Piecing Together a Case of Bullous Systemic Lupus Erythematosus in a Boy: Turning to the Clinical Laboratory for Critical Clues

Bir Erkek Çocukta Büllöz Sistemik Lupus Eritematozus Olgusunu Bir Araya Getirmek: Kritik İpuçları için Klinik Laboratuvarına Dönmek

Asrul Abdul Wahab[1], Chuan Hun Ding[1], Kon Ken Wong[1], Husna Farhanah Ahmad[2], Ikmal Hisyam Bakrin[3]

[1]Department of Medical Microbiology & Immunology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[2]Department of Pathology, Hospital Tengku Ampuan Rahimah, Ministry of Health of Malaysia, Klang, Selangor, Malaysia
[3]Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia

ABSTRACT

Bullous systemic lupus erythematosus (BSLE) is a rare autoimmune blistering condition. A 10-year-old boy presented with generalized vesiculobullous skin eruptions and was initially diagnosed with bullous disease of childhood. Indirect immunofluorescence testing for antinuclear antibodies (ANA) was positive, with a homogeneous pattern and a titre of ≥1:640. His skin biopsy revealed the presence of subepidermal bullae with linear deposition of IgG and C3 along the basement membrane. Renal biopsy showed class III lupus nephritis. Our case illustrates that bullous skin lesion can be the initial presentation of SLE especially in children. Thus, a high index of suspicion and the right diagnostic tools are crucial to unmask the true diagnosis.

Key Words: Bullous systemic lupus erythematosus, lupus nephritis, antinuclear antibody

Received: 02.04.2020 **Accepted:** 10.05.2020

ÖZET

Büllöz sistemik lupus eritematozus (BSLE), nadir görülen bir otoimmün bir durumdur. Yaygın vezikülobüllöz deri döküntüleri ile başvuran 10 yaşındaki bir erkek çocuk başlangıçta çocukluk çağı büllöz hastalığı tanısı aldı. Antinükleer antikorlar (ANA) için dolaylı immünofloresan testi, homojen bir model ve ≥1: 640 titre ile pozitifti. Deri biyopsisi, bazal membran boyunca lineer IgG ve C3 birikimi ile subepidermal büllerin varlığını ortaya çıkardı. Böbrek biyopsisi sınıf III lupus nefritini gösterdi. Olgumuz, büllöz deri lezyonunun özellikle çocuklarda SLE'nin ilk prezentasyonu olabileceğini göstermektedir. Bu nedenle, yüksek bir şüphe indeksi ve doğru teşhis araçları, doğru teşhisi ortaya çıkarmak için çok önemlidir.

Anahtar Sözcükler: Büllöz sistemik lupus eritematozus, lupus nefriti, antinükleer antikor

Geliş Tarihi: 04.02.2020 **Kabul Tarihi:** 05.10.2020

ORCID IDs: A.A.W. 0000-0001-8283-6028, C.H.D. 0000-0001-6040-219X, K.K.W. 0000-0003-2565-6084, H.F.A. 0000-0003-3479-717X, I.H.B. 0000-0002-9681-4118

Address for Correspondence / Yazışma Adresi: Asrul Abdul Wahab, MD Department of Medical Microbiology and Immunology Faculty of Medicine Universiti Kebangsaan Malaysia Jalan Yaacob Latif 56000 Cheras Kuala Lumpur, Malaysia E-mail: asrulwahab@hotmail.com

doi:http://dx.doi.org/10.12996/gmj.2021.52

INTRODUCTION

SLE is an autoimmune disorder uncommonly diagnosed in the paediatric population. A study conducted in Australia reported an annual incidence rate of only 0.32 per 100,000 children aged less than 16 years (1). Cutaneous lesions in SLE can be classified as either lupus erythematous (LE)-specific or non-LE-specific lesions with majority of them presented as LE-specific lesions. BSLE is a part of non-LE specific lesions, represents only in one percent of all cutaneous SLE lesions (2).

CASE REPORT

A 10-year-old boy presented with one-month history of generalized vesiculobullous skin lesions associated with intermittent low-grade fever. The lesions started from his neck and trunk and subsequently spread to both his upper and lower limbs. The bullae were preceded by erythematous plaques. The larger and tenser bullae ruptured and evolved to become hypo pigmented skin lesions (Figure 1). Secondary bacterial infections developed in some of the bullae. Otherwise, he did not complaint of any other symptoms.

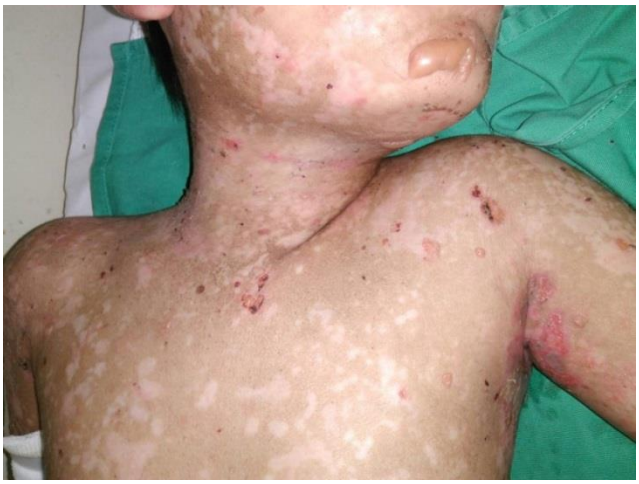

Figure 1. Multiple hypopigmented skin lesions appeared following the eruption of bullous lesions. A particularly large and tense bulla can be seen on the chin.

On examination, there was tense and flaccid bullae with areas of eroded and hypo pigmented skin seen. He was started on oral prednisolone 10 mg 12-hourly because the preliminary skin biopsy report showed the evidence of underlying autoimmune disease. The total white cell count on admission was 5.6 x 10^9/L, the haemoglobin level was 10 g/dL, and the platelet count was 302 x 10^9/L. The C-reactive protein level and erythrocyte sedimentation rate (ESR) were not raised at 3.7 mg/L and 17 mm/hr, respectively. His blood sample was also sent for several diagnostic tests. Other laboratory tests were as shown in Table 1. His anti-nuclear antibody (ANA) test by indirect immunofluorescence was positive at significantly high titration (1≥1:640), showing homogeneous pattern (Figure 2). Anti-double-stranded DNA (anti-dsDNA), anti-Smith and anti-ribonucleoprotein (U1RNP) antibodies were also positive.

Table 1: Laboratory investigation during the time of admission.

Parameters		Result	Normal Range	Unit
1.	***Renal Profile***			
	Urea	3.0	3.6-7.6	mmol/L
	Sodium	140	132-146	mmol/L
	Potassium	3.5	3.5-5.5	mmol/L
	Chloride	105	99-109	mmol/L
	Creatinine	33	61.9-110.9	umol/L
2.	***Urinalysis***			
	Glucose	Negative		mmol/l
	Ketone	Negative		mmol/L
	Nitrite	Negative		mmol/L
	Leukocytes	Negative		WBC/uL
	Blood	Negative		RBC/uL
	Protein	2+		g/L
3.	***Urine 24-hour protein***	2.410	0.05-0.08	g/24hour
4.	***Serum complement***			
	C3	0.58	0.87-1.58	g/L
	C4	0.12	0.14-0.36	g/L
5.	***Serum albumin***	30	39-49	g/L

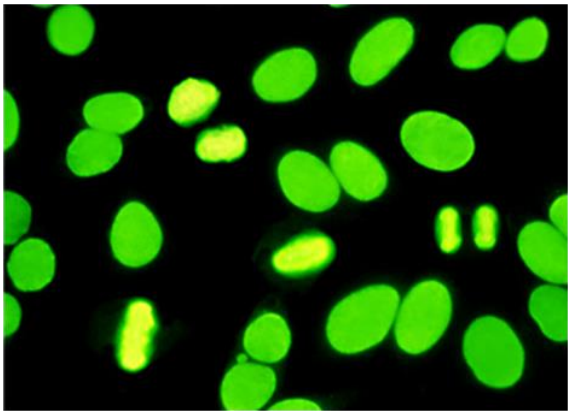

Figure 2: Indirect immunofluorescence testing for serum antinuclear antibodies revealed a homogeneous nuclear staining pattern.

The final histopathological report of the skin biopsy revealed subepidermal bullae with clear separation between the dermal and epidermal junctions contains of neutrophils. The papillary dermis showed moderate perivascular neutrophilic cells infiltrate mixed with lymphocytes (Figure 3). There was no significant number of eosinophils seen. The adjacent non-blistering epidermis also showed subtle vacuolar degeneration (Figure 3). Direct immunofluorescence (DIF) study demonstrated deposition of linear IgG and C3 at the basement membrane. No deposition of IgA, IgM and C4 were noted. A renal biopsy was also performed in view of significant proteinuria, and the result was consistent with Lupus Nephritis Class III.

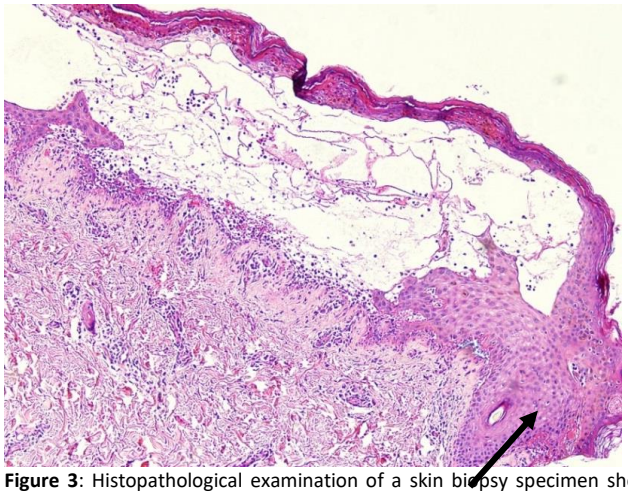

Figure 3: Histopathological examination of a skin biopsy specimen showing a subepidermal blister contains of mainly neutrophils mixed with lymphocytes. The adjacent epidermis (arrow) showed vacuolar degeneration (Hematoxylin and eosin stain, original magnification x 40).

The clinical and laboratory investigations confirmed that the patient fulfilled the criteria for SLE. The diagnosis of BSLE with lupus nephritis was made as the final diagnosis for this patient. Thus, he was started on high-dose steroid therapy, intravenous hydrocortisone 4 mg/kg 6-hourly. He responded well to treatment and did not require dialysis for his renal impairment. Subsequently, he was transferred to rheumatology centre for further management of his condition.

DISCUSSION

The diagnosis of SLE in this patient was made because he fulfilled the score to be classified as SLE. He had fever, low serum complements concentration, positive anti-nuclear antibody at significant titration, positive anti-double stranded DNA, significant proteinuria and renal biopsy that showed class III lupus nephritis. According to the new SLE classification criteria he scored more than 10 which made the diagnosis of SLE was very likely (3).

At the same time he also had bullous skin lesions which was not a typical cutaneous lesion seen in SLE. The skin biopsy showed a bullous lesion most likely of BSLE. BSLE is indeed a rare cutaneous manifestation of SLE and must be differentiated from other bullous diseases of childhood, particularly epidermolysis bullosa and dermatitis herpetiformis (4). Histopathological examination plays an indispensable role in confirming the diagnosis. The presence of subepidermal bullae with neutrophilic cells infiltrate and the visualisation of a linear, granular or a mixture of both immunoglobulins deposition at the basement membrane zone (BMZ) through direct immunofluorescence (DIF) help to confirm the diagnosis (4). The dermal-epidermal separation observed at the BMZ is the result of autoantibodies that bind to type VII collagen. This type VII collagen helps to maintain adhesion at the dermo-epidermal junction by cross linking between lamina densa and matrix of papillary dermis (5). As described previously, BSLE affects both genders and occurred on both sun-exposed and sun-shielded skin (6-8).

Other laboratory investigations play important role for diagnosis of SLE. Anti-nuclear antibody positivity was the most consistent American College of Rheumatology criterion fulfilled by paediatric SLE patients at the time of diagnosis, with frequency approaching 100% (1). Similar to our case, most of the paediatric SLE cases were found to have ANA titres in excess of 1:640 (9). Other important and highly specific autoantibodies (albeit at lower frequencies) are anti-dsDNA and anti-Smith, at frequencies of 34.7-78.1% and 34.8%, respectively (1,9). These two autoantibodies may also potentially aid the diagnosis of SLE. Lupus nephritis was noted to occur in 34-60% of paediatric SLE at the time of diagnosis (1,9). Renal biopsy is crucial to confirm the diagnosis. Majority of the patients were diagnosed with class IV lupus nephritis (1-2). In this particular case, the renal biopsy which showed class III lupus nephritis was performed when patient's urine 24-hour protein showed significant proteinuria at 2.410 g/24 hour. BSLE and lupus nephritis were commonly reported to be diagnosed concurrently at the time of presentation (6-8). In this case, the similarity with previously reported cases was noted. The pathogenesis of developing nephritis in BSLE is not well understood. The presence of nephritogenic autoantibodies such as anti-double stranded DNA may be crucial for renal involvement in SLE (10).

Dapsone, which is an anti-leprosy medication, is the drug of choice for the treatment of BSLE. However, there are some patients who demonstrate no clinical improvement with dapsone or has high SLE disease activity index. Alternative medications, such as corticosteroids, methotrexate and azathioprine can be used in this patient (11). Considering that this patient had been diagnosed with class III lupus nephritis, the specific treatment can further be divided into induction and maintenance phases (12). The induction phase include the use of intravenous cyclophosphamide or mycophenolate mofetil (MMF) in combination with glucocorticoid. Azathioprine or MMF are the medications recommended during the maintenance phase in combination with low-dose oral glucocorticoids (12). Unfortunately, we were unable to get the detail on further treatment as he was transferred to a specialised centre for further management of his condition.

CONCLUSION

This case illustrates that generalized vesiculobullous lesions in a child can be an initial presentation of SLE. Both anti-nuclear antibody and histopathological examination play crucial role in establishing accurate diagnosis.

Conflict of interest

No conflict of interest was declared by the authors.

Acknowledgement

The authors would like to thank the Dean of the Faculty of Medicine, Universiti Kebangsaan Malaysia, and the Director General of the Ministry of Health of Malaysia for their support and permission to publish this case report.

REFERENCES

1. Mackie FE, Kainer G, Adib N, Boros C, Elliott EJ, Fahy R, et al. The national incidence and clinical picture of SLE in children in Australia-a report from Australian Paediatric Surveillance Unit. Lupus. 2015; 24: 66-73.

2. Dickey BZ, Holland KE, Drolet BA, Galbraith SS, Lyon VB, Siegel DH, Chiu YE. Demographic and clinical characteristics of cutaneous lupus erythematosus at a paediatric dermatology referral centre. British Journal of Dermatology. 2013; 169: 428-433.

3. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/ American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis & Rheumatology. 2019; 71(9): 1400-1412.

4. Gammon WR, Briggaman RA. Bullous SLE: A phenotypically distinctive but immunologically heterogenous bullous disorder. J Invest Dermatol. 1993; 100(1): 28S-34S.

5. Chan LS, Lapiere JC, Chen M, Traczyk T, Mancini AJ, Paller AS et al. Bullous systemic lupus erythematosus with autoantibodies recognizing multiple skin basement membrane components, bullous pemphigoid antigen 1, laminin-5, laminin-6, and type VII collagen. Arch Dermatology. 1999; 135(5):569-73.

6. Vijayalakshmi AM, Jayavardhana A. Bullous systemic lupus erythematosus and lupus nephritis in a 10-year-old boy. Indian Pediatrics. 2007; 44(11): 861-863.

7. Lourenço DMR, Gomes RC, Aikawa NE, Campos LMA, Romiti R, Silva CA. Childhood-onset bullous systemic lupus erythematosus. Lupus. 2014; 23: 1422-1425.

8. Mahesh E, Madhyastha PR, Karma V, Gurudev KC, Gireesh MS, Bande SR. Unusual presentation of systemic lupus erythematosus. Saudi J Kidney Dis Transpl. 2017; 28(3): 653-656.

9. Ilias MI, Ali JM, Ismail NZ, Rostenberghe HV, Rahman AA. Pediatric Systemic Lupus Erythematosus (SLE) manifestations and outcomes in a tertiary hospital. Lupus Open Access. 2017; 2: 123.

10. Yung S, Chan TM. Anti-DNA antibodies in the pathogenesis of lupus nephritis-the emerging mechanisms. Autoimmun Rev. 2008; 7(4):317-21.

11. Duan L, Chen L, Zhong S, Wang Y, Huang Y, He Y, et al. Treatment of bullous systemic lupus erythematosus. J Immunol Res. 2015; 2015: 167064. DOI: 10.1155/2015/167064

12. Wilhelmus S, Bajema IM, Bertsias GK, Boumpas DT, Gordon C, Lightstone L, et al. Lupus nephritis management guidelines compared. Nephrol Dial Transplan. 2016; 31: 904-913.