observed in the dermis as well. Positive direct immunofluorescence was found IgG and/or IgM and IgA in the basement membrane zone.[6,8]

Tincopa M. et al. reported bullous systemic lupus erythematosus. A 13-year-old African American girl complained of painful and slightly pruritic vesiculobullous eruption involving her skin and mucous membranes. By report, the lesions progressed over three weeks, beginning with a single vesicle on her abdomen near an infected umbilical piercing. Histology showed subepidermal bullae; the papillary dermis was edematous with numerous neutrophils and only occasional eosinophils. Direct immunofluorescence (DIF) revealed heavy linear deposition of IgG and IgA along the basement membrane zone (BMZ).[9]

Bullous systemic lupus erythematosus tends to be unresponsive to systemic corticosteroid therapy that is typically helpful for other SLE manifestations. Our patient responded to corticosteroids, although she required relatively high doses. The mainstay of treatment for BSLE is dapsone. Patients tended to have a dramatic response with cessation of new blister formation in 1–2 days and healing of existing lesions within several days, even at low doses of 25–50 mg daily.[9] Miziara et al. reported bullous systemic lupus erythematosus. A 27-year-old female presented painful bullous lesions in the left nasal wing and left buccal mucosa

that displayed sudden and rapid growth. She sought advice from emergency dermatology staff 15 days after onset and was hospitalized with the suspected bullous disease. Histopathological results indicated mucositis with extensive erosion and the presence of a predominantly neutrophilic infiltrate with degeneration of basal cells and apoptotic keratinocytes.[1]

Under direct immunofluorescence, the skin showed anti-IgA, anti-IgM, and anti-IgG linear fluorescence on the continuous dermal side of the cleavage. The patient took 100 mg dapsone, 250 mg chloroquine, 50 mg azathioprine, and 50 mg prednisone as initial treatment. Although this resulted in improved lesions, there was the persistence of some scarring plaques on the trunk and lower lip.[1] Ali et al. reported bullous systemic lupus erythematosus. A 25-year-old female presented with multiple tense blisters on her face, neck, front and back of the trunk, both upper & lower extremities. Histopathological examination revealed subepidermal bulla with eosinophils and some neutrophils. DIF showed linear deposition of IgG and C3 in the basement membrane zone. The patient was treated with systemic steroid and dapsone and got a good response.[11]

Raman et al. reported bullous systemic lupus erythematosus. A 27-year-old female, she had tense progressive unilateral vesiculobullous lesions over face, neck & upper chest wall region in multiple crops, with rupture of vesicles. Histo-section showed an intact neutrophil-rich subepidermal vesicle with neutrophils infiltrating the dermal papillae and lined up along the dermal-epidermal junction. DIF revealed 2+ IgG & C1q granular staining at the dermal-epidermal junction, trace IgA, IgM & C3 staining at the dermal-epidermal junction. The patient was treated with intravenous methylprednisolone 1 mg/ day for 3 days followed by 1 mg/ kg/ day, Hydroxychloroquine 200 mg/day, IV cyclophosphamide 15 mg/kg/month. After two weeks, all the bullous lesions had healed completely.[14]

Maggio et al. reported bullous pemphigoid in systemic lupus erythematosus. An 11-year-old female was diagnosed with SLE. Since the age of 10, she developed a vesiculobullous eruption with clinical and histological features of BP, with typical skin features. Histopathology revealed subepidermal blister, and perivascular neutrophils and eosinophil infiltration. For the skin lesions relapses, she received corticosteroids (prednisone 1 mg/kg/day), resulting in the remission of the clinical manifestations. At the tapering off prednisone dose, the patient had new skin lesions requiring an increased dose. Due to the frequent relapses, she started oral administration of dapsone at the dosage of 1 mg/kg/day, which resulted in the dramatic disappearance of the lesions and allowed gradual dose tapering of prednisone down to 2.5 mg/day.[15]

In our patient, histopathological examination of the lesion showed sub-epidermal bullae containing PMN leukocytes consist of abundant neutrophils, only occasional eosinophils and the presence of keratotic plugs. Direct immunofluorescence (DIF) of the skin showed strong linear deposition of IgG, less IgA, IgM and C1q at the dermo-epidermal junction. The physician must be able to combine clinical, histological and immunofluorescence finding for the diagnosis approach. Before the histopathological examination results, immunofluorescence and antibody examination, the patient was given prednisone therapy 12 mg peroral and fusidic acid cream 2% was applied twice daily at erosion. But during treatment, a tense blister still appeared on the face, lip, ears, neck, abdomen and wrists. Broken blisters were compressed with NaCl 0.9% thrice daily for

15 minutes.

The patient was admitted to the internal medicine ward. Therapy in these patients was given high-dose corticosteroids (125 mg methylprednisolone, equivalent to 155 mg prednisone) for three days. Then, the dose was reduced to 12mg/day. The patient was also given 200 mg hydroxychloroquine to suppress inflammation and increase the anti-inflammatory effect of corticosteroids. The patient went home on her own decision before the result of histopathology and DIF came out. She never controlled outpatient Dermatology and Venereology Dr. M. Djamil Hospital until now.

The prognosis on this patient was dubia ad malam for quo ad vitam, dubia ad malam for quo ad sanationam, dubia ad bonam for quo ad cosmeticum and quo ad functionam.

IV. Conclusion

One case of BSLE was reported based on clinical, laboratory, histological, and direct immunofluorescence findings. In this case, the diagnosis BSLE was made based on Camisa and Sharma criteria: ARA criteria found 5 out of 11 symptoms: the presence of arthritis, haematological disorders, renal disorders (3+ proteinuria) and oral ulcer. ANA profile examination was ds-DNA (+++) and ribosomal protein associated with SLE. Histological examination of the lesion showed separation of the dermis, epidermis, and subepidermal bulla. Direct immunofluorescence (DIF) demonstrated a strong linear deposition of IgG and less IgA, IgM and C1q deposition at the dermo-epidermal junction.

This patient exhibited similar features to both BSLE and BP with tensed clear blisters and subepidermal cleft. BSLE differ from BP by abundant neutrophils found on histopathological examination, whereas BP has abundant eosinophils. Immunofluorescence examination showed linear IgG in BP and linear or granular IgG in BSLE.

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